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Ring forming transformations of ynamides *via* cycloaddition

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Ynamides are *N*-alkyne compounds bearing an electron withdrawing group at the nitrogen atom. They offer unique pathways for the construction of versatile building blocks owing to their exceptional balance between reactivity and stability. Recently several studies have been reported that explore and illustrate the synthetic potential of ynamides and ynamide-derived advanced intermediates in cycloadditions with different reaction partners to yield heterocyclic cycloadducts of synthetic and pharmaceutical value. Cycloaddition reactions of ynamides are the facile and preferable routes for the construction of structural motifs having striking importance in synthetic, medicinal chemistry, and advanced materials. In this systematic review, we highlighted the recently reported novel transformations and synthetic applications that involved the cycloaddition reaction of ynamides. The scope along with the limitations of the transformations are discussed in detail.

1. Introduction

Ynamides are scaffolds that have *N*-alkyne as an active core, with the nitrogen atom further linked to an electron withdrawing group (EWG) (Fig. 1). Stimulated by the atom-economical and facile synthesis of ynamides, the scope, and reactivity of ynamides were explored and expanded in recent years.[1] In the past decade, exceptional reactivity and stability of ynamides have been featured persistently and employed in a wide array of synthetic manifestations to realize the synthesis of natural as well as synthetic products. Ynamide is a modern functional group that can be employed as a versatile tool in organic synthesis to realize the synthesis of a diverse range of cyclic/polycyclic building blocks containing nitrogen within or close to the ring.[2–5] The nitrogen atom in the ynamides accounts for its unusual reactivity and regioselectivity as it induces strong polarization in the alkyne triple bond.[6] Owing to polarization, alkyne's α-carbon end serves as an electrophilic center while the β-carbon serves as a nucleophilic center. The electrophilic and nucleophilic centers generated within the same molecule render the alkyne with exceptional reactivity. Moreover, by varying the EWG attached to the nitrogen atom, the electronic properties could be modulated, which ultimately controls the reactivity of ynamides.[7,8]

With the advent of ynamide's reactivity and novel methodologies for more efficient and regioselective transformations, there is a surge of ongoing interest in the development and synthetic applications of cycloaddition reactions.[5,9–12] Among the several conceivable synthetic transformations of ynamides, cycloaddition reactions are one of the preferable routes that offer rapid assembly of novel complex frameworks with structural as well as molecular diversity.[5] An impressive number of ynamide's cycloaddition reactions realizing the C–C and C–X (X = heteroatom) bond synthesis with excellent regioselectivity, stereoselectivity, and chemoselectivity expanded the asymmetric synthesis toolbox.[10]

The catalyst-activated ynamides afford the generation of advanced reaction intermediates that readily underwent cycloaddition (either intermolecular or intramolecular) to yield cycloadduct. This review aims to highlight the most prominent progress by discussing the novel and improved reported methodologies of ynamides and ynamide derived intermediates, along with a brief discussion on product diversity and selectivity during cycloaddition reactions (from 2014 to 2021). Moreover, in this review applicability, limitations, and mechanistic rationale of the synthetic transformations for the construction of structural motifs having high synthetic value is discussed. We anticipate that this review will expand the research spectrum by providing the reader with a broad and thorough overview of the expanding area of ynamide's chemistry.

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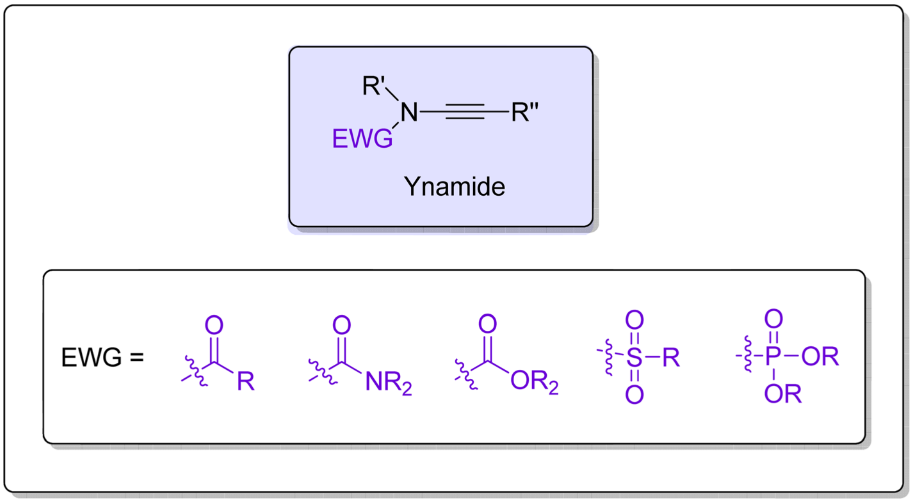
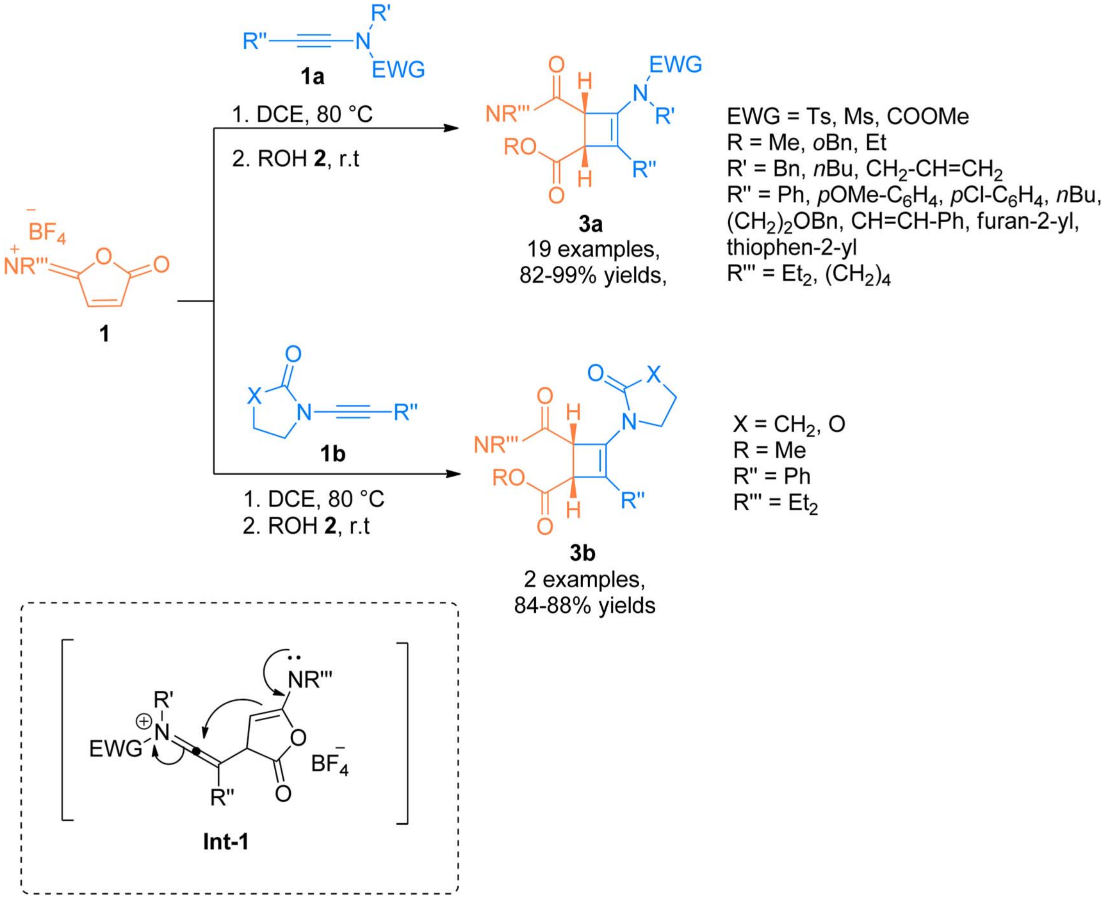


Fig. 1 The general structure of ynamide.

2. Cycloaddition reactions of ynamides

The cycloaddition reactions of ynamides have been reported extensively and furnished a diverse range of synthetically and biologically important cores such as carbocycles and heterocycles. The transformation of ynamides provided efficient and direct access to a wide array of cyclic products.[13,14] The following section comprises a brief overview of the prominent progress in the cycloaddition reactions.



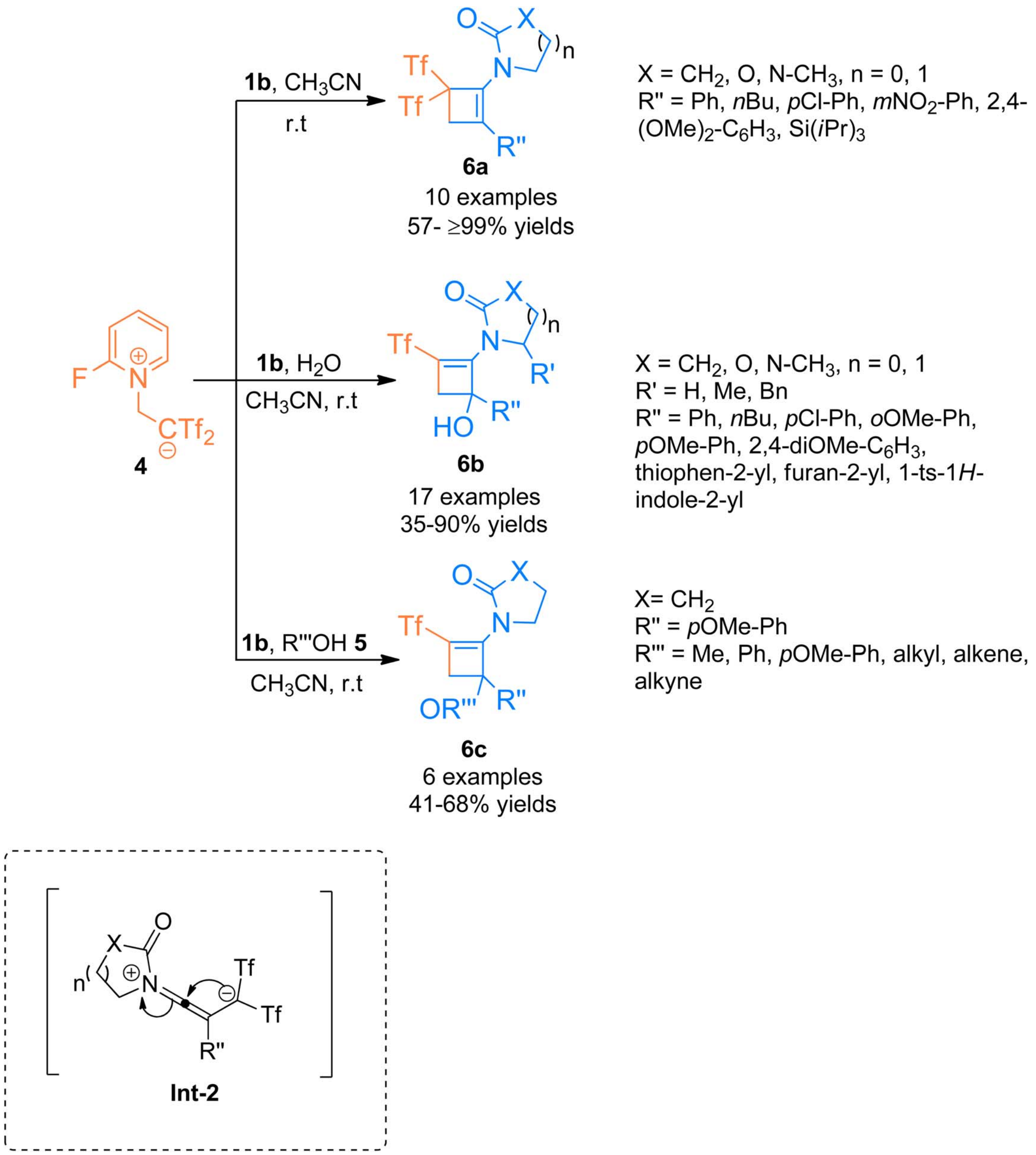
Scheme 1 Synthesis of substituted aminocyclobutenes **3a** and **3b** *via* [2 + 2]-cycloaddition of ynamides **1a** and **1b** and reaction partner iso-imidium salt **1** and alcohol **2**, respectively.

2.1. [2 + 2]-cycloaddition

2.1.1. Synthesis of cyclobutenes *via* [2 + 2]-cycloaddition.

There is a surge of interest to develop atom economical and facile methodologies to afford functionalized cyclobutenes *via* cycloaddition of ynamides.[15] Yuan *et al.* (2014), established a unique and efficient catalyst-free synthetic route for catalyst-free, [2 + 2]-cycloaddition of ynamides. The ynamides **1a**/**1b** reacted with cyclic isoimidium salt (α,β-unsaturated carbonyl compound) **1** (serving as electron-deficient alkene partners), and alcohol **2** *via* thermally driven regiospecific Ficini [2 + 2]-cycloaddition reaction *via in situ* generation of carbene intermediate **Int-1**. The reaction sequence happened using dichloroethane at 80 °C followed by the reaction with alcohol **2** at room temperature to yield stable cyclobutenamides **3a** (19 examples, 82–99% yields) and **3b** (2 examples, in 84–88% yields) (Scheme 1).[16]

In addition to the above, the catalyst-free regiospecific [2 + 2]-cycloaddition of the ynamide **1b** and zwitterion **4** as a source of bis((trifluoromethyl)sulfonyl)ethane was described by Alcaide *et al.* (2016), under mild conditions to afford aminocyclobutenes **6a–c**. Aminocyclobutene **6a** was afforded using acetonitrile at room temperature within a short reaction time of two minutes (10 examples, 57- ≥99% yields) (Scheme 2). Electron-rich aromatic scaffolds tethered at the carbon terminal of ynamide **1b** switched the reactivity with the zwitterion **4** using water/alcohol **5**. The synthetic route proceeded *via* a cyclization reaction of the intermediate **Int-2** followed by a hydroalkoxylation reaction within a single step. Using acetonitrile



Scheme 2 Synthesis of substituted aminocyclobutenes **6a–c** *via* [2 + 2]-cycloaddition of ynamides **1b**.

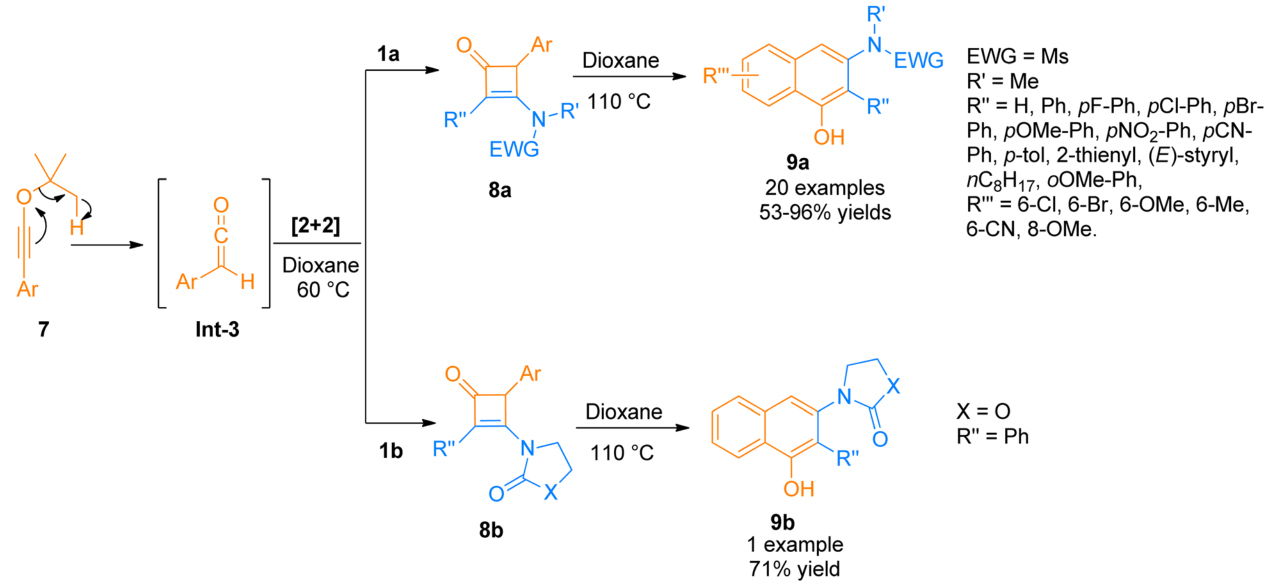
and water solvents the cycloaddition reaction furnished aminocyclobutenyl alcohols **6b** at room temperature (17 examples, 35–90% yields). While the three-component cycloaddition reaction between ynamides **1b**, zwitterion **4**, and alcohols **5** yielded aminocyclobutenyl ethers **6c** (6 examples, 41–68% yields) using acetonitrile (anhydrous) at room temperature. This synthetic manifestation offers the advantage of catalyst-free transformation at room temperature with short reaction times.[17]

2.1.2. Synthesis of cyclobutenones *via* [2 + 2]-cycloaddition.

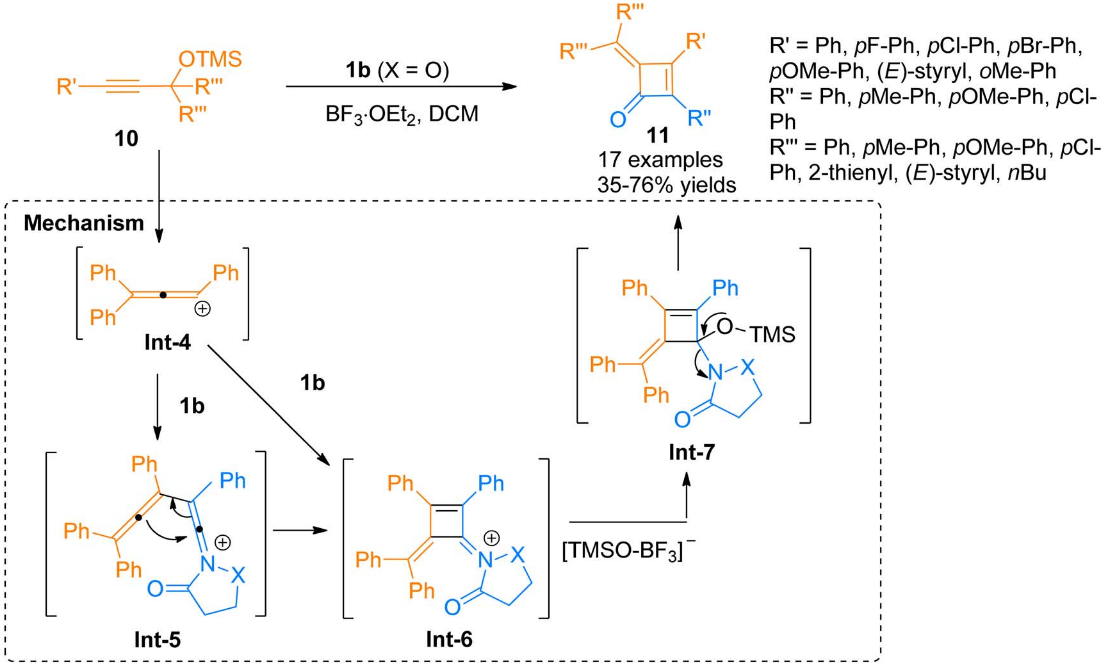
Cyclobutenone is an important class of synthetic intermediates owing to their high reactivity. The ring strain associated with high reactivity makes them suitable for a variety of imperative synthetic transformations. Strained cyclobutenones having unsaturation and a carbonyl group undergo facile carbon–carbon bond cleavage.[18] One of the most convenient approaches for synthesizing cyclobutenones is the [2 + 2]-cycloaddition reaction of ketene with alkynes. Hence, a novel protocol for benzannulation was developed by Bai *et al.* (2015), using readily available aromatic *t*Bu-ynol ethers **7** (as a precursor of aryl ketene intermediate **Int-3** *via* [1,5] H-shift), and the aryl ketene intermediate **Int-3** react with ynamides **1a**/**1b** to afford substituted cyclobutanone **8a**/**8b** as key intermediate *via* [2 + 2]-cycloaddition using dioxane at 60 °C. Further, cyclobutanone **8a**/**8b** underwent 4π electron electrocyclic cleavage/6 electron electrocyclic ring closure followed by a tautomerization process in dioxane solvent at 110 °C to yield 3-amino-1-naphthols **9a**/**9b** (21 examples, 53–96% yields and 1 example, 71% yield) (Scheme 3). The synthetic route supported a wide array of ynamides functionalized with different moieties but the imidazole tethered ynamide did not undergo reaction at all under the given conditions.[19]

Chen *et al.* (2016), developed a Lewis acid-catalyzed novel, and facile protocol for regioselective [2 + 2]-cycloaddition to afford polysubstituted cyclobutenones. The developed protocol used readily available ynamides **1b** and propargyl silyl ethers **10** as substrates to afford four-membered cyclic enones **16** in $BF_3 \cdot OEt_2$ catalyzed [2 + 2]-cycloaddition in dichloromethane solvent at room temperature. The reaction involved the reaction of *in situ* generated carbocation intermediate **Int-4** (from propargyl silyl ether **10**), with the ynamide **1b** to either access the intermediate **Int-6** *via* concerted [2 + 2] cycloaddition or afford keteniminium ion **Int-5** which further underwent 4π electron electrocyclization to yield highly unstable intermediate **Int-6**. In the next step, the addition of the $[TMSO\text{-}BF_3]^-$ and elimination of OTMS in subsequent steps yielded intermediate **Int-7** and product **11**, respectively. The synthesized alkylidene cyclobutenones **11** can further undergo valuable transformations by reacting with primary amines, water, and organometallic compounds such as organolithium compounds and Grignard reagents to yield structurally diverse products of significant importance *via* ring-opening and ring expansion reactions. However, the reaction was found with certain limitations as the styryl substituted ynamide afforded the product in lower yield (35%). Moreover, the reaction did not afford the title product when the R‴ group in propargyl silyl ether was methyl or hydrogen (Scheme 4).[20]

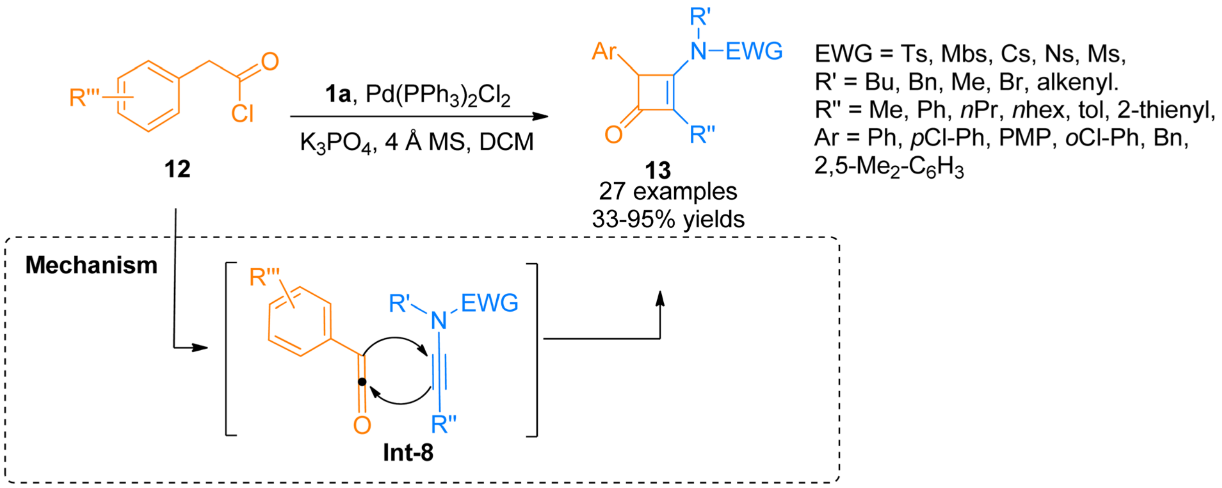
In 2018, Peng *et al.* used acyl chlorides in a palladium-catalyzed cyclization reaction taking ynamides as reaction partners to realize the synthesis of 3-aminocyclobutenones. Acyl chloride **12** generated monosubstituted ketenes *in situ via* dehydrohalogenation reaction. The *in situ* generated monosubstituted ketenes react with ynamides **1a** *via* a [2 + 2]-cycloaddition in a concerted step to yield 3-aminocyclobutenones **13** *via* intermediate **Int-8** (Scheme 5). The reaction was carried out in dichloromethane solvent by maintaining the temperature at 60 °C under a nitrogen atmosphere (27 examples, 33–95% yield range). The generated 3-aminocyclobutenones could be subsequently transformed *via* a pericyclic ring-opening/ring-closure reaction catalyzed by heat to



Scheme 3 Synthesis of 3-amino-1-naphthols **9a**/**9b** *via* cycloaddition and benzannulation of ynamide **1a**/**1b** and ynol-ethers **7**.



Scheme 4 Synthesis of cyclobutenones **11** *via* [2 + 2]-cycloaddition between ynamide **1b** and propargyl silyl ether **10**.

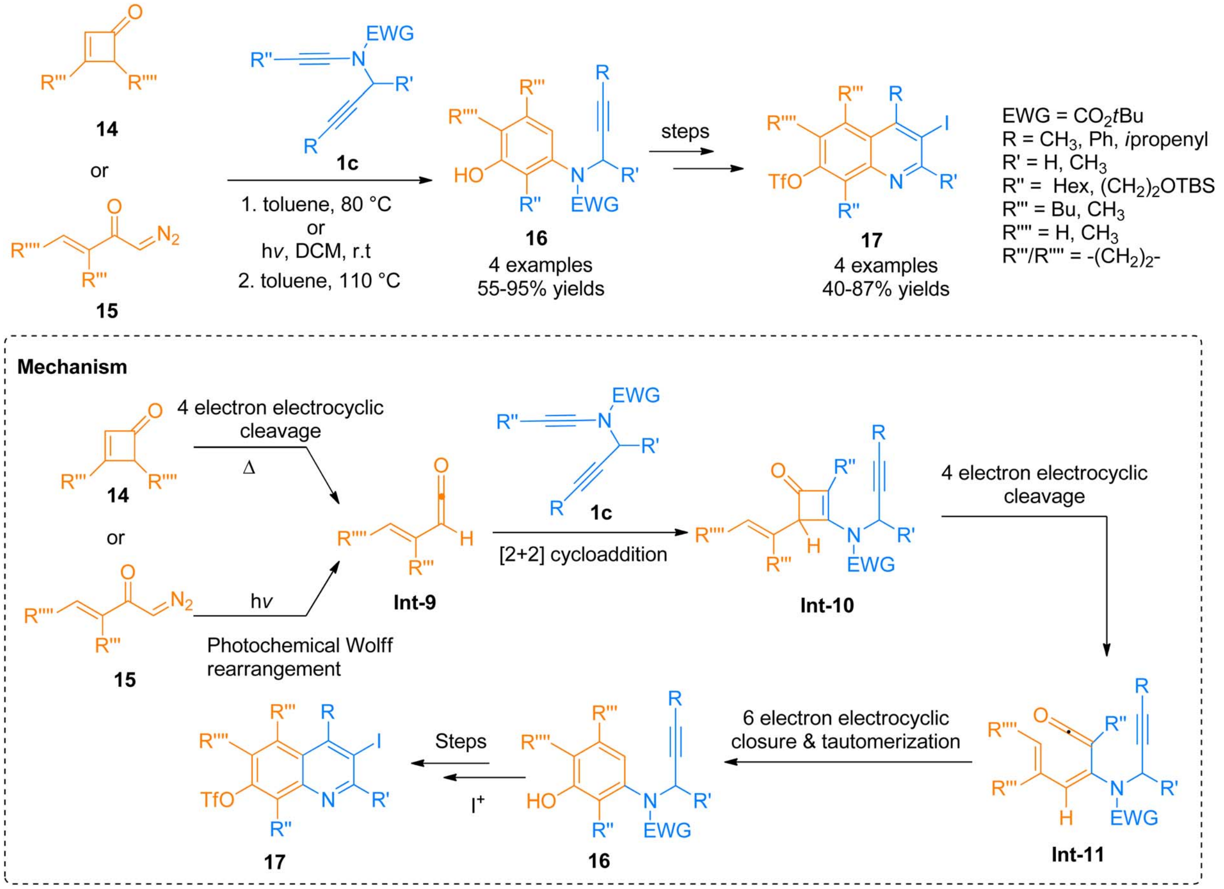


Scheme 5 Synthesis of cyclobutenones **13** *via* [2 + 2]-cycloaddition of ynamide **1a** and acyl chlorides **12**.

generate synthetically important scaffolds 3-amino-1-naphthols in promising yields.[21]

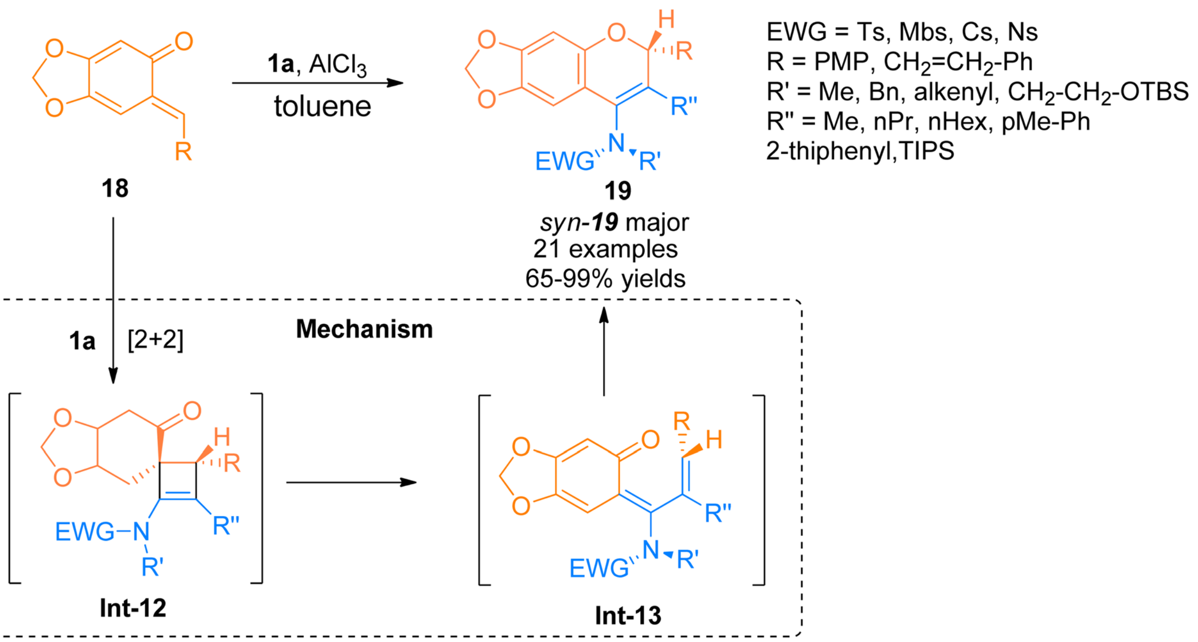
2.1.3. Synthesis of quinolines *via* [2 + 2]-cycloaddition. A tandem regiocontrolled benzannulation strategy for the construction of highly substituted quinolones **23** *via* a single-step reaction of *N*-propargyl functionalized ynamide **1c** and cyclobutenones **14**/diaoketones **15** was described by Willumstad *et al.* (2015). The benzannulation initiates with the thermolysis or irradiation of the cyclobutenone and the reaction proceeds *via* a cascade strategy involving four types of pericyclic transformations. Cascade reaction involved the 4π electron electrocyclic ring-opening reaction of cyclobutenone derivative **14** or photochemical Wolff rearrangement of α-diazo ketone derivative **15** to generate vinyl ketene intermediate **Int-9**, followed by [2 + 2]-cycloaddition to afford new cyclobutenone intermediate **Int-10**. Cyclobutanone intermediate **Int-10** readily underwent a reversible 4π electron electrocyclic ring-opening reaction to generate dienyl ketene intermediate **Int-11** that cyclize *via* 6π electron electrocyclic ring closure to form highly substituted aniline derivatives **16** in a regiocontrolled manner. The substituted aniline derivatives **16** (4 examples, 55–95% yields) with a suitable electrophile such as iodine underwent Larock cyclization to afford highly functionalized quinolones **17** (4 examples, 40–87% yields) (Scheme 6).[22]

2.1.4. Synthesis of 4-amino-2*H* chromenes *via* [2 + 2]-cycloaddition. For the construction of these amino substituted



Scheme 6 Synthesis of substituted quinolones **17** *via* [2 + 2]-cycloaddition of ynamide **1c** with cyclobutenones **14** or diaoketones **15**.

chromene scaffolds, only a few studies have been reported taking ynamides as starting materials. In this respect, Yang *et al.* (2016) reported the facile route for the annulation reaction of terminally substituted ynamide **1a** with *o*-quinone methides **18** with excellent control over central as well as axial chirality. The reaction sequence followed the $AlCl_3$ promoted [2 + 2]-



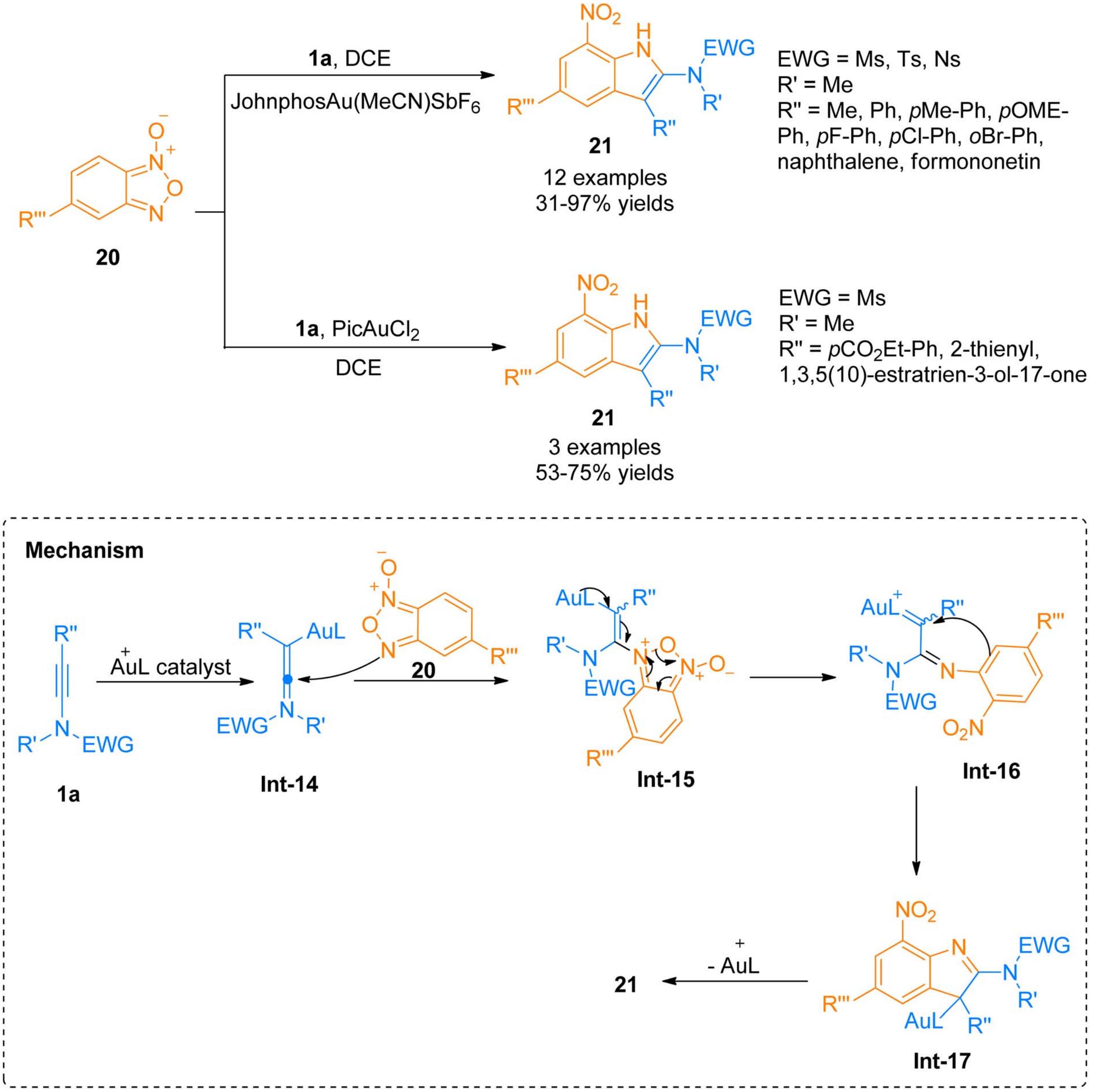
Scheme 7 Synthesis of 4-amino-2*H*-chromenes **19** *via* [2 + 2]-cycloaddition of ynamide **1a** and *o*-quinone methides **18**.

cycloaddition reaction to yield spiro cyclic intermediate **Int-12**, which underwent 4π electron electrocyclic torquoselective ring-opening reaction to yield **Int-13**. Further, the 6π-electrocyclic ring closure of **Int-13** afforded the diastereomeric 4-amino-2*H*-chromenes **19** (21 examples, 65–99% yield range) with high stereoselectivity in toluene solvent at −40 °C (Scheme 7). Terminal substitution at ynamides plays a significant role in determining the [2 + 2]-cycloaddition or [4 + 2]-cycloaddition pathway for the construction of 4-amino-2*H* chromenes and 2-amino-4*H*-chromenes, respectively. The terminally substituted ynamides selectively underwent [2 + 2] cycloaddition while terminally unsubstituted ynamides underwent [4 + 2] cycloaddition. The reaction provided a facile route to construct non-biaryl atropimers which can be further transformed into novel atropisomers.[23]

2.2. [3 + 2]-cycloaddition

2.2.1. Synthesis of indole derivatives *via* [3 + 2]-cycloaddition

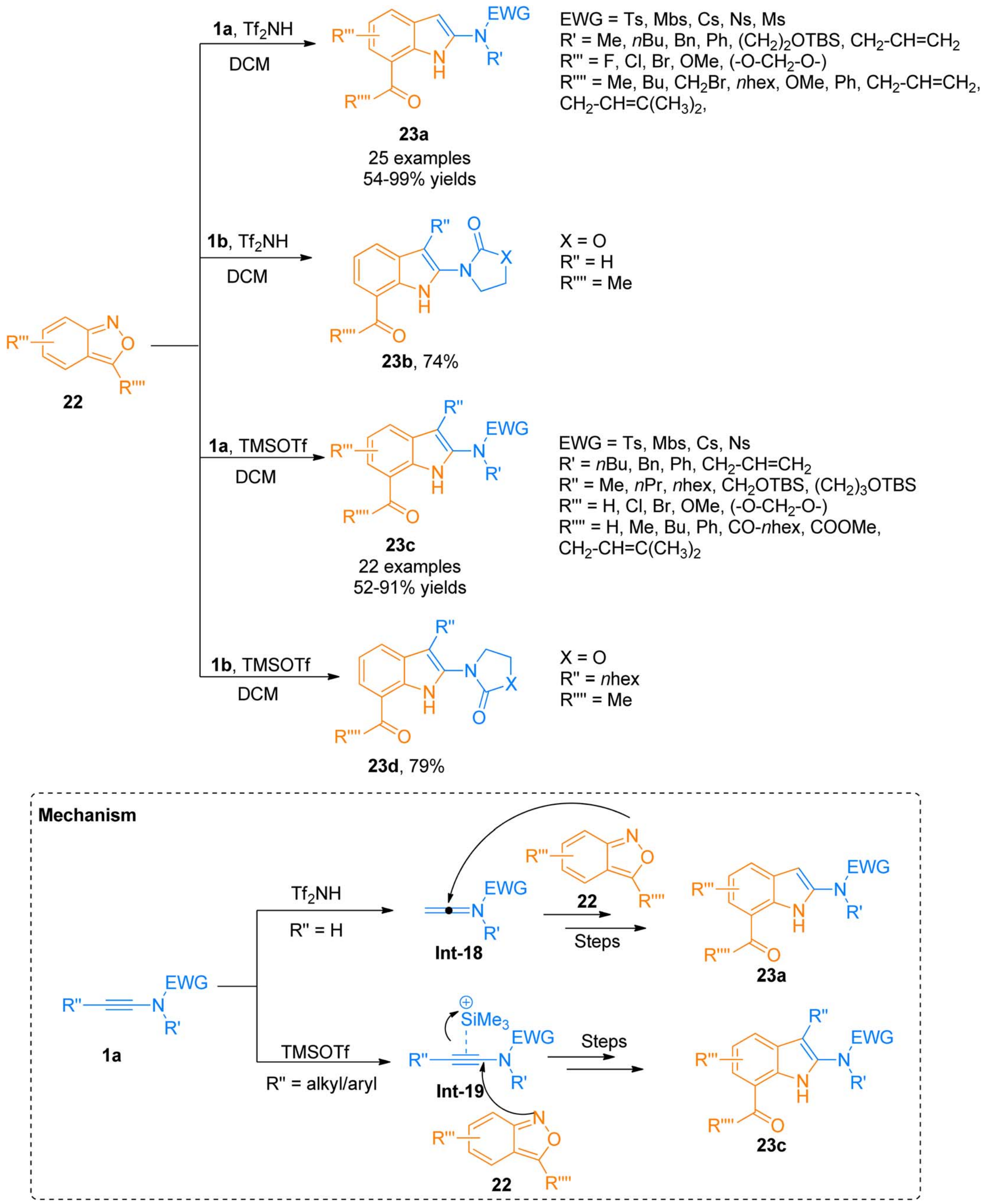
2.2.1.1. Synthesis of 2-aminoindoles. Among the N-heterocycles, synthesis of 7-nitroindoles has been previously reported by limited synthetic routes that have serious drawbacks such as harsh reaction conditions and narrow substrate scope. Moreover, the achievement of higher regioselectivity is one of the major challenges.[24–26] In 2019, Xu *et al.* the gold(I) complex as catalyst was found to be an efficient catalyst to afford α-imino-Au-carbene intermediate taking benzofuran *N*-oxide **20** as a precursor which further undergoes [3 + 2]-cycloaddition with ynamide **1a** to achieve functionalized 7-nitroindoles **21** as reported by Xu *et al.* The optimized parameters involved the



Scheme 8 Synthesis of 7-nitroindoles **21** *via* [3 + 2]-cycloaddition of ynamides **1a** with benzofuran *N*-oxide **20**.

use of (acetonitrile)[(2-biphenyl)di-*tert*-butylphosphine]gold(I) hexafluoroantimonate (Johnphos Au(MeCN)SbF$_6$) catalyst (5 mol%), dichloroethane, and 25 °C temperature. The proposed reaction mechanism (based on the controlled reactions) involves the formation of ynamide derived advanced intermediate, keteniminium ion **Int-14** that reacts with the *N*-oxide **20** to afford **Int-15**. **Int-15** transforms to α-imino-gold-carbene intermediate **Int-16** *via* ring fragmentation reaction. Nucleophilic attack of the phenyl ring on gold carbene **Int-16** furnished **Int-17**. It was followed by subsequent aromatization and denaturation of **Int-17** which provided access to 7-nitroindole **21**. This reaction with moderate substrate scope afforded required substituted 7-nitroindoles **21** (12 examples, 31–97%) (Scheme 8). However, some of the ynamides *i.e.* heteroaryl substituted ynamide, under standard conditions, afforded several side products, but catalyst switching to PicAuCl$_2$ (5 mol%) obtained the products in promising yields (3 examples, 53–75% yields).[27]

Although many powerful synthetic routes to realize the synthesis of indole structural motifs have been developed, approaches for the efficient synthesis of 2-aminoindoles are limited. Zhang *et al.* (2021), recently developed a metal-free protocol for [3 + 2]-cycloaddition of the ynamide **1a**/**1b** with anthranils **22** that provided a flexible and facile route for the

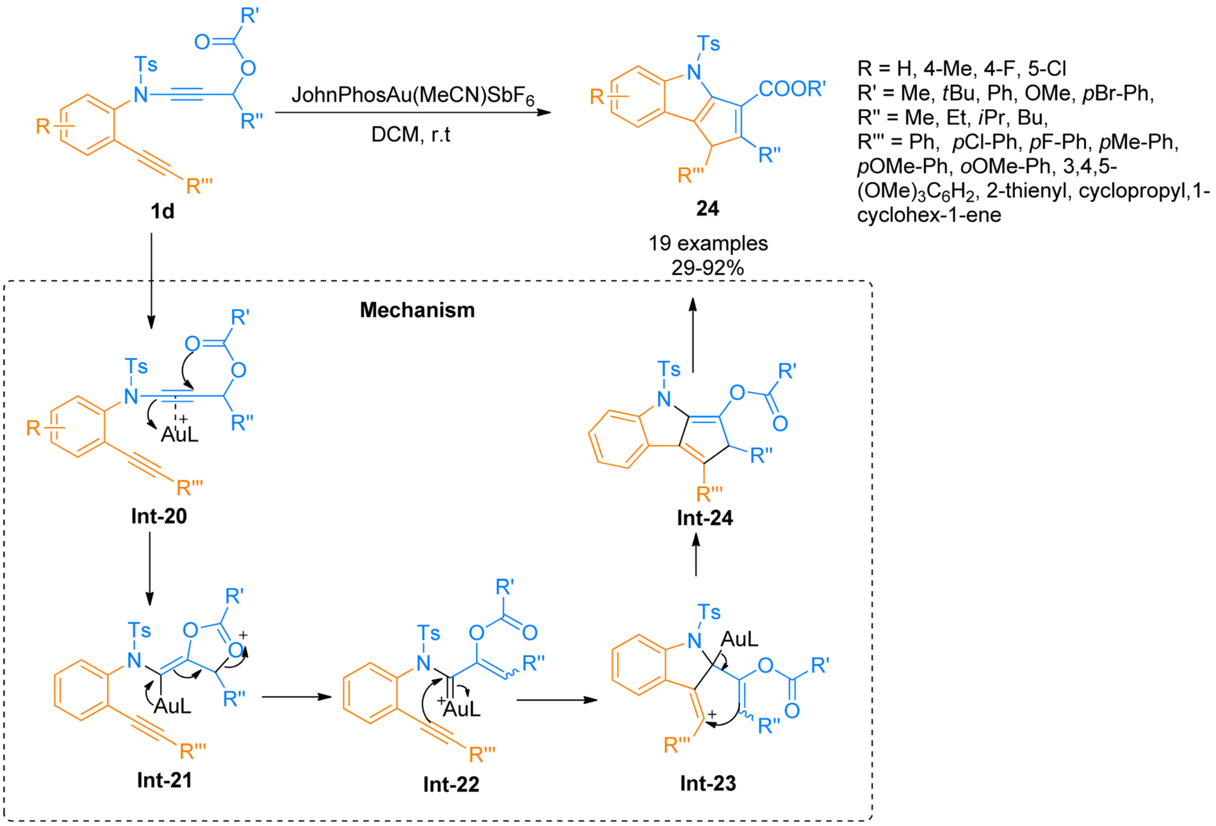


Scheme 9 Synthesis of 2-aminoindoles **23a–d** *via* [3 + 2]-cycloaddition of ynamide **1a,b** with anthranils **22**.

synthesis of functionalized 2-aminoindoles **23a–d** (Scheme 9). The terminally unsubstituted ynamides **1a**/**1b** underwent this transformation using Tf_2NH (0.5 equiv.) in dichloromethane as solvent at room temperature to afford **23a** (25 examples, 54–99% yields)/**23b** (1 example, 74% yield). While terminally substituted ynamide **1a**/**1b** afforded the products **23c** (23 examples, 52–91% yields)/**23d** (1 example, 79% yield) *via* TMSOTf (0.5 equiv.) catalyzed cycloaddition reaction using dichloromethane. The reaction afforded the products in excellent regioselectivity under mild conditions (temperature −20 to −50 °C). According to the postulated mechanism, the reaction initiates with the electrophilic addition of a proton to the ynamide **1a** that generates keteniminium ion intermediate **Int-18**, while in the case of terminally substituted ynamide, the silicon π-alkyne species **Int-19** generates as a result of coordination of TMSOTf catalyst with ynamide alkyne core. Further, in the next step anthranil **22** traps both intermediates which are followed by the same reaction sequence of ring fragmentation, aromatization, and hydride shift to afford their respective final products. The metal-free protocol for annulation provides an efficient route for the interesting synthesis of 2-aminoindoles **23a**/**23c**, which are building blocks for the construction of diverse 2-aminoindolyl frameworks (Scheme 9).[28]

2.2.1.2. Synthesis of cyclopenta[b]indoles. Gold catalyzed 1,2-acyloxy migration reaction in internal alkynes has been reported rarely. Liu *et al.* (2014), developed the cycloisomerization of 1,6-diynes tethered ynamide having propargyl ester/carbonate core **1d** using the gold catalyst. The novel protocol afforded the construction of highly functionalized cyclopenta[*b*]indoles **24** using dichloromethane solvent at room temperature. The optimized conditions to realize the transformations involved the use of gold(I) complex (JohnPhos Au(MeCN)SbF_6) catalyst (5 mol%) and 4 Å MS. The proposed reaction sequence involves the selective activation of the alkyne core ynamide by catalyst that yields **Int-20**. The reaction proceeds by *in situ* generation of the vinyl gold-carbenoid intermediate **Int-22** *via* cyclization of **Int-20** followed by 1,2-acyloxy migration of the **Int-21** in sequence. Further, subsequent nucleophilic attack (**Int-22** to **Int-23**) and elimination of the gold catalyst (**Int-23** to **Int-24**) and 1,5-H shift (**Int-24** to **24**) delivered the respective product. This methodology offered a preferable and efficient alternative to multistep deprotection and double-bond isomerization reaction (19 examples, 29–92% yields). However, the ynamides bearing butyl and phenyl substituents at R″ and R‴ did not afford target products instead they yielded alkene (Scheme 10).[29]

2.2.2. Synthesis of pyrroles *via* [3 + 2]-cycloaddition. The conventional multistep methods such as Paal Knorr synthesis and Hantzch reaction for the construction of pyrrole rings have various drawbacks such as poor step economy, low yields, and limited functional group compatibility. In this regard, the cycloaddition reactions of the ynamides and advanced intermediates derived from ynamides are preferable alternatives for the construction of functionalized pyrrole scaffolds.[30–33]

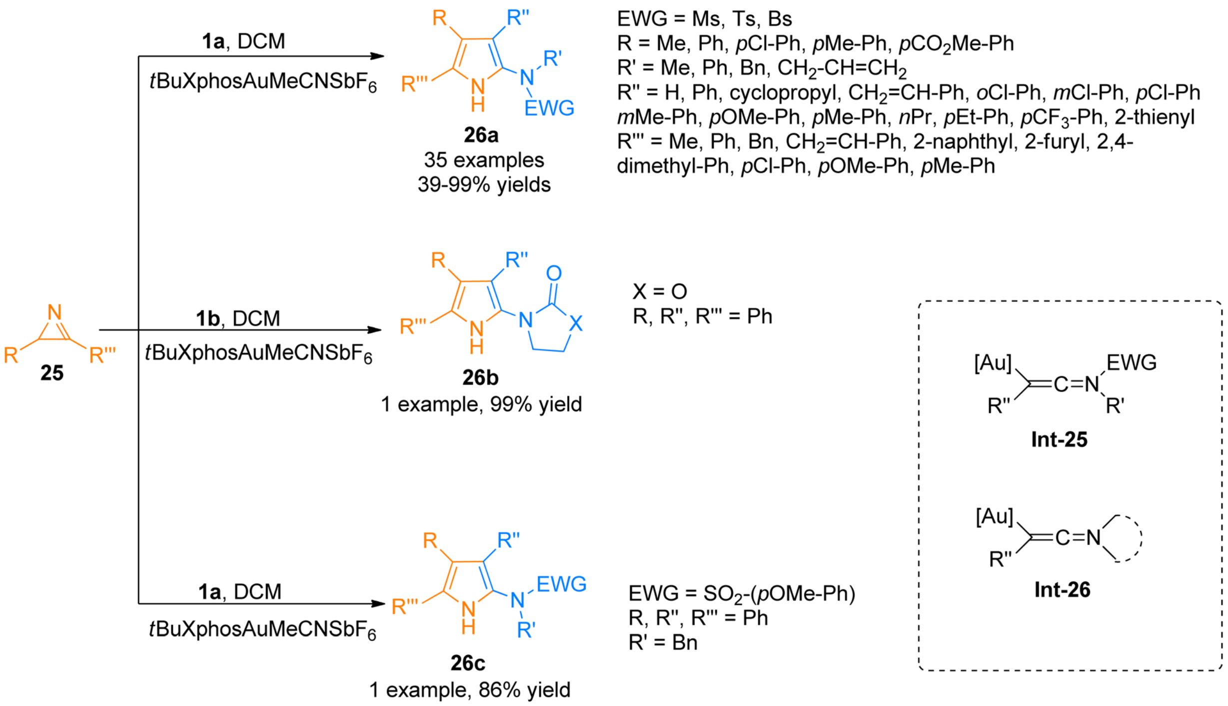


Scheme 10 Synthesis of cyclopenta[*b*]indoles **24** *via* intramolecular [3 + 2]-cycloaddition of ynamide **1d**.

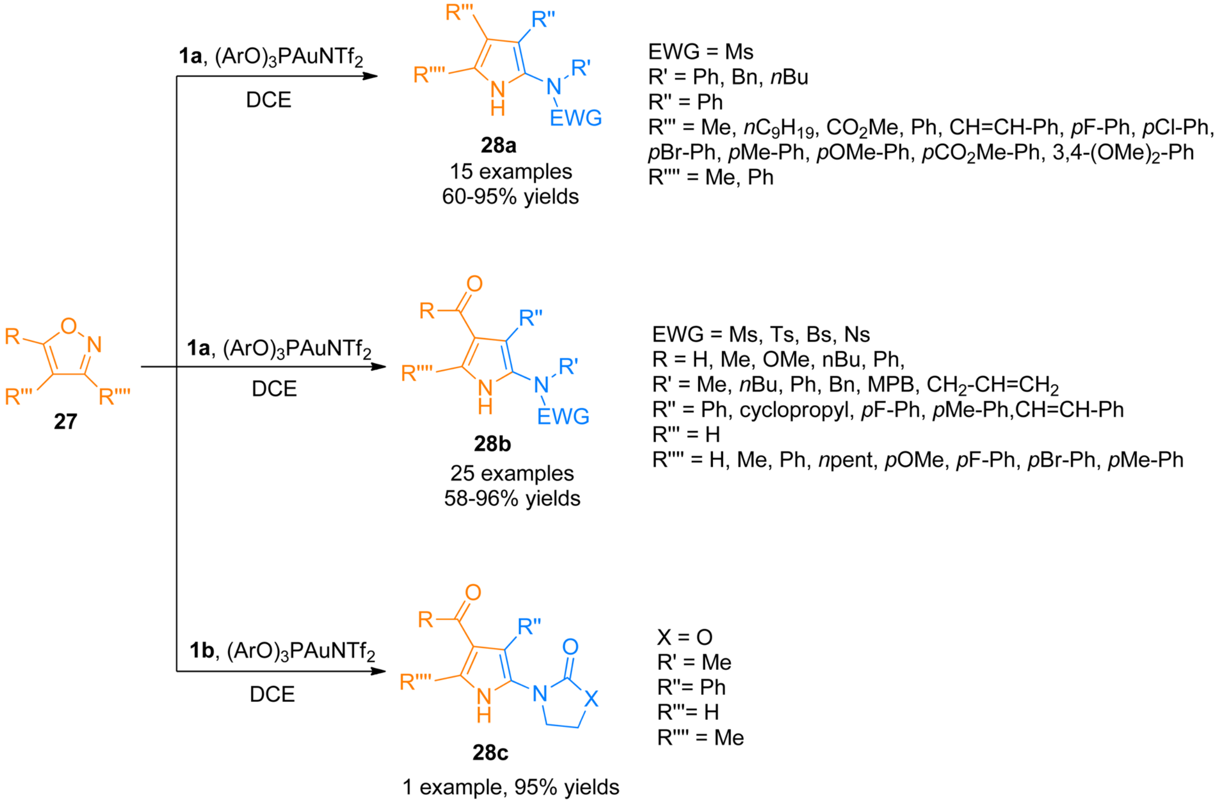
2.2.2.1. Synthesis of polysubstituted pyrroles. Pyrroles are considered versatile building blocks and are used as precursors for the construction of pyrrolepyrimidine, pyrrolotriazine, and pyrrolopyridine analogs in organic synthesis.[34,35] Zhu *et al.* (2015), developed an efficient method of [3 + 2]-cycloaddition reaction of ynamides **1a** with 2*H*-azirines **25** that involved intermolecular nitrene transfer using the gold catalyst for the synthesis of highly substituted pyrroles **26a** (35 examples, 39–99% yields). The ynamide containing cyclic electron withdrawing group **1b** and substituted sulfonyl group **1a** reacted with 2*H*-azirines **25** to afford **26b** (99% yield) and **26c** (86% yield). The reaction provides a facile route through which the ynamides **1a**/**1b** activation by gold catalyst yield keteniminium intermediate **Int-25**/**Int-26** which is highly electrophilic and reacts with **32** to realize the transformation into respective products **26a–c** (Scheme 11). The reaction was realized using mild reaction conditions, and low catalyst loading. It afforded a broad range of polysubstituted pyrroles **26a–c** with higher atom economy. However, the ynamide bearing Ns electron withdrawing group was not found compatible with the said cycloaddition reaction.[36]

Moreover, the generation of the gold-carbene intermediate in the gold catalyzed intermolecular reaction of alkynes and nucleophiles has been of considerable interest but the developed protocols have the disadvantage of low atom economy.[37–40] Zhou *et al.* (2015), developed the atom economical approach to construct highly functionalized 2-aminopyrroles **28a–c** by formal [3 + 2]-cycloaddition reaction of ynamides **1a**/**1b** with isoxazoles **27** using a gold(I) catalyst (Scheme 12). The reaction proceeded by the generation of α-amino-gold-carbene intermediate providing a novel and atom-economical route to access gold carbene intermediates using $(ArO)_3PAuNTf_2$ (5 mol%) (Ar = 2,4-di-*tert*-butylphenyl) catalyst, dichloroethane solvent at 80 °C. The developed protocol can introduce up to four substituents to the pyrrole ring **28a** (15 examples, 60–95% yields), **28b** (25 examples, 58–96% yields), **28c** (1 example, 95% yields).[41]

2.2.2.2. Synthesis of pyrrole-fused bridged [2.2.1] skeletons. The generation of metal ylides from metal carbenes is one of the significant advancements in homogenous transition metal catalyzed 1,3-dipolar cycloadditions. However, the substrate scope of this transformation is limited to triazole or diazo compounds.[42,43] Hong *et al.* (2020), demonstrated a novel one-step transformation of alkenyl *N*-propargyl tethered ynamides and alkenes *via* [3 + 2]-cycloaddition reaction catalyzed by the copper catalyst to form pyrrole-fused bridged [2.2.1] products. The reaction was proceeded by the addition of $Cu(CH_3CN)_4PF_6$ catalyst (10 mol%), ligand **L1** (12 mol%), sodium tetrakis-[3,5-bis(trifluoromethyl)phenyl]borate (12 mol%) and dichloroethane at the temperature of 35 °C. The proposed reaction mechanism follows a novel route of 1,3 dipole generation *via* copper-carbene intermediate **Int-27** formation from ynamide **1e** which further transforms into 1,3-dipole intermediate **Int-38**. The 1,3-dipole intermediate **Int-28** undergoes formal [3 + 2] cycloaddition with the alkene reaction partner **29** in the last step. Bridged N-heterocycles **30** having up to three stereocenters were synthesized in a single step using mild reaction conditions with excellent stereospecificity from acyclic structural motifs having no stereocenters. The developed protocol achieved a range of chiral bridged N-heterocycles (45 examples, 52–90% yield up to 99% ee). Bridged N-heterocycles substituted with complex styrene derivatives such as ibuprofen, naproxen,



Scheme 11 Synthesis of polysubstituted pyrroles **26a–c** *via* [3 + 2]-cycloaddition of ynamides **1a**/**1b** with 2*H*-azirines **25**.



Scheme 12 Synthesis of polysubstituted 2-aminopyrroles **28a–c** *via* [3 + 2]-cycloaddition of ynamides **1a**/**1b** with isoxazoles **27**.

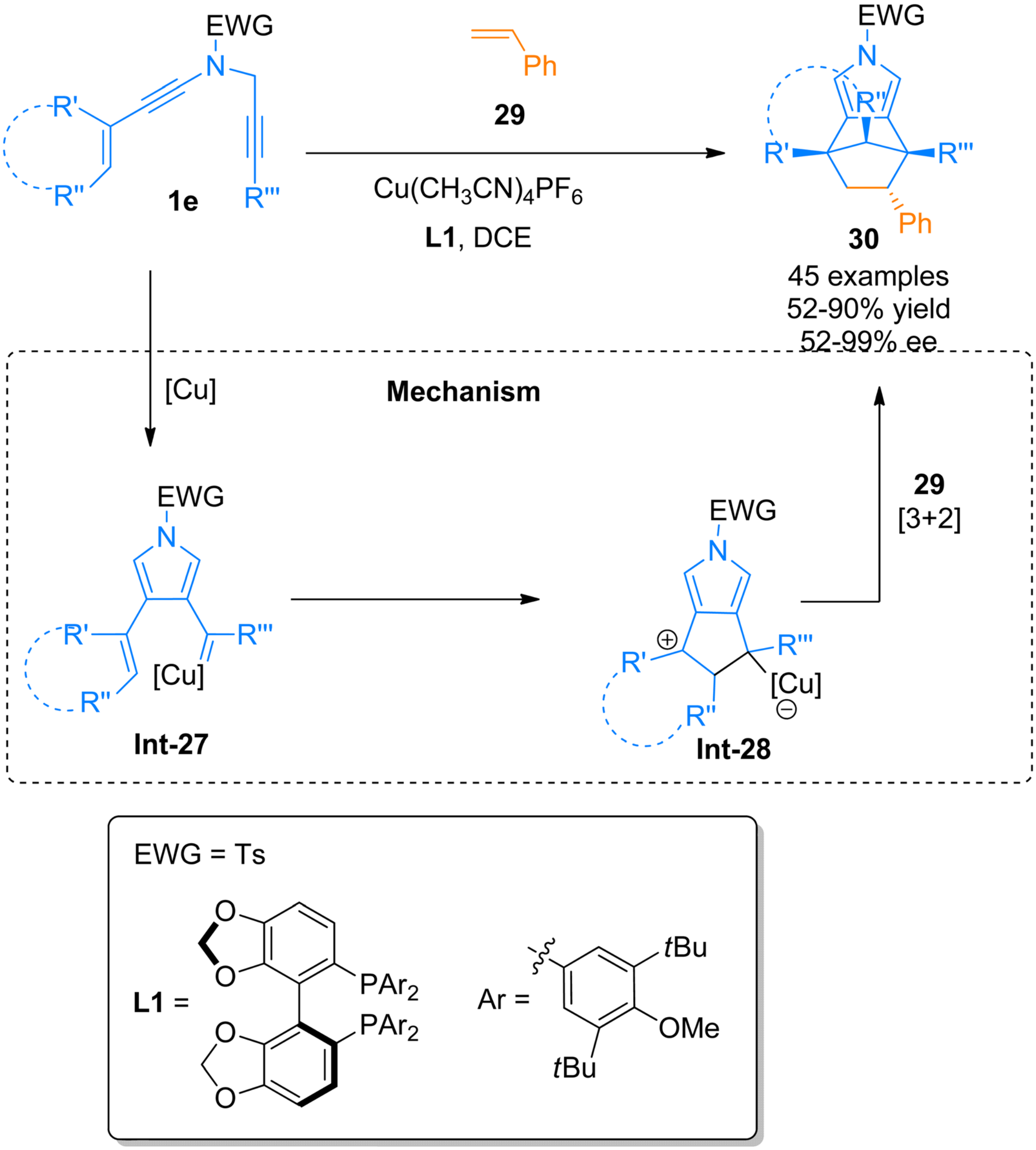
menthol, and indomethacin were also accessed with promising diastereoselectivities (dr > 50/1) and enantioselectivities (>99%) in good to excellent yield range (Scheme 13).[44]

2.2.3. Synthesis of triazoles *via* [3 + 2]-cycloaddition. Ferrini *et al.* (2015), devised a protocol for [3 + 2]-cycloaddition reaction of ynamides **1a** and azides **31a** using ruthenium metal catalyst to yield protected triazoles **32a** containing amino acid in a regio-controlled manner (Scheme 14).[45] Further the work on Rhodium catalyzed azide–alkyne 1,3-dipolar cycloaddition was extended and modified by Liao *et al.* (2017).[46] The reaction afforded functionalized 5-aminotriazoles *via* regioselective 1,3-dipolar cycloaddition reaction of ynamide and azides in acetonitrile solvent at room temperature or 100 °C in an open flask. The transformation also involves the $[Rh(CO_2)Cl]_2$ catalyzed cycloaddition of internal ynamides that yielded aminotriazoles in excellent yield and regioselectivity. The developed methodology expanded the substrate scope of the methodology reported by Ferrini *et al.* (2015)[45] by employing a range of substituted azides with diversely functionalized ynamides bearing Ms, Ts, and Bs electron withdrawing groups (31 examples, 17–98% yield range).[46]

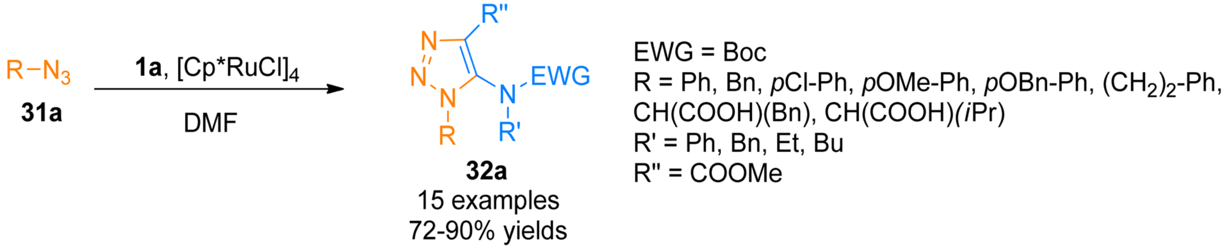
Similarly, Song and Zheng, (2017), developed an iridium-catalyzed regioselective route to access functionalized 5-amido-1,2,3-triazoles **32b–c** *via* [3 + 2]-cycloaddition of azide **31b** and ynamide **1a**/**1b** by addition of $[Ir(cod)Cl]_2$ catalysts in dichloromethane or water as a solvent in open air flask at room temperature. The methodology achieved excellent regioselectivity (1 : 0) *via* iridium-ynamide coordination complex that reverses the regioselectivities of Cu-catalyzed azide–alkyne cycloaddition while enhancing the regioselectivities of Ru-catalyzed azide–alkyne cycloaddition. The advantages of the developed methodology involve low catalyst toxicity, room temperature, insensitivity to oxygen and water, compatibility with organic, aqueous as well as biological reaction environments, and higher yields (14 examples, 70–96% yield range) (Scheme 15).[47]

2.2.4. Synthesis of imidazole-fused oxo-substituted frameworks *via* [3 + 2]-cycloaddition

2.2.4.1. Synthesis of heteroaromatic ring-fused 4-amino-imidazoles. Oxo-substituted imidazole frameworks are attractive targets owing to their vital importance in medicinal and agrochemical industries.[48–50] Arce, *et al.* (2020), developed a method to access oxo-substituted heteroaromatic-fused 4-amino-imidazoles **34** by the cycloaddition of nucleophilic nitrenoid **33** with sulfenyl substituted ynamides **1f.** This protocol offered a proficient and regioselective synthetic route to access geminally substituted amino sulfenyl containing N-heterocycles by the addition of $PicAuCl_2$ (5 mol%) catalyst in 1,4-dioxane at 90 °C, or 1,2-dichlorobenzene at 125 °C (23 examples, 34 to quantitative yields) (Scheme 16). The mechanism of the synthetic route starts with the gold-coordinated ynamide **Int-29** derived through the coordination of gold catalyst with the alkyne core of ynamide. **Int-29** converts to keteneiminium ion intermediate **Int-30**. The nitrenoid specie **33** reacts with **Int-30** and afforded the final product **34** *via* cyclization and elimination of gold catalyst from **Int-31** and **Int-32**, respectively. This transformation could also afford highly hetero-substituted heterocycles which can be



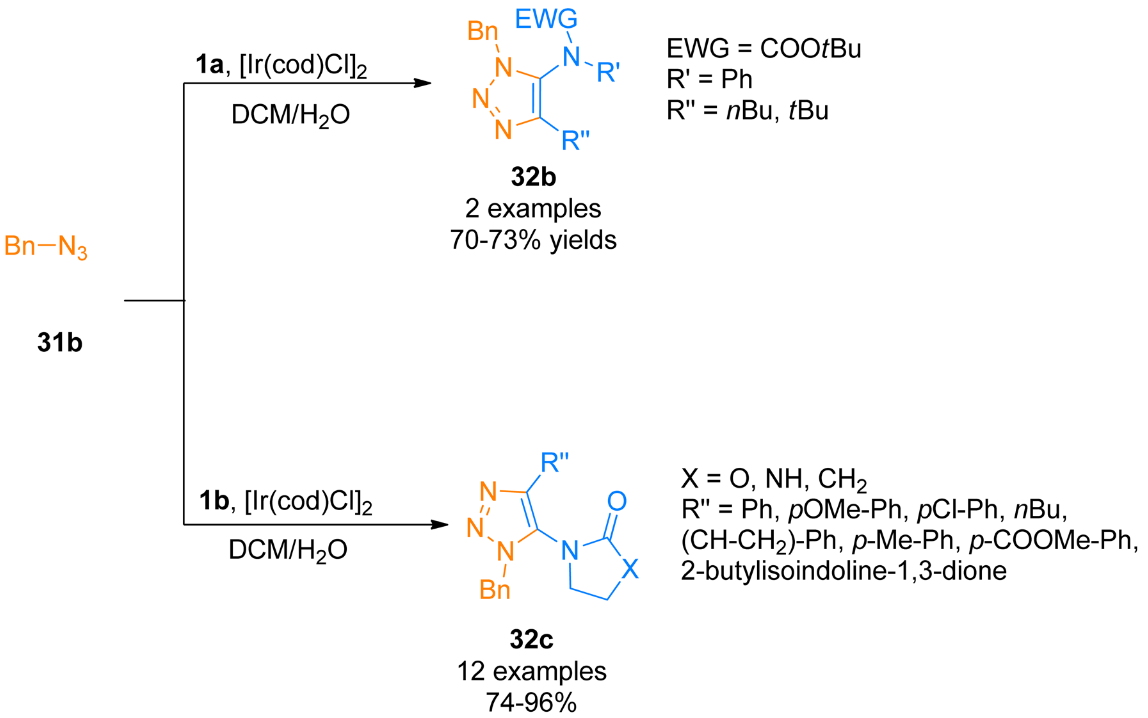
Scheme 13 Synthesis of pyrrole-fused scaffolds **30** *via* [3 + 2]-cycloaddition of ynamides **1e** and alkenes **29**.



Scheme 14 Synthesis of 1,2,3-triazoles **32a** *via* [3 + 2]-cycloaddition of ynamides **1a** with azide **31a**.

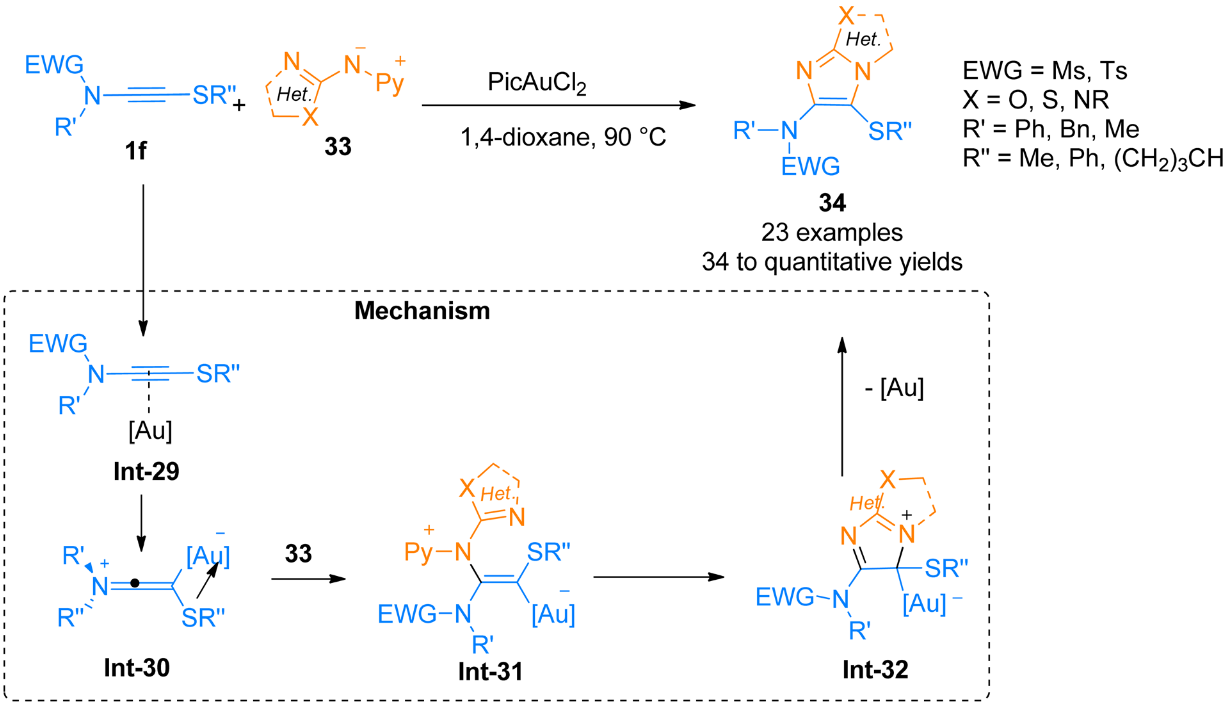
transformed into desirable compounds such as heteroarylsulfoxide and heteroarylsulfone.[49]

2.2.4.2. Synthesis of substituted 4-aminoimidazoles. For the construction of substituted 4-aminoimidazoles, Zhao *et al.* (2017), employed a Tf_2NH catalyst for the [3 + 2]-cycloaddition of ynamides and oxadiazolones. The formal metal-free, Tf_2NH (15 mol%) catalyzed, [3 + 2]-cycloaddition offered the facile route to access the aminoimidazoles, with a wide substrate

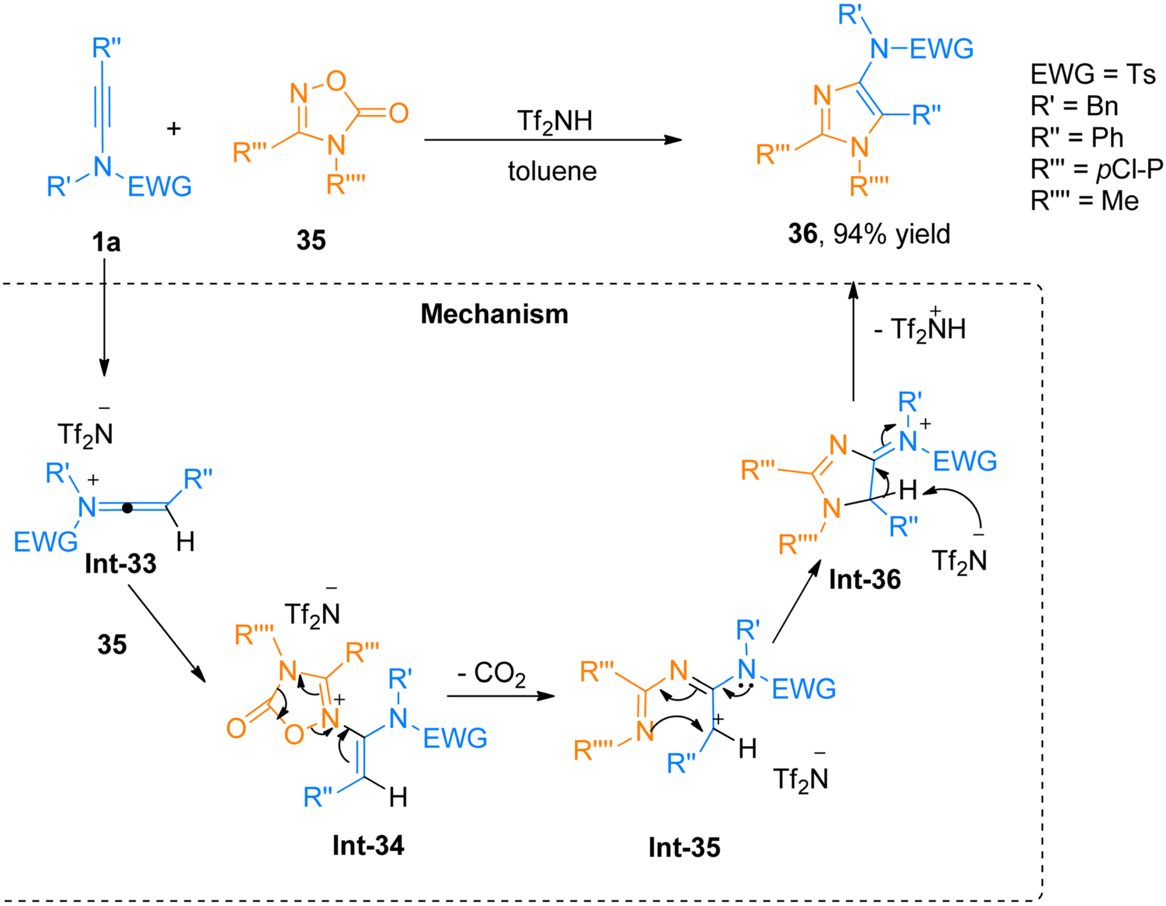


Scheme 15 Synthesis of 1,2,3-triazoles **32b**/**32c** *via* [3 + 2]-cycloaddition of ynamides **1a**/**1b** with azide **31b**.

scope in toluene solvent at 90 °C. Moreover, the *N*-methylated products could be easily converted into *N*–*H*-aminoimidazoles. The highly efficient metal-free synthesis and excellent yields for steric and highly substituted substrates (25 examples, 42–94% yields). However, the ynamide with cyclic electron with drawing group and the ynamide bearing TIPS group at R$''$ did not furnish the target product. With optimized conditions, product **36** was synthesized *via* cycloaddition reaction between ynamide **1a** and oxadiazolone **35** in 94% yield. The proposed reaction mechanism involves the protonation of the ynamide by the Tf_2NH



Scheme 16 Synthesis of *o*–*o*′-heteroatom-linked imidazole derivative **34** *via* [3 + 2]-cycloaddition of ynamide **1f** and nitrenoid **33**.



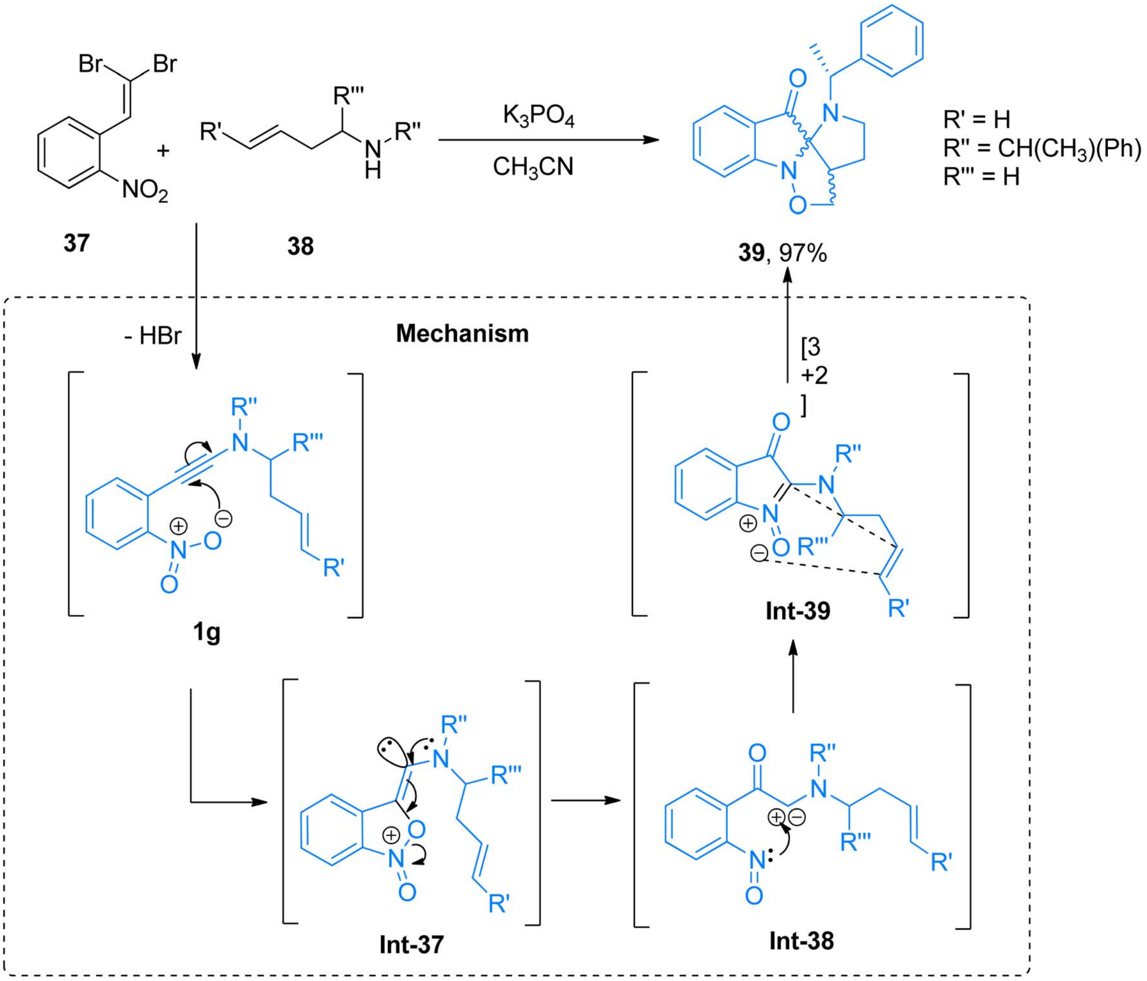
Scheme 17 Synthesis of 5-aminoimidazoles **36** *via* [3 + 2]-cycloaddition of ynamides **1a** and oxadiazolones **35**.

catalyst leading to the formation of keteniminium ion intermediate **Int-33** which further reacts with **35** to generate **Int-34**. **Int-34** undergoes ring fragmentation and elimination of CO_2 (**Int-35**), followed by a cyclization process to yield iminium ion intermediate **Int-36.** In the last step, Tf_2N^- quenches the H and yields the imidazole derivative as the final product (Scheme 17).[51]

2.2.5. Synthesis of spiropseudoindoxyls *via* [3 + 2]-cycloaddition. Marien *et al.* (2018), described a domino reaction to afford polycyclic spiropseudoindoxyls in a metal-free, one-pot multicomponent reaction of 1-dibromovinyl-2-nitro-substituted arene and 2° amines. The reaction was afforded by the addition of K_3PO_4 in acetonitrile solvent at a reaction temperature of 70 °C. The reaction mechanism was predicted based on the control experiments and theoretical calculations based on topological analysis tools.[52] The scaffold with the fused ring was achieved by the generation of *ortho*-nitroarylated ynamine/ynamide intermediate **1g** (generated *in situ*) which further underwent cycloisomerization (involving the generation of **Int-37** to **Int-39**) to yield *N*-alkenyl-tethered 2-aminoisatogens *via* a route that is different than standard electron pair donation. The developed methodology afforded spiro-compounds in poor to excellent yield range (28 examples, 11–97% yields). Spiropseudoindoxyl obtained through this methodology are novel scaffolds that find their practical applications in medicinal chemistry. A highlighted example of this methodology is presented in Scheme 18. The compound **39** was afforded in 97% yield *via* cycloaddition of the ynamide **1g** generated *in situ* by the reaction of arene **37** and secondary amine **38.**[52]

2.2.6. Synthesis of oxazole derivatives *via* [3 + 2]-cycloaddition. Classical methods for the construction of oxazoles involve the ring derivatization or cyclization of acyclic precursors. But recent developments in organometallic reagents catalyzed and transition metal-catalyzed bimolecular cycloaddition reactions offer alternative approaches to furnish oxazole derivatives using mild reaction conditions.[53,54]

2.2.6.1. Synthesis of 4-aminooxazoles. Chen *et al.* (2016), developed a facile route for the construction of highly substituted oxazole based scaffolds *via* regioselective [3 + 2]-cycloaddition reaction between 1,4,2-dioxazoles and ynamides using a gold catalyst. In the reaction mechanism, the **Int-40** reacts with 1,4,2-dioxazole that acts as *N*-acyl nitrene species, to generated iminium ion intermediate **Int-41.** Further **Int-41** *via* the ring opening converters to α-imino-gold-carbene intermediate **Int-42** by elimination of ketone using $IPrAuNTf_2$ catalyst (5 mol%), in dichloroethane at room temperature or 80 °C. The α-imino-gold-carbene **Int-42** further undergoes subsequent steps of cyclization and elimination of gold catalyst to afford the



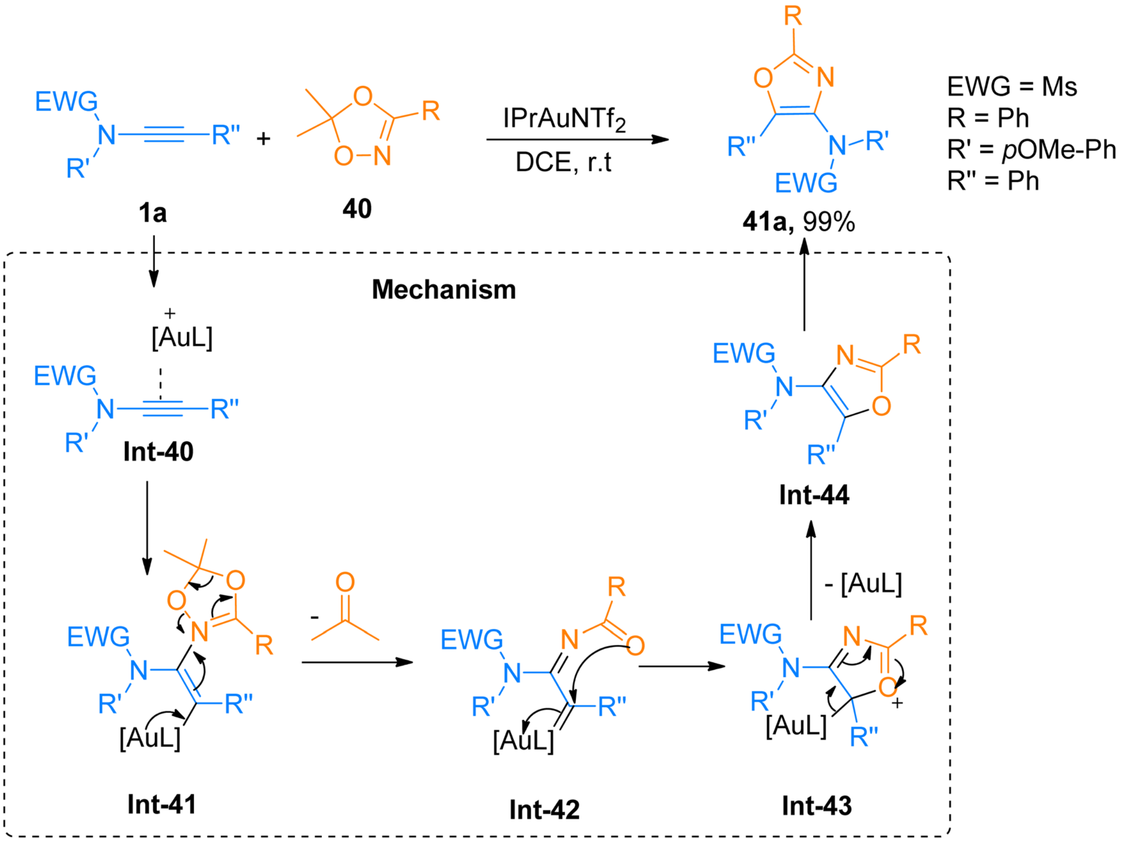
Scheme 18 Synthesis of spiropseudoindoxyls **39** *via* intramolecular [3 + 2]-cycloaddition of ynamide intermediate **1g**.

title product *via* the formation of **Int-43** and **Int-44**, respectively. The product **41a** was accessed in 99% yield *via* cycloaddition of **1a** and 1,4,2-dioxazole **40** and the reaction was carried out using IPrAuNTf$_2$ catalyst (5 mol%) and dichloroethane (Scheme 19). The selectivity of the cycloaddition reaction provided the access to functional oxazoles with biologically active chiral centers (36 examples, 30–99% yields).[55]

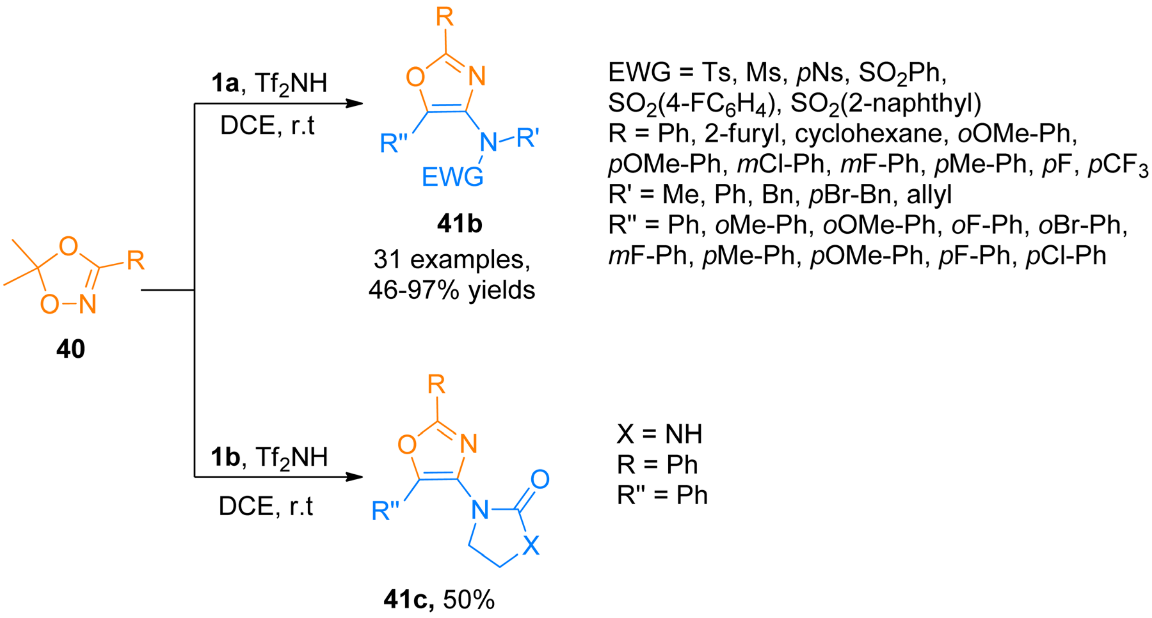
Similarly, Zhao *et al.* (2017), accessed 4-aminooxazoles **41b** *via* Tf$_2$NH-catalyzed, [3 + 2]-cycloaddition reaction of various ynamides **1a** and dioxazoles **40** using dichloroethane solvent at room temperature. Along with the ynamide bearing aliphatic electron withdrawing group, ynamides **1b** was also employed in the developed methodology, which underwent a cycloaddition reaction with dioxazoles **40** to afford **41c** in 50% yield (Scheme 20). The predicted reaction mechanism suggested the role of the catalyst in the stabilization of the keteniminium ion and further, it facilitates the elimination of the H in the last step, in the same manner as depicted previously in Scheme 19. This protocol offers a metal-free approach under mild reaction conditions to carry out the transformation in short reaction times. The developed methodology offered the advantages of low cost and readily available catalyst, highly efficient transformation, and broad substrate scope to afford 4-aminooxazoles (32 examples, 46–97% yields). This metal-free approach suggests the potential application of the metal-free methodology for the synthesis of pharmaceutically important scaffolds.[56]

2.2.7. Synthesis of cyclopentenes *via* [3 + 2]-cycloaddition. Mackay *et al.* (2014), described the [3 + 2] cyclization of ynamides **1a** and cyclopropanes **42** to attain corresponding cyclopentene sulfonamides **43** in excellent yields. Subsequent deprotection and hydrolysis of cyclopentene sulfonamides furnished 2,3-substituted cyclopentanones with high diastereoselectivities. Ynamides **1a** underwent cycloaddition with cyclopropanes **42** by adding Sc(OTf)$_3$ catalyst (10 mol%) and dichloromethane solvent at room temperature (Scheme 21). In this scandium-catalyzed annulation, cyclopropanes **42** acts as a donor while ynamides **1a** as an acceptor. The developed synthetic route afforded the products with high diastereoselectivities in a moderate to quantitative yield range (15 examples, 46 to >99% yields).[57]

2.2.8. Synthesis of cyclopentadienes and cyclopentenones *via* [3 + 2]-cycloaddition. Cheng *et al.* (2017), investigated the gold-catalyzed intermolecular cycloisomerization of ynamides

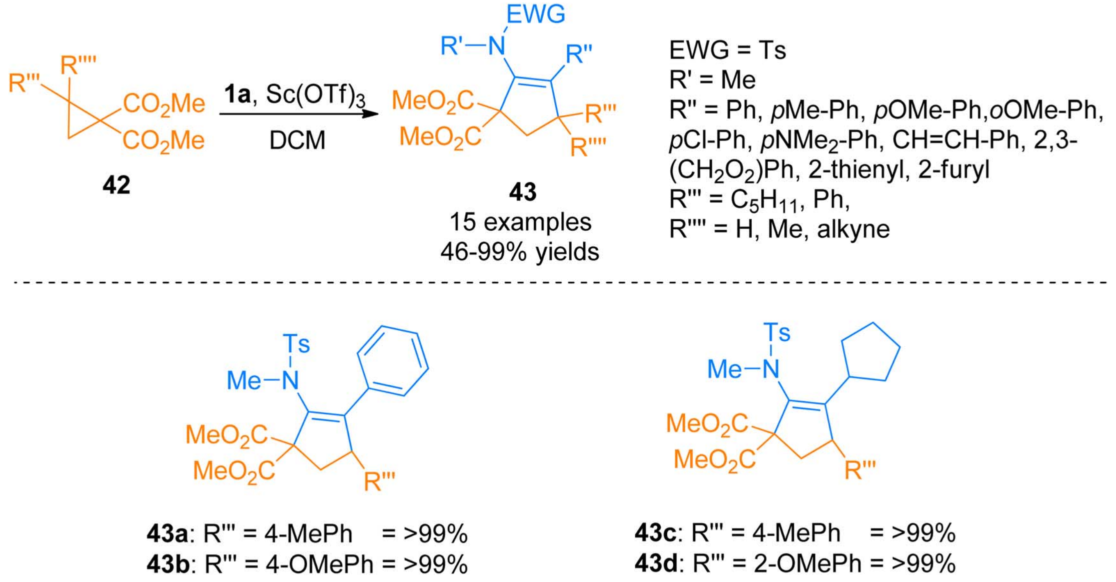


Scheme 19 Synthesis of 4-aminooxazoles **41a** from [3 + 2]-cycloaddition of ynamides **1a** with dioxazole **40**.

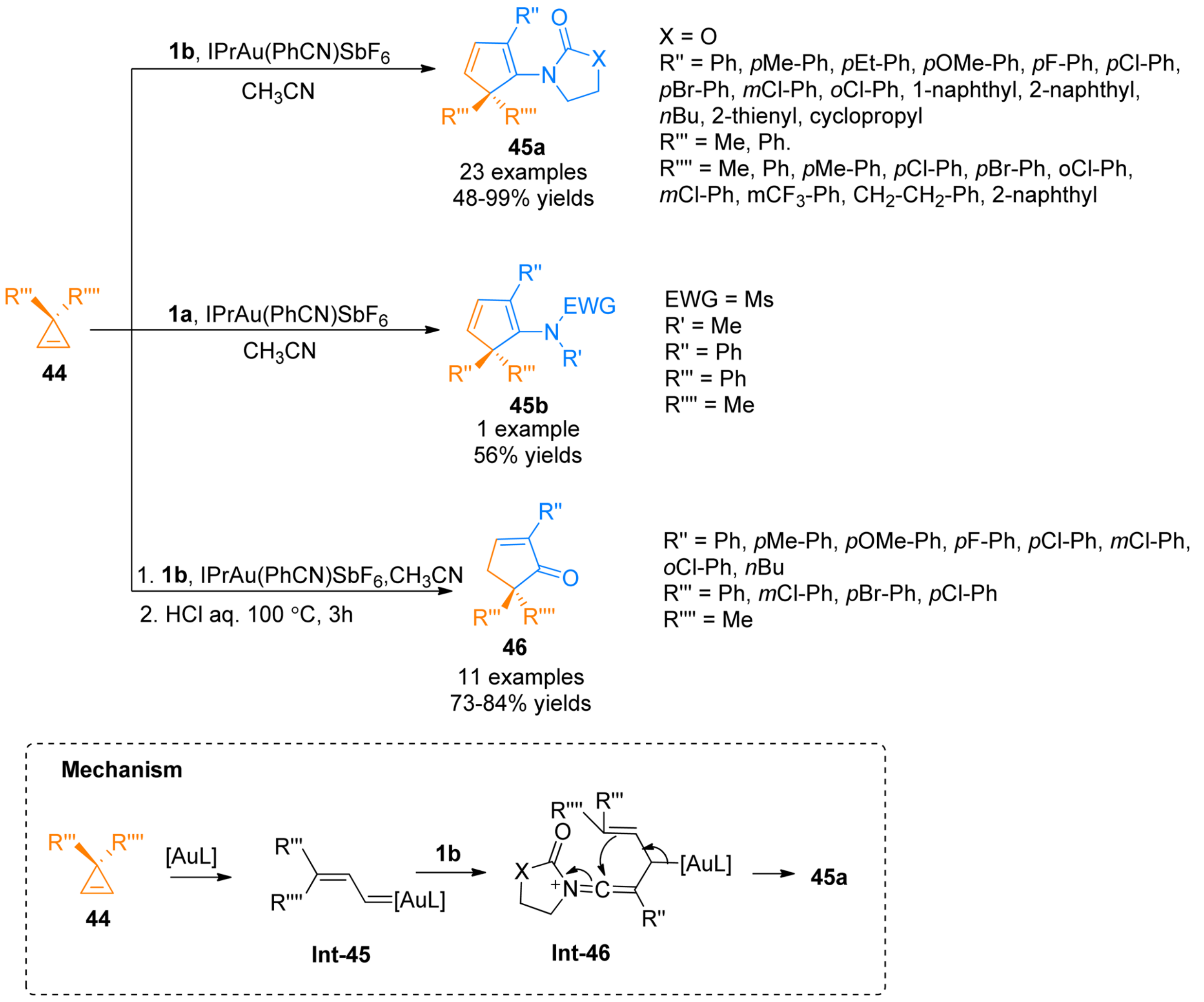


Scheme 20 Synthesis of 4-aminooxazoles **41b-c** from [3 + 2]-cycloaddition of ynamides **1a**/**1b** and dioxazoles **40**.

1a/**1b** and cyclopropenes **44** to yield cyclopentadienes **45a–b** and cyclopentenones **46.** The transformation involves the activation of double bonds over triple bonds and achieving cyclopentadienes in high yields. In comparison with the already reported transformations involving gold-catalyzed enyne cycloisomerization, this novel methodology presented a rare example of the gold-catalyzed transformation with alkenes activation priority over alkynes (formation of **Int-45** and **Int-46**). The



Scheme 21 Synthesis of cyclopentene sulfonamides **43** *via* [3 + 2]-cycloaddition of ynamides **1a** with cyclopropanes **42**.



Scheme 22 Synthesis of cyclopentadienes **45a**/**45b** and cyclopentenones **46** *via* [3 + 2]-cycloaddition between ynamides **1a**/**1b** and cyclopropenes **44**.

reaction afforded the cyclopentadienes **45a** and **45b** *via* cycloaddition of cyclopropenes **44** with ynamides **1a** and **1b**, respectively with optimized conditions of IPrAu(PhCN)SbF$_6$ catalyst (5 mol%) in acetonitrile solvent at 100 °C. Moreover, the developed protocol could be extended to realize the synthesis of functionalized cyclopentenone **46** *via* one-pot, formal [3 + 2]-cycloaddition between cyclopropenes **44** and ynamides **1b** using optimized conditions followed by the treatment with concentrated HCl at 100 °C (Scheme 22). The reaction afforded cyclopentadienes **45a–b** (24 examples, 48–99% yields) and cyclopentenones **46** (11 examples, 64–84% yields) in a moderate to excellent yield range.[58]

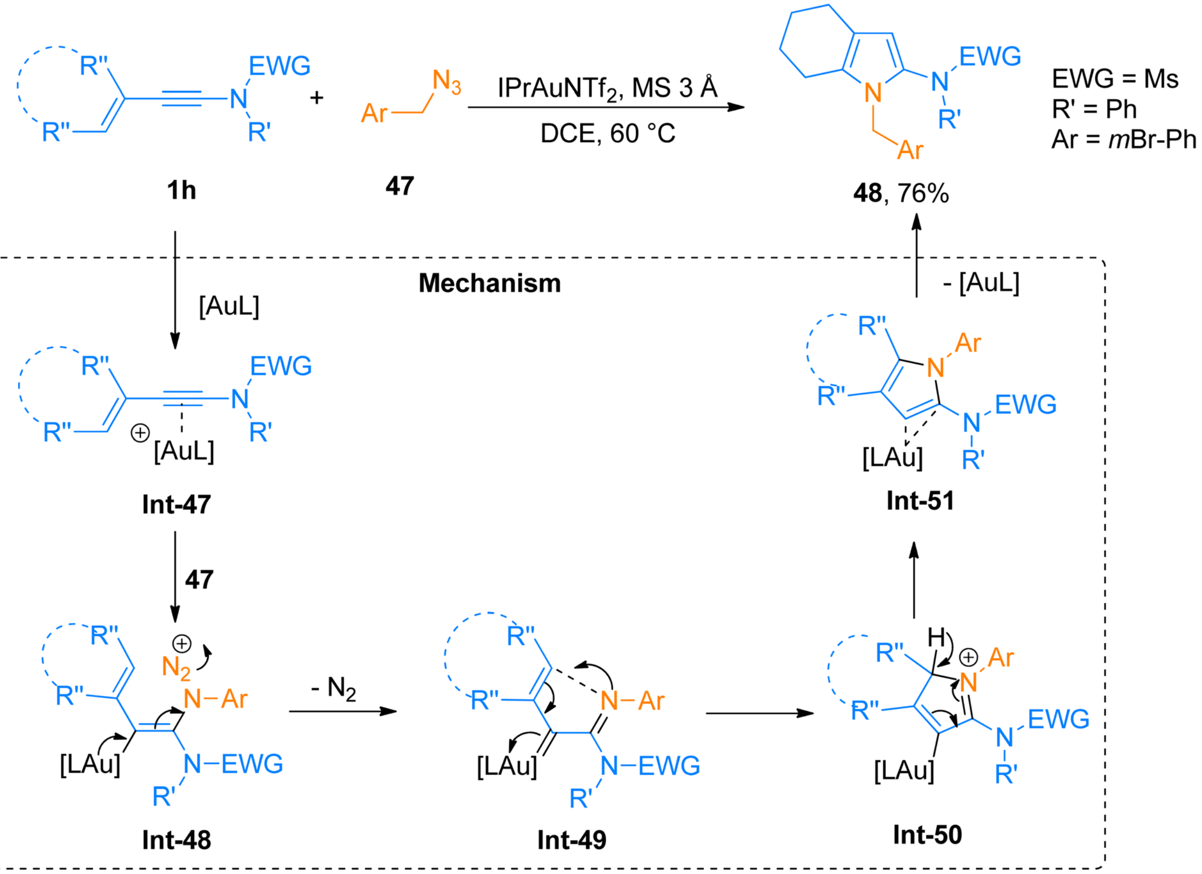
2.3. [4 + 1]-cycloaddition

2.3.1. Synthesis of 2-aminopyrroles *via* [4 + 1]-cycloaddition. Shu *et al.* (2016), carried out a novel gold-catalyzed aza-Nazarov cycloaddition *via* intermolecular ynamide amination for facile synthesis of substituted 2-aminopyrroles in promising yields. The reaction generated highly functionalized aminopyrroles *via* formal [4 + 1]-cycloaddition of 3-en-1-ynamides with azides using the gold catalyst. This tandem reaction sequence afforded the title products (17 examples, 50–76% yields) in high regioselectivity by using IPrAuNTf$_2$ catalyst (10 mol%) and MS 3 Å in dichloroethane solvent at 60 °C. Among the synthesized series compound **48** was afforded 76% yield *via* cycloaddition of ynamide **1h** and azide **47** (Scheme 23). The reaction mechanism was proposed based on DFT calculations of the relative free energies of the intermediates and transition states.[59] The gold activated ynamide intermediate **Int-47** reacted with **47** to generate imine-gold-carbene intermediate **Int-49.** The **Int-49** undergoes cyclization and proton transfer in subsequent steps affording **Int-50** and **Int-51**, respectively. Finally, the elimination of gold catalyst from **Int-51** yielded the final product. The facile and convenient synthetic route with wide substrate scope suggested this strategy as a preferable alternative for the construction of a diverse range of substituted 2-aminopyrroles.[59]

2.4. [4 + 2]-cycloaddition

2.4.1. Synthesis of quinolines *via* [4 + 2]-cycloaddition

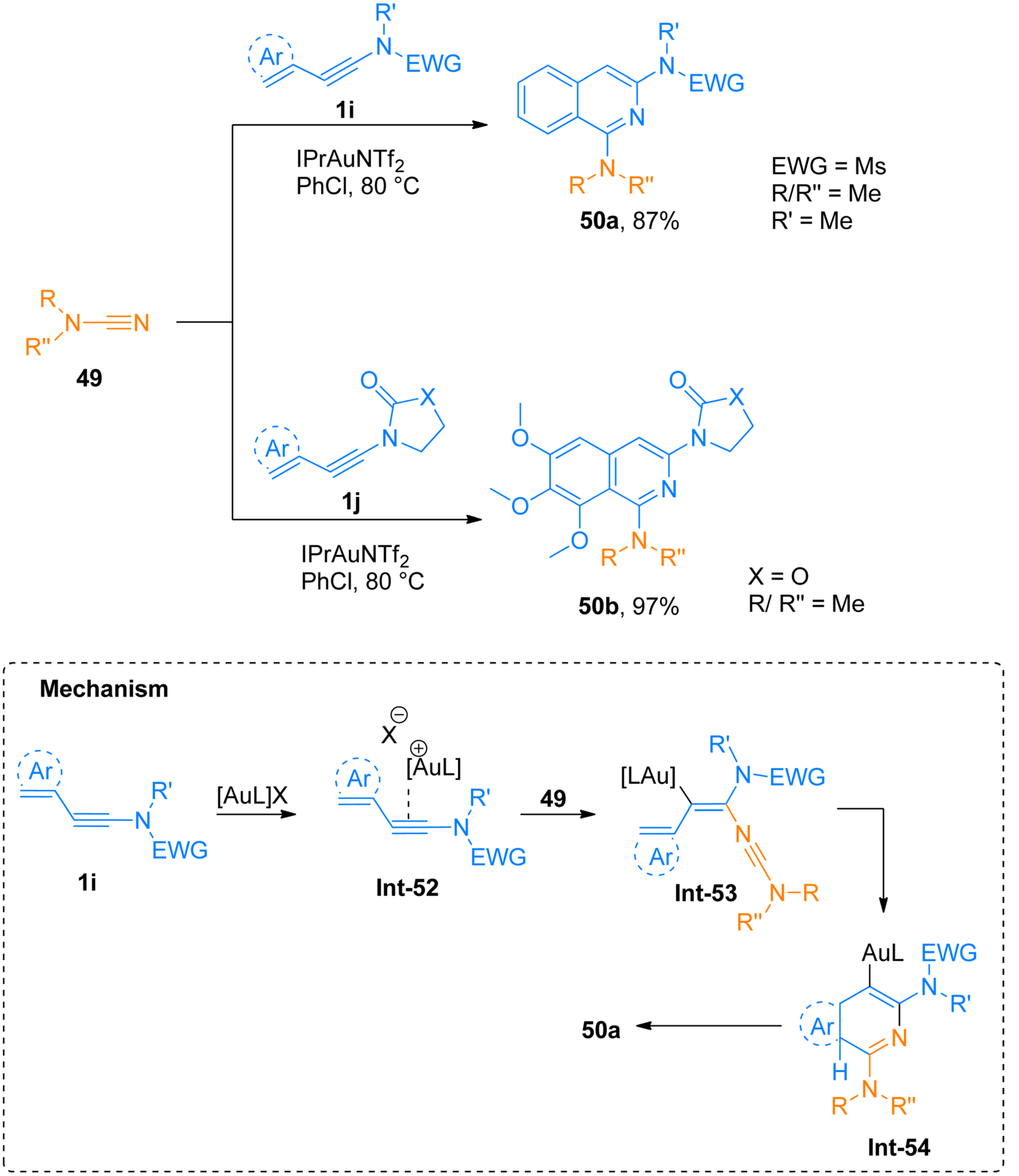
2.4.1.1. Synthesis of isoquinolines. Cyanamides differ in reactivity from conventional nitriles due to the dual nature of cyanamide scaffold bearing electrophilic and nucleophilic nitrogen atoms. Because of this dual reactivity cyanamides are called push–pull nitriles.[60] Amino groups present in ynamide and cyanamides allow the one-step and facile introduction of valuable functional substituents in title products. Dubovtsev *et al.* (2020), described thermodynamically controlled conditions to modulate the reactivity switch either as [2 + 2 + 2] or [4 + 2]-cycloaddition resulting in 1,3-diaminoisoquinolines. The reaction underwent [4 + 2]-cycloaddition of ynamides and



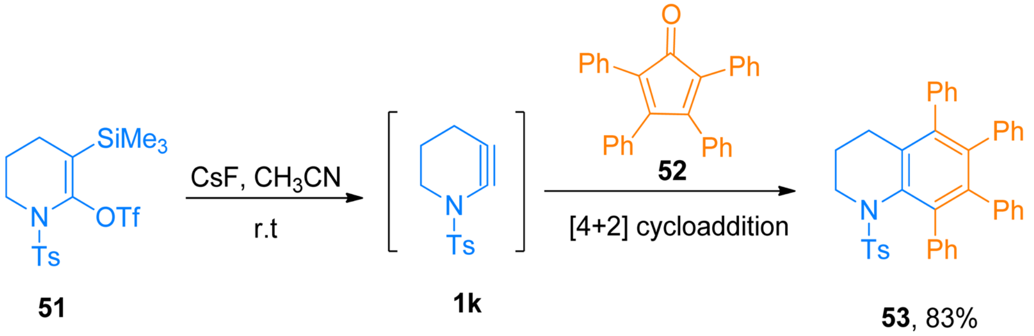
Scheme 23 Synthesis of 2-aminopyrrole **48** *via* [4 + 1]-cycloaddition of 3-en-1-ynamide **1h** with azide **47**.

cynamides using IPrAuNTf$_2$ catalyst (5 mol%) in chlorobenzene solvent at 80 °C affording diaminoisoquinolines with acyclic electron withdrawing groups (5 examples, 62–87%) and diaminoisoquinolines bearing cyclic electron withdrawing groups (13 examples, 41–97%) (Scheme 24). The reaction mechanism under thermodynamically controlled conditions involves the reaction of activated ynamide intermediate **Int-52** with **49** to generate **Int-53** that undergoes cyclization and quenching of proton to afford the final product *via* **Int-54**. The reaction is of remarkable importance as it proceeded efficiently using mild conditions and open the possibilities of introduction of dialkyl, diaryl, and amino substituents to isoquinoline cores with excellent regioselectivity. Under optimized reaction conditions ynamides, **1i** and **1j** reacted with cyanamides **49** to afford products **50a** and **50b** with 87% and 97% yields, respectively.[61]

2.4.1.2. Synthesis of tetrahydroquinoline. Talias and Rick (2014), described the first synthetic manifestation for the synthesis of six-membered cyclic ynamide **1k**, and further its [4 + 2]-cycloaddition reaction with cyclopentadienone **52** to attain tetrahydroquinoline **53**. Strained ynamide intermediate **1k** was generated *in situ* by fluoride-promoted 1,2 elimination from azacyclohexyne **51** using CsF, and acetonitrile solvent at room



Scheme 24 Synthesis of 1,3-diaminoisoquinolines **50a** and **50b** *via* [4 + 2]-cycloaddition of cyanamides **49** with ynamides **1i** and **1j**, respectively.



Scheme 25 Synthesis of tetrahydroquinoline **53** *via* [4 + 2]-cycloaddition of cyclic ynamide **1k** with cyclopentadienone **52**.

temperature. The strained heterocyclic alkyne **1k** subsequently got trapped either by a nucleophile, electrophile, or cycloaddition reaction partner. The strained ynamide **1k** generated *in situ*, underwent [4 + 2]-cycloaddition with 2,3,4,5-tetraphenylcyclopentadienone **70** in a highly regioselective manner leading to tetrahydroquinoline **53** in 83% yield by the spontaneous release of carbon monoxide (Scheme 25).[62]

2.4.1.3. Synthesis of 1,2-dihydroisoquinolines. Xin *et al.* (2014), described a novel protocol to access 1,2-dihydroisoquinolines derivatives **55a**/**55b**. This developed methodology involves the formal [4 + 2]-cycloaddition between ynamides **1i**/**1j** and imines **54** forming carbon and carbon–nitrogen bonds in a single step using the gold catalyst. Along with ynamide **1i**/**1j**, aldimine, or ketimine, both could be used as reaction partners. The developed methodology afforded products (19 examples, 46–96% yields) using IPrAuNTf$_2$ catalyst (5 mol%) or (PPh$_3$)AuNTf$_2$ catalyst (5 mol%) in dichloroethane solvent at 60 °C. Using the Ms electron withdrawing group only product **55a** was afforded in 92% yield, by the reaction of **54** and **1i** using IPrAuNTf$_2$ catalyst. While among the 18 products synthesized using cyclic electron withdrawing group containing ynamides **1j** product **55b** was afforded with the highest yield of 96% *via* IPrAuNTf$_2$ catalyzed cycloaddition of **54** and **1j**. The reaction mechanism involves the attack of gold activated ynamide **Int-55** with the **54** to afford **Int-56** which further undergoes cyclization *via* [4 + 2] addition, hydrogen ion transfer, and elimination of gold catalyst to afford the final product (Scheme 26). The developed protocol is the first method for the simultaneous generation of C–C bond at 1 and 8 positions and C–N bond at 2 and 3 positions of 1,2-dihydroisoquinolines which can be further extended for the synthesis of dihydrofuropyridine.[63]

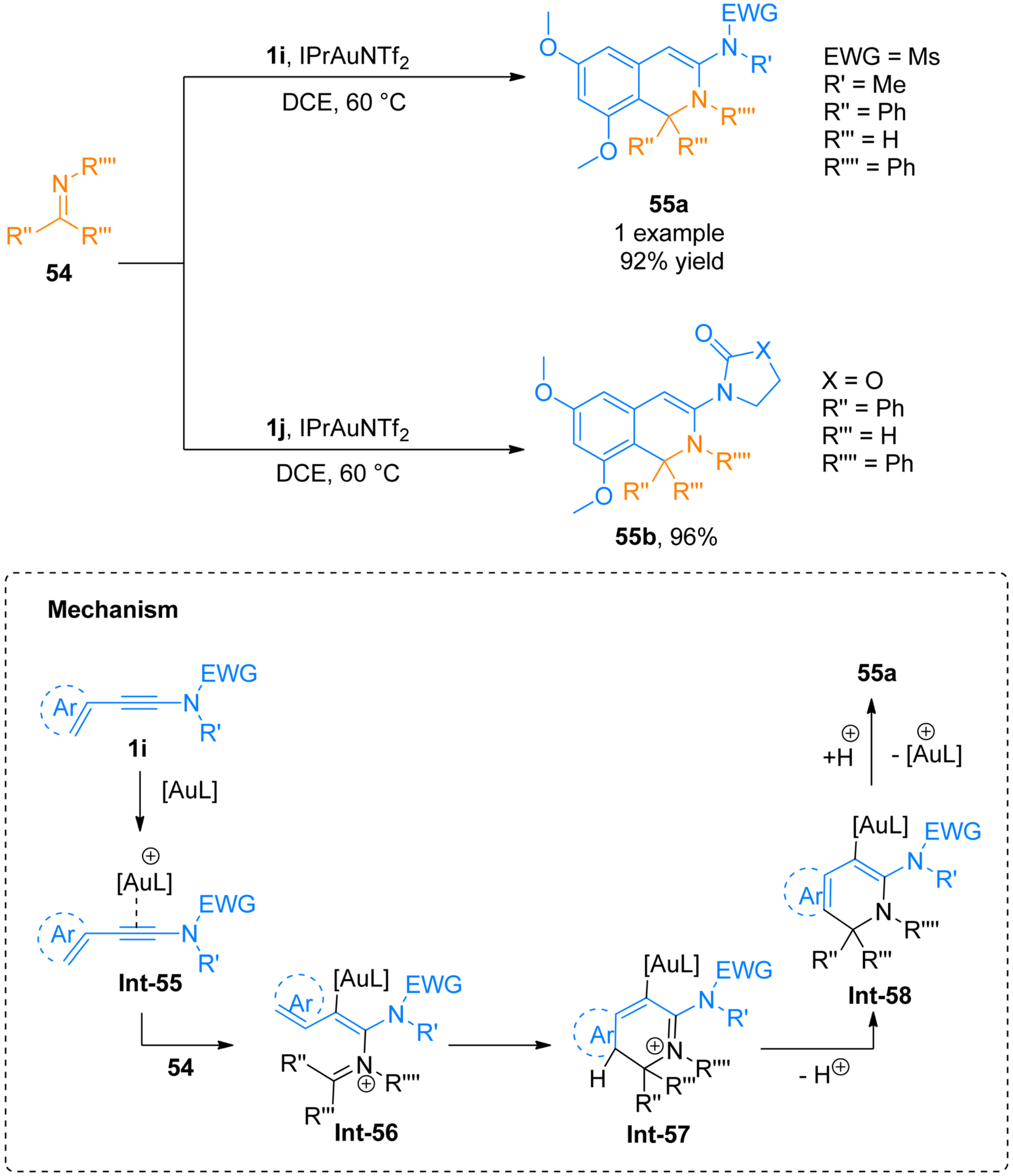
2.4.2. Synthesis of 1,2-dihydroquinazoline *via* [4 + 2]-cycloaddition.

Quinazoline is an imperative core present in alkaloids and medicinal compounds. Quinazolines attracted great interest owing to their potent biological activities as antifungal, anticancer, and antihypertensive agents.[64] Wu *et al.* (2019), described the efficient and straightforward TfOH catalyzed [4 + 2]-cycloaddition of ynamides and nitriles to yield 1,2-dihydroquinazoline derivatives in dichloromethane solvent, using MS 4 Å, inert environment (N$_2$), at 40 °C (25 examples, 34–93% yields). The highest yield of 93% of product **57** was afforded *via* cycloaddition of ynamide **1l** and nitrile **56** (Scheme 27). The proposed mechanism suggests the activation of ynamide **1l** by TfOH to yield keteniminium ion **Int-59**. In the next step nitrile **56** attack the keteniminium ion **Int-59** to generate **Int-60**. Subsequently, 6-*endo-dig* cyclization of the **Int-60** realized the formation of **Int-61** which *via* elimination reaction afforded the respective product. The straightforward and atom-economical synthesis yields the functionalized 1,2-dihydroquinazoline derivatives in a short reaction time with higher yields and excellent diastereoselectivity. Moreover, the use of non-toxic and inexpensive catalysts made it an auspicious pathway to realize pharmaceutically active constructs.[64]

2.4.3. Synthesis of 2-amino-4*H*-chromenes *via* [4 + 2]-cycloaddition.

Due to the notable and highly pronounced activities of 2-amino-4*H*-chromenes, a multitude of protocols has been developed for the convenient and facile synthesis of 2-amino-4*H*-chromenes.[23,65] Chen *et al.* (2016), recently reported a Lewis acid-catalyzed cycloaddition reaction of **58** and ynamides **1a** or **1b** to construct title compounds **59a** (3 examples, 41–58% yield) and **59b** (4 examples, 56–65% examples), respectively, by ZnBr$_2$ promoted transformation using N$_2$ atmosphere at room temperature. The reaction mechanism proceeds by the ZnBr$_2$ promoted the removal of the OTMS group from silyl ether **58** resulting in carbocation intermediate **Int-62** which further reacts with ynamide **1a** to yield **Int-63**. The final product was afforded by the cyclization followed by the elimination of the methyl group from **Int-64** (Scheme 28). However, the developed methodology faced certain drawbacks such as low yields and limited substrate scope.[65]

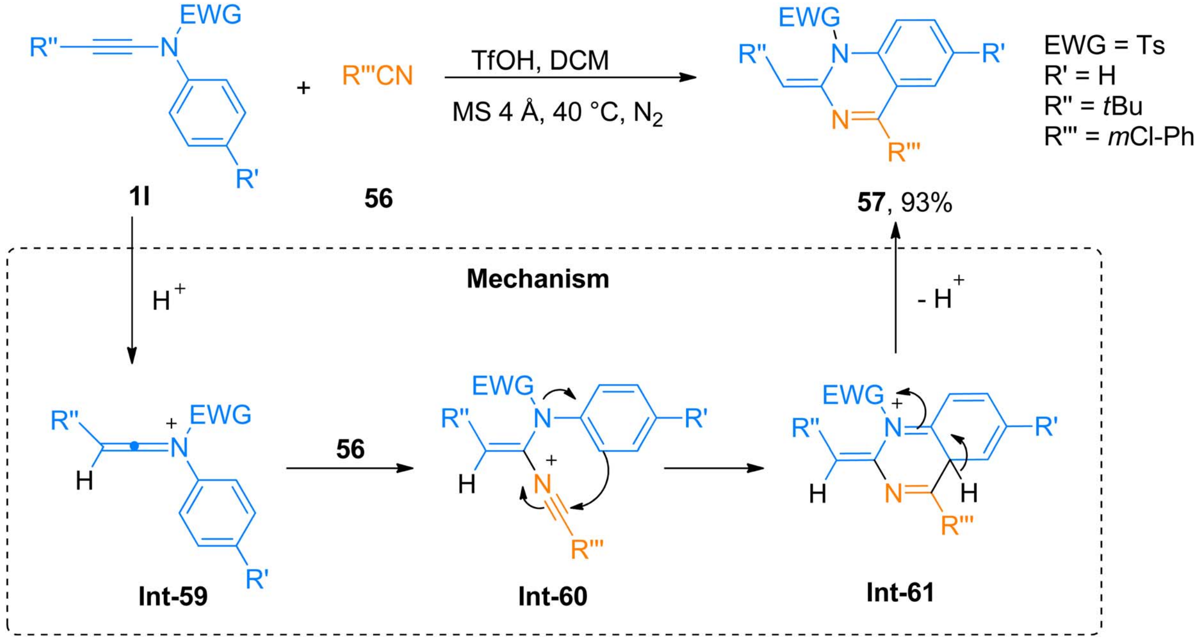
Wen *et al.* (2020), presented one of the well-developed methods for the synthesis of the 2-amino-4*H*-chromenes *via* catalyst-free cycloaddition of ynamides by overcoming the salient drawbacks of previously reported methods. The novel concise and flexible route for the construction of functionalized 2-amino-4*H*-chromenes **59d–e** and α-halo enamides **61a–b** involves [4 + 2]-cycloaddition reaction of ynamides **1a** and **1b** and 2-halomethyl phenols **60** *via* keteniminium intermediate formation under catalyst-free conditions (Scheme 29). Moreover, the facile protocol afforded higher yields of **59d** (23 examples, 45–95% yields) and **59e** (1 example, 59% yield) using mild conditions and reliable tolerance for a broad range of functionalities. Along with functionalized 2-amino-4*H*-



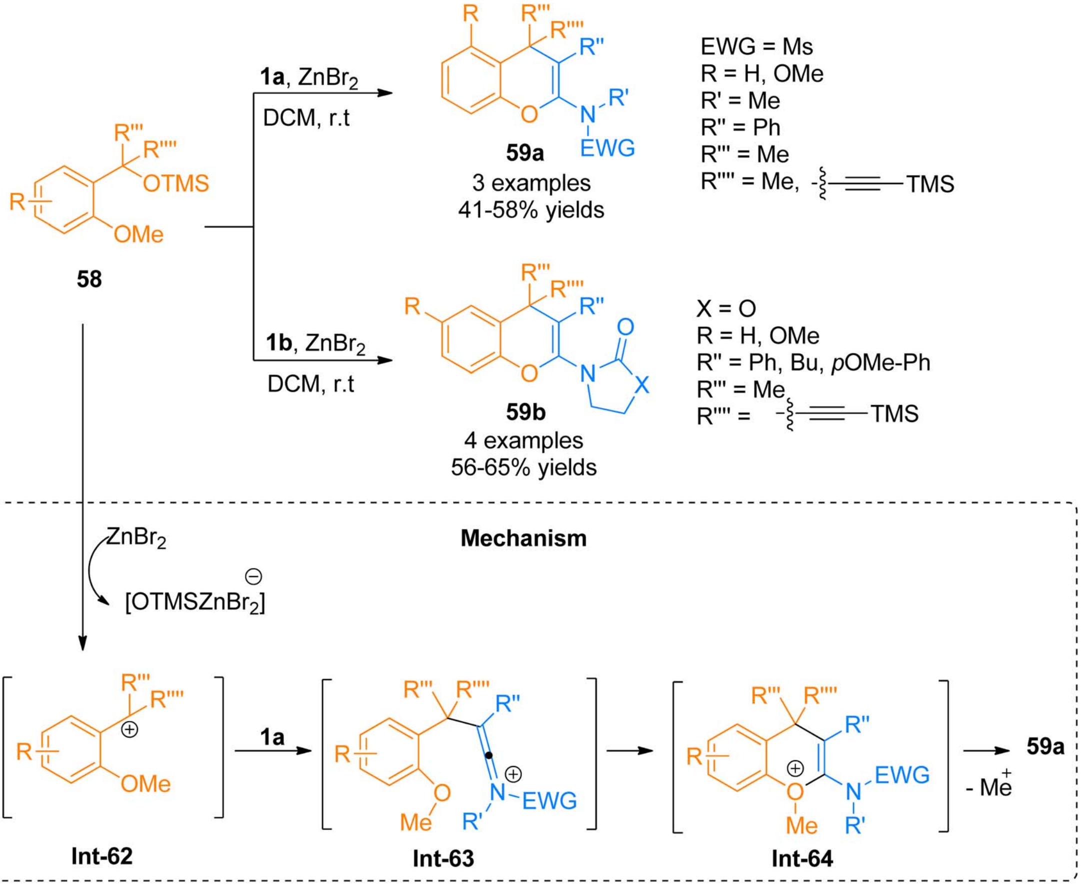
Scheme 26 Synthesis of 1,2-dihydroisoquinolines **55a**/**55b** *via* [4 + 2]-cycloaddition of ynamides **1i**/**1j** with imines **54**.

chromenes, this reaction also afforded α-halo enamides **61a** (22 examples, 31–93% yields) and **61b** (1 example, 47% yield) in good to excellent yields which are key intermediates for versatile transformations and can be readily converted into a range of functional groups by halogen metal exchange reaction.[66]

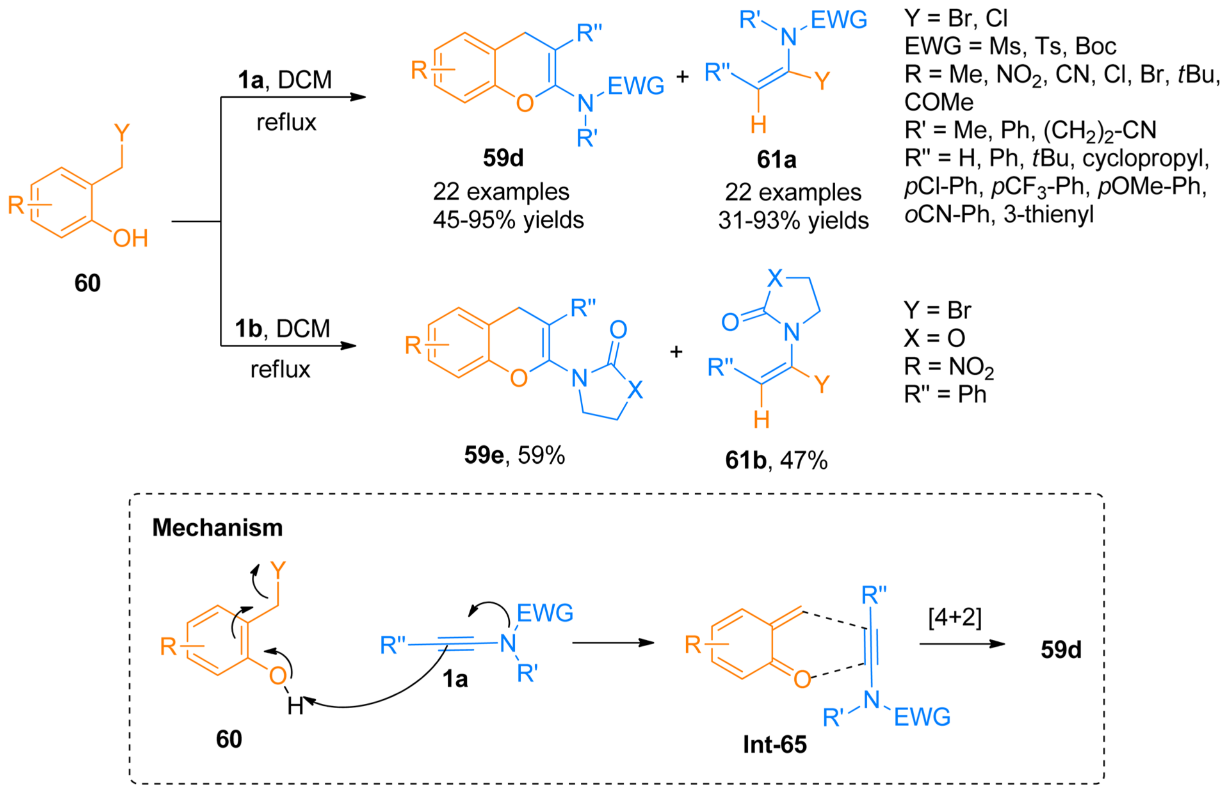
2.4.4. Synthesis of oxa/azacyclic six-membered heterocycles *via* [4 + 2]-cycloaddition. The use of oxetanes and azitidines for the construction of four-membered frameworks *via* metal-catalyzed [4 + *n*]-cycloaddition reactions is limited. The less strained ring is responsible for their lower reactivity due to which they require metal complexes in large quantities.[67] Pawar *et al.* (2014), developed an alternative route to cover this drawback which provided a facile route to access oxa and aza cyclic six-membered heterocycles. The [4 + 2]-cycloaddition reaction between ynamides and oxetanes using gold catalyst afforded required oxa/azacyclic six-membered heterocycles (15 examples, 64–88% yields). In **L1**-AuCl/AgNTf$_2$ catalyzed (5 mol%) cycloaddition, gold-*p*-ynamides act as electrophiles and oxetanes as nucleophiles affording the cycloadducts in a regioselective manner in dichloromethane solvent at room temperature. While for azetidines, [4 + 2]-cycloaddition reaction with ynamides occurred more efficiently using a silver catalyst, AgSbF$_6$ (10 mol%), and dichloromethane solvent at room temperature affording nitrogen-containing 6-membered



Scheme 27 Synthesis of 1,2-dihydroquinazoline **57** *via* [4 + 2]-cycloaddition of ynamides **1l** with nitrile **56**.



Scheme 28 Synthesis of 2-amino-4*H*-chromenes **59** *via* [4 + 2]-cycloaddition of ynamides **1a**/**1b** with silyl ether **58**.

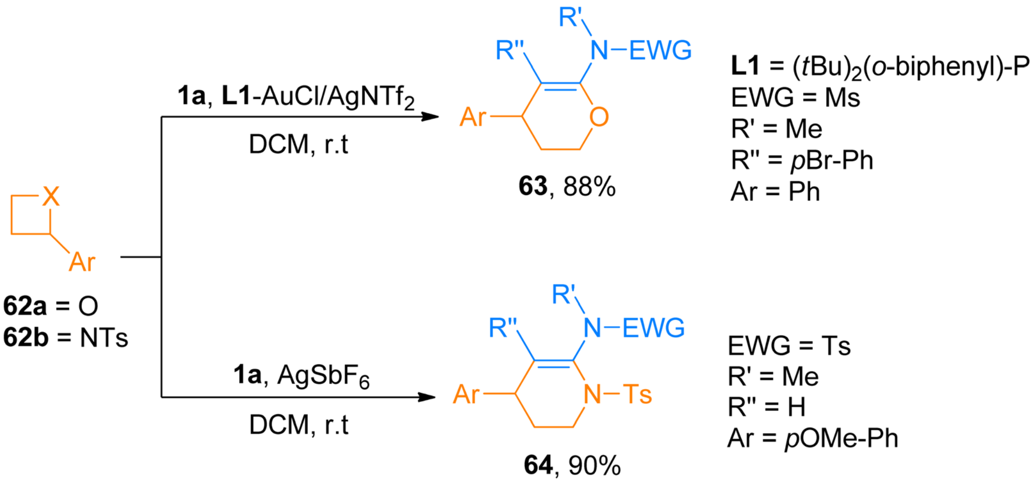


Scheme 29 Synthesis of 2-amino-4*H*-chromenes **59d–e** *via* [4 + 2]-cycloaddition of ynamides **1a**/**1b**.

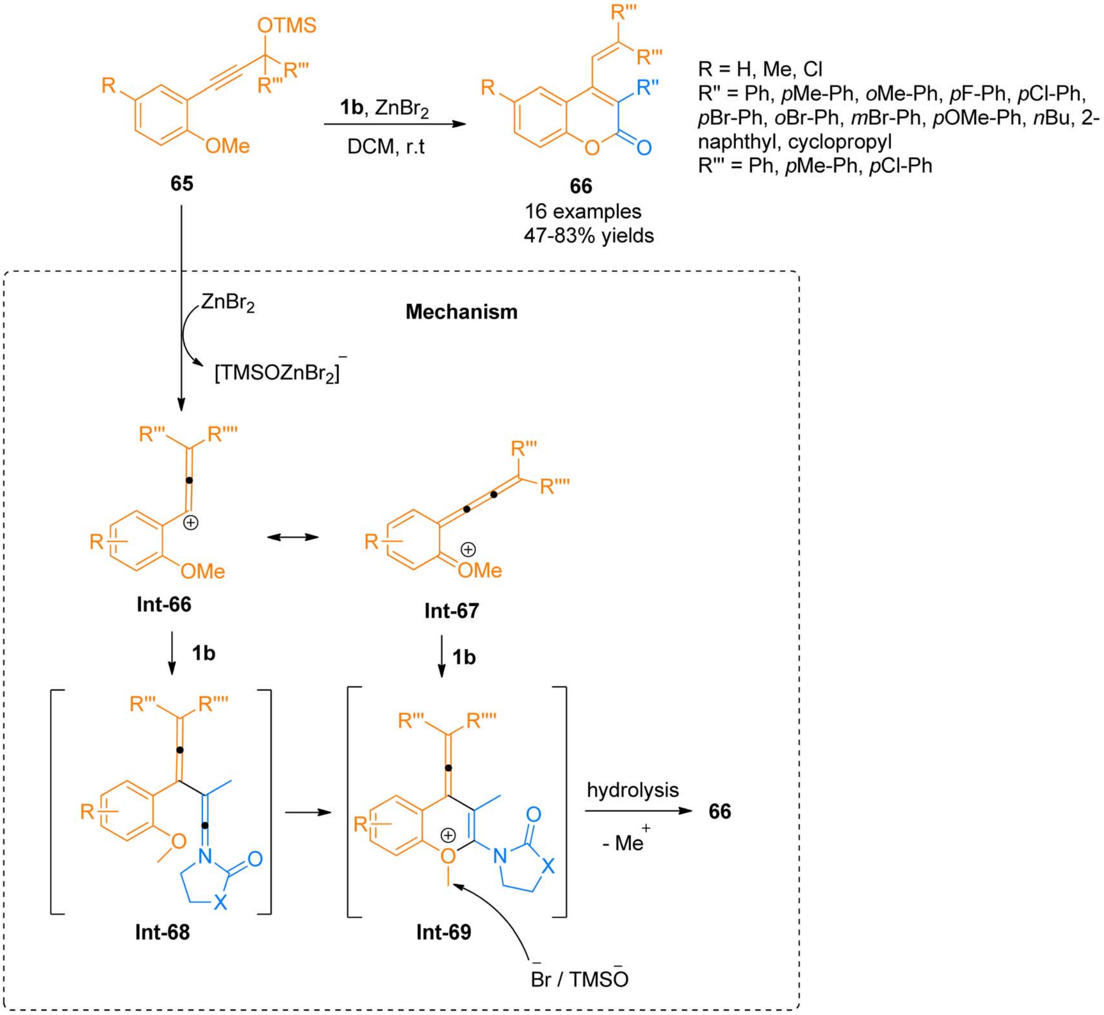
heterocycles (14 examples, 45–90% yields). Both gold and silver catalyst work similarly to activate ynamide which get attacked by heteroatom of oxetane or azetidine. Among the synthesized series of oxa cyclic heterocycles, compound **63** was afforded an 88% yield by the gold-catalyzed reaction of ynamide **1a** and oxetane **62a**. Similarly, in the aza cyclic heterocyclic series, compound **64** was afforded the highest yield of 90% by silver catalyzed cycloaddition of ynamide **1a** and azetidine **62b** (Scheme 30).[68]

2.4.5. Synthesis of coumarins *via* [4 + 2]-cycloaddition.

Chen *et al.* (2016), described a novel synthetic manifestation for the [4 + 2]-cycloaddition reaction of *o*-anisole functionalized propargyl silyl ethers **65** with ynamides **1b** to afford polycyclic 4-vinylcoumarins **66** (16 examples, 47–83% yields). Fluorescence analysis was used for the screening and optimization of the reaction conditions for 6π-electrocyclization. The synthesis was carried out using $ZnBr_2$ as a Lewis acid catalyst, in dichloromethane solvent at room temperature (Scheme 31). The



Scheme 30 Synthesis of six-membered oxa-heterocycle **63** and aza-heterocycle **64** *via* [4 + 2]-cycloaddition of ynamide **1a** and oxetane **62a**/azetidine **62b**.

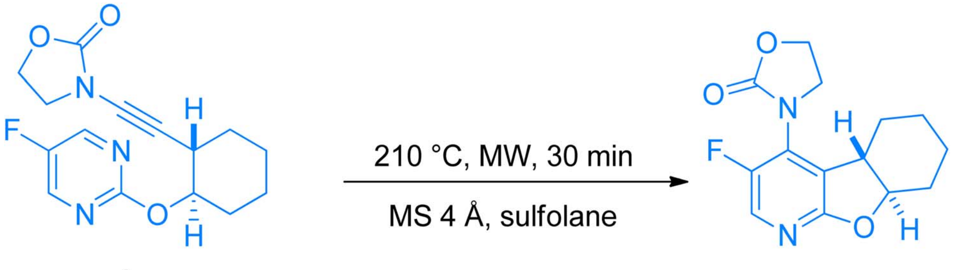


Scheme 31 Synthesis of substituted coumarins **66** *via* [4 + 2]-cycloaddition of ynamide **1b** with 4-vinylcoumarins **65**.

proposed reaction suggests the initiation of reaction by $ZnBr_2$ promoted propargyl silyl ether **65** conversions to carbocation **Int-66** which is in conjugation with **Int-67**. There are two possible pathways, during the first pathway ynamide **1b** reacts with **Int-66** to yield highly unstable intermediate **Int-68** which ultimately converts to **Int-69** *via* nucleophilic attack and cyclization. While the alternative pathway involves the concerted [4 + 2]-cycloaddition of the **Int-67** and ynamide **1b** to directly afford **Int-69**. Elimination of the methyl group followed by hydrolysis yields the final product.[69]

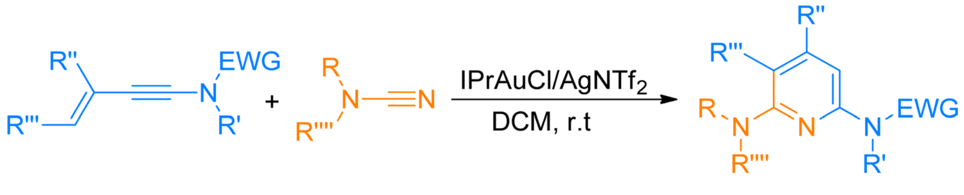
2.4.6. Synthesis of 4-aminopyridines *via* [4 + 2]-cycloaddition. 4-Aminopyridines are biologically as well as synthetically important scaffolds that attracted the attention of the pharmaceutical and agrochemical industry.[70] Despite the skeletal diversity associated with the 4-aminopyridines, the synthetic manifestations of this class still have shortcomings and limitations. However, an intramolecular inverse electron demand hetero Diels–Alder reaction (IEDDA)/retro-Diels–Alder reaction (rDA) could provide direct access to this synthetically challenging, and valuable class of compounds. Duret *et al.* (2017), presented the synthetic manifestation to access diverse polycyclic fused and spiro 4-aminopyridines exhibiting considerable structural variability from commercially available pyrimidines. This methodology reported the use of ynamides in IEDDA for the first time to yield aminopyridines. The three-step transformation includes the retro [4 + 2]-cycloaddition between ynamide bearing cyclic group at the nitrogen terminal and pyrimidine (electron-deficient heterodiene) as a key step which set up the first example of ynamide behaving as an electron-rich dienophile in [4 + 2]-cycloaddition reaction. Furthermore, IEDDA in heated toluene overcomes the limited scalability of the reaction. Starting from C2-substituted pyrimidines, tetra or penta substituted 4-aminopyridines can be achieved in excellent yields (26 examples, 11–95% yields) using MS 4 Å, and sulfolane by microwave irradiation at 225 °C for 1 min and further at 210 °C, for 30 min. Compound **67** was furnished in 95% yield by the novel methodology *via* microwave-promoted cycloaddition of ynamide **1m** at 210 °C (Scheme 32).[71]

2.4.7. Synthesis of diaminopyridines *via* [4 + 2]-cycloaddition. Hetero-tetradehydro-Diels–Alder reaction (TDDA) for the construction of pyridines is unique and only a few examples have been reported yet.[72,73] For TDDA reaction between

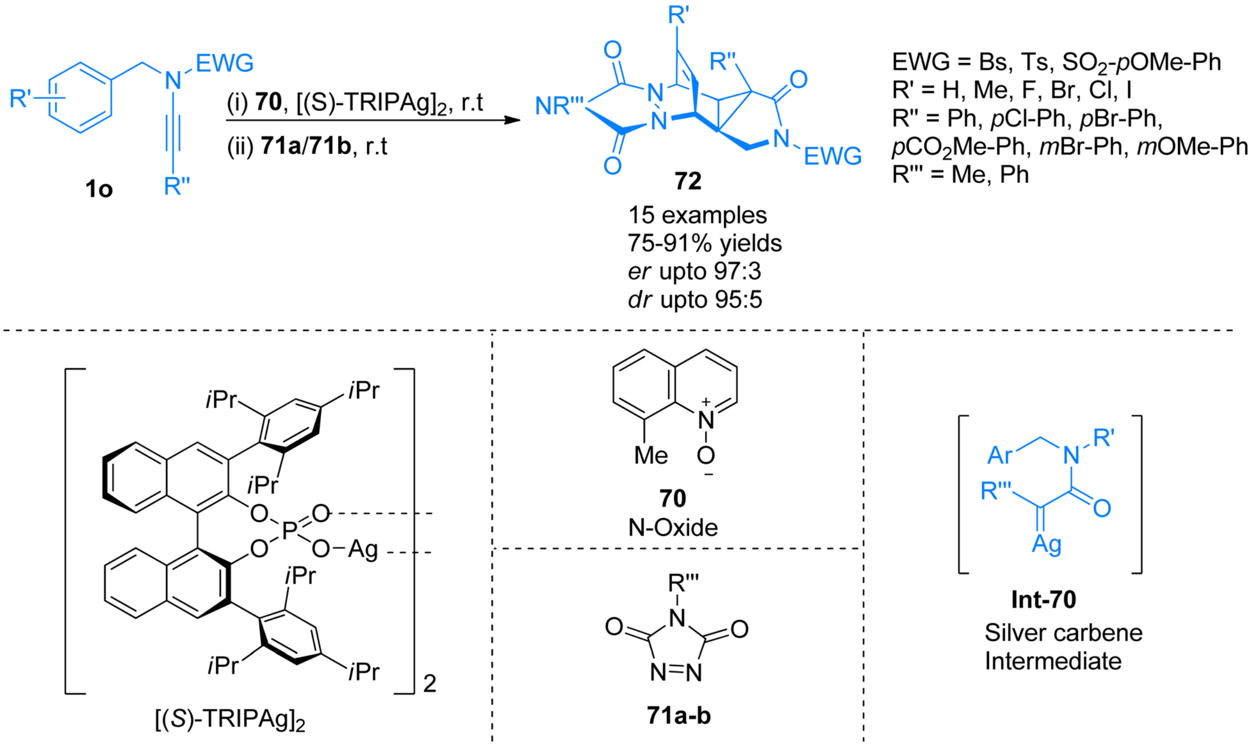


Scheme 32 Synthesis of 4-aminopyridines **67** *via* intramolecular inverse [4 + 2]-cycloaddition of ynamide **1m**.

enynamide and cyanamide reaction partners to afford diaminopyridines. Shcherbakov *et al.* (2021), developed a gold(I) catalyzed protocol. The novel protocol proceeds under mild reaction conditions such as IPrAuCl/AgNTf$_2$ (5 mol%) catalyst, in dichloromethane solvent at room temperature, and presents an efficient route for diversely functionalized 2,6-diaminopyridines. In addition to the above, the developed methodology also possessed broad substrate scope as different substituents on cyanamide and ynamides were tolerated well (28 examples, 70–99% yields). Among the synthesized series compound **69** was afforded in 99% yield *via* hetero-TDDA between ynamide **1n** and cyanamide **68** (Scheme 33).[74]



Scheme 33 Synthesis of 2,6-diaminopyridines **69** *via* hetero-TDDA reaction between enynamide **1n** and cyanamide **68**.

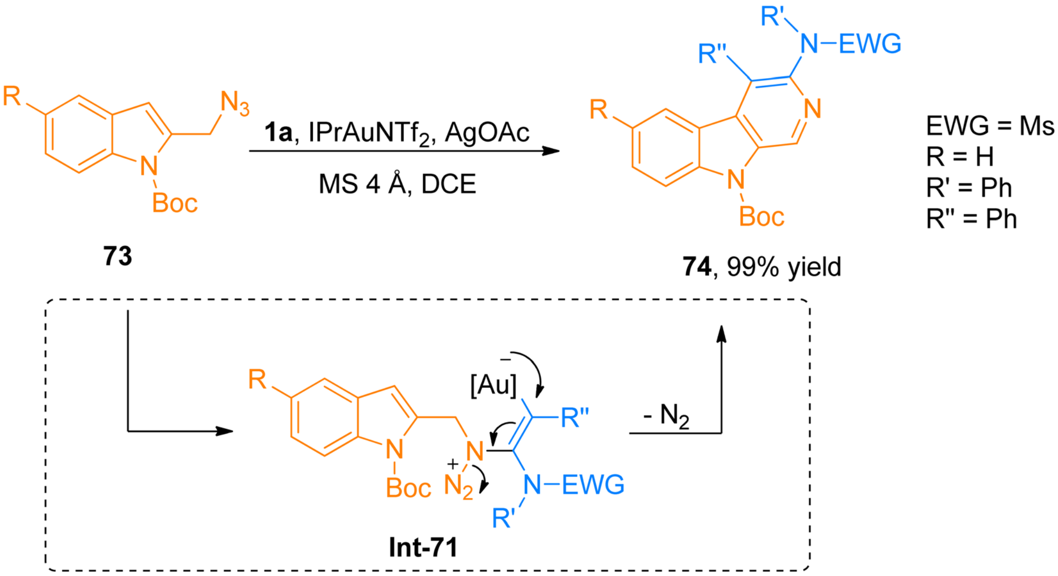


Scheme 34 Synthesis of polycycles **72** *via* [4 + 2]-cycloaddition of ynamide **1o**.

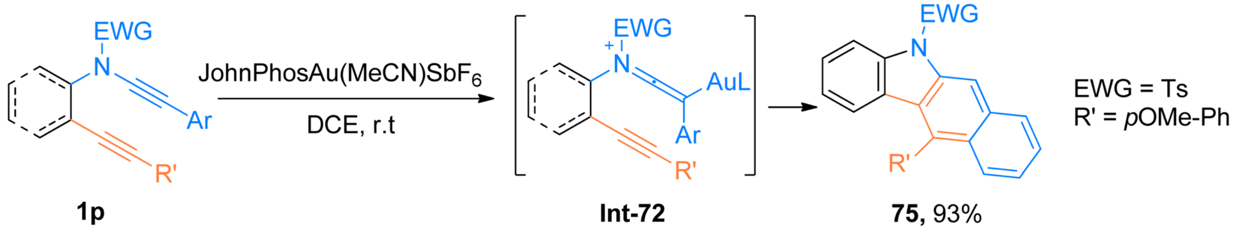
2.4.8. Synthesis of polycyclic aromatic compounds *via* [4 + 2]-cycloaddition. Dearomatization of arenes is a direct method to convert aromatic compounds to functionalized carbocycles, however, protocols for highly enantioselective dearomatization of arenes are limited as compared to indoles and phenols. Ito and coworkers (2021), developed a diazo-free novel protocol for the construction of silver carbene species using ynamide **1o** to employ in the enantioselective dearomatization of nonactivated arenes. Norcaradiene species **Int-70** generated as a transition state and trapped *via* intermolecular [4 + 2]-cycloaddition to afford polycycles **72** with five consecutive stereogenic centers (Scheme 34). The reaction mechanism involved the dearomatization reaction in the presence [(*S*)-TRIPAg]$_2$ (2.5 mol%), *N*-oxide **70** (2 equiv.), and MS 3 Å, in PhCl solvent at room temperature. It was followed by pericyclic reactions and [4 + 2]-cycloaddition reaction using **71a**/**71b** (1 eq.) and PhCl solvent at room temperature which serves as the basis for achieving chemo and enantioselectivity. The reaction tolerated a range of ynamides with different aryl groups at the terminal position. The reaction observed wide substrate scope as ynamide terminally with aryl groups having electron-rich, as well as electron withdrawing substituents, were employed to access a series of functionalized fused-cyclohexenes with excellent yields and stereoselectivity (15 examples, 75–91% yields). On the other hand, the developed methodology faced certain limitations as intermolecular reactions with benzene did not afford the target product.[75]

2.4.9. Synthesis of 3-amino-β-carboline *via* [4 + 2]-cycloaddition. Shu *et al.* (2015), disclosed the generation of α-imino-gold-carbenes during gold catalyst promoted intermolecular [4 + 2]-cycloaddition of ynamide and azide to provide regioselective access to the 3-amino-β-carboline product in promising yield range (17 examples, 65–99% yields). The synthesis of 3-amino-β-carboline **74** (99% yield) was afforded *via* the generation of α-imino carbene intermediate from ynamide **1a** and azide **73** by the addition of IPrAuNTf$_2$ (5 mol%), AgOAc (1.1 eq.), and MS 4 Å in dichloroethane solvent at 60 °C (Scheme 35). During the reaction, α-imino carbene intermediate got trapped by nucleophilic indolyl core to yield respective 1-*H*-pyrido[3,4-*b*]indole derivative which upon dehydrogenative oxidation afforded 3-amino-β-carboline species. When compared to previous methods reported for the synthesis of gold-carbene intermediate his protocol offers various advantages such as atom economical synthesis and flexible amino group introduction. A wide array of different ynamides and substituted azides were successfully engaged with the reaction. This transformation provided a straightforward route to access the biologically important 3-amino-β-carbolines having potent antitumor activities rather than tedious synthetic pathways, however, alkyl-substituted ynamide failed to afford the targeted product and furnished α,β-unsaturated imidamide instead of 3-amino-β-carboline.[76]

2.4.10. Synthesis of benzo[*b*]carbazoles *via* [4 + 2]-cycloaddition. Practical applications of tetradehydro Diels–Alder (TDDA) cycloaddition are limited due to the requirement of pre-functionalized substrates and harsh reaction conditions. As the TDDA allows the single-step construction of benzene rings, hence the demand for advancements in the facile and synthetically valuable TDDA is continuously increasing.[77,78] Xu *et al.* (2018), carried out cycloisomerization of ynamide-ynes **1p** following a gold catalyst-promoted dehydro-Diels–Alder reaction that provided facile access to benzo[*b*]carbazole derivatives. The cycloaddition involved the regioselective attack by alkyne scaffold to gold-ketenium intermediate which ultimately underwent benzannulation to yield the final product using JohnPhosAu(MeCN)SbF$_6$ (5 mol%) catalyst and dichloroethane solvent at room temperature. Among synthesized series, compound **75** afforded the highest yield of 93% *via* the generation of gold-ketenium ion **Int-72** as an intermediate during intramolecular cycloaddition of ynamide-ynes **1p** (Scheme 36). This protocol offered a highly efficient route with mild reaction



Scheme 35 Synthesis of 3-amino-β-carboline **74** *via* [4 + 2]-cycloaddition between ynamides **1a** and azides **73**.



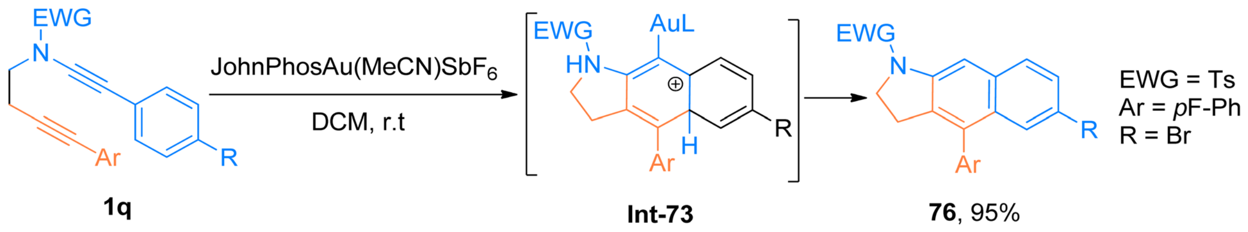
Scheme 36 Synthesis of benzo[*b*]carbazole derivatives **75** *via* intramolecular tetrahydro-Diels–Alder reaction of ynamides **1p**.

conditions and moderate substrate scope (15 examples, 18–93% yields), which also serves as a competitive alternative to the thermal dehydro-Diels–Alder reaction.[79]

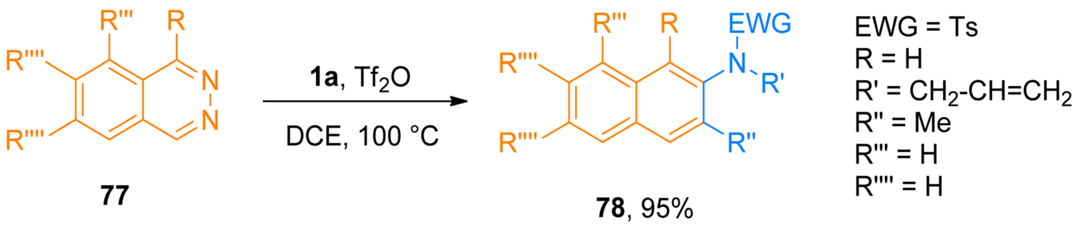
2.4.11. Synthesis of dihydrobenzo[*f*]indoles *via* [4 + 2]-cycloaddition. Prabagar *et al.* (2019), described gold-catalyzed intramolecular TDDA of aryl substituted ynamides **1q** to access 2,3-dihydrobenzo[*f*]indole derivatives. Substrates having aryl groups at ynamide terminus are crucial for gold-catalyzed TDDA reaction using JohnPhosAu(MeCN)SbF_6 (2 mol%), dichloromethane solvent. The reaction sequence involves the *in situ* construction of vinyl cation by following 5-*exo*-dig cyclization reaction of alkyne and Au-keteniminium ynamide species. The reaction was not possible if the vinyl cation do not get trapped by the aryl group substituted at the ynamide terminus. The protocol showed good tolerance for different substituents and afforded the products good to excellent yields (17 examples, 30–95% yields). The compound **76** was accessed in 95% yield *via* the formation of intermediate **Int-73** during cycloaddition of **1q** (Scheme 37).[80]

2.4.12. Synthesis of 2-aminonaphthalenes and 2-aminoanthracenes *via* [4 + 2]-cycloaddition. The cycloaddition reaction between diene (electron-rich) and dienophile (electron-deficient) species is called the normal electron demand Diels–Alder reaction. It has been well developed and has considerable applications in current organic synthesis.[81–83] In contrast the Diels–Alder reaction of diene (electron-deficient) and dienophile (electron-rich) is known as inverse electron demand Diels–Alder reaction (IEDDA) which is relatively less developed.[84,85] Xue *et al.* (2018), developed a novel metal-free IEDDA reaction between ynamides and 1,2-diazines to afford. Tf_2O-catalyzed IEDDA allowed the efficient construction of functionalized 2-aminonaphthalene derivatives and 2-aminoanthracene derivatives in a promising yield range (24 examples, 56–95% yields). Moreover, the developed novel protocol offered a straightforward way to synthesize diversified products using a Tf_2O catalyst and dichloroethane solvent at 100 °C. Product **78** was accessed using the developed methodology in 95% yield by IEDDA reaction of ynamide **1a** and 1,2-diazine 77 (Scheme 38).[86]

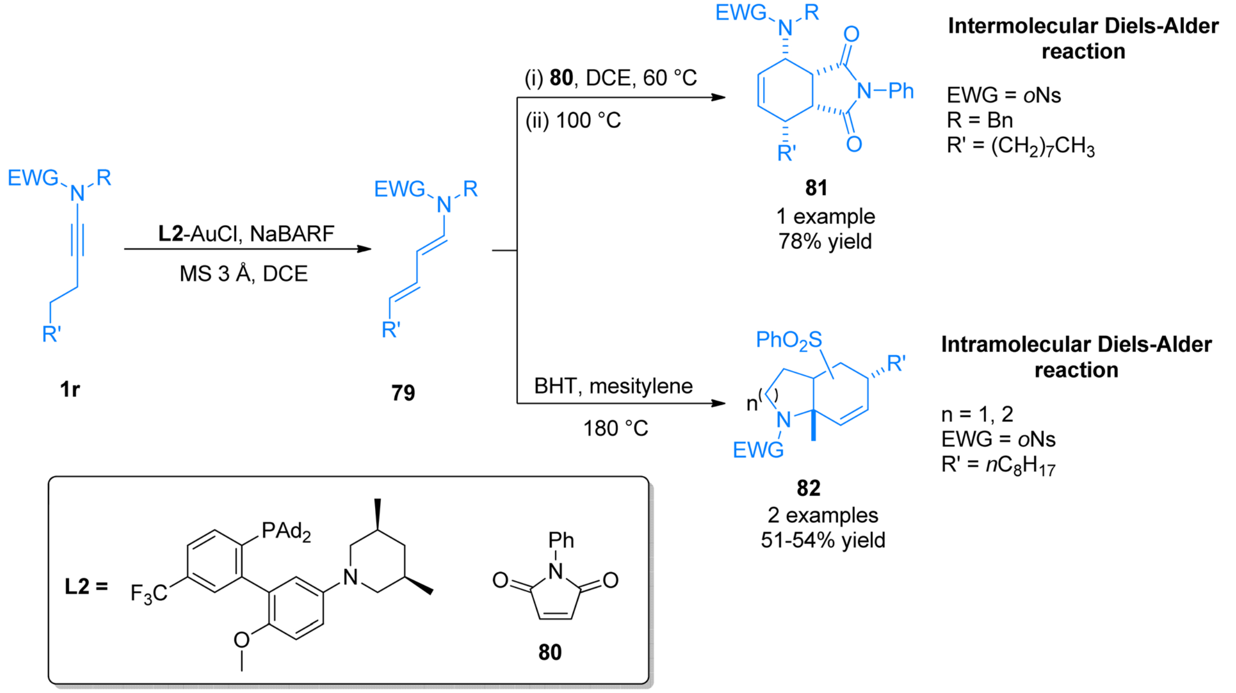
2.4.13. Synthesis of tetrahydroisoindoledione, hexahydroindole, octahydroquinoline *via* [4 + 2]-cycloaddition. Li *et al.* (2017), disclosed the synthetic pathway of gold catalyst promoted one-pot Diels–Alder reaction to furnish nitrogen-containing bicyclic scaffolds. The developed methodology directly converted *N*-alkynyl-*o*-nosylamides **1r** to (1*E*,3*E*)-1-amido-1,3-dienes **79** in high diastereoselectivities and excellent yields. The reaction involves *via* gold-catalyzed ynamide isomerization reaction using **L2**-AuCl (5 mol%) catalyst, tetrakis[3,5-bis(trifluoromethyl)phenyl]boron sodium complex (NaBARF), MS 3 Å, and dichloroethane solvent at 60 or 80 °C. The isomerization reaction was followed by intermolecular or intramolecular one-pot Diels–Alder reaction to afford



Scheme 37 Synthesis of dihydrobenzoindole derivatives **76** *via* intramolecular tetrahydro-Diels–Alder reaction of ynamides **1q**.



Scheme 38 Synthesis of 2-aminonaphthalenes **78** *via* IEDDA reaction between ynamides **1a** and 1,2-diazines **77**.



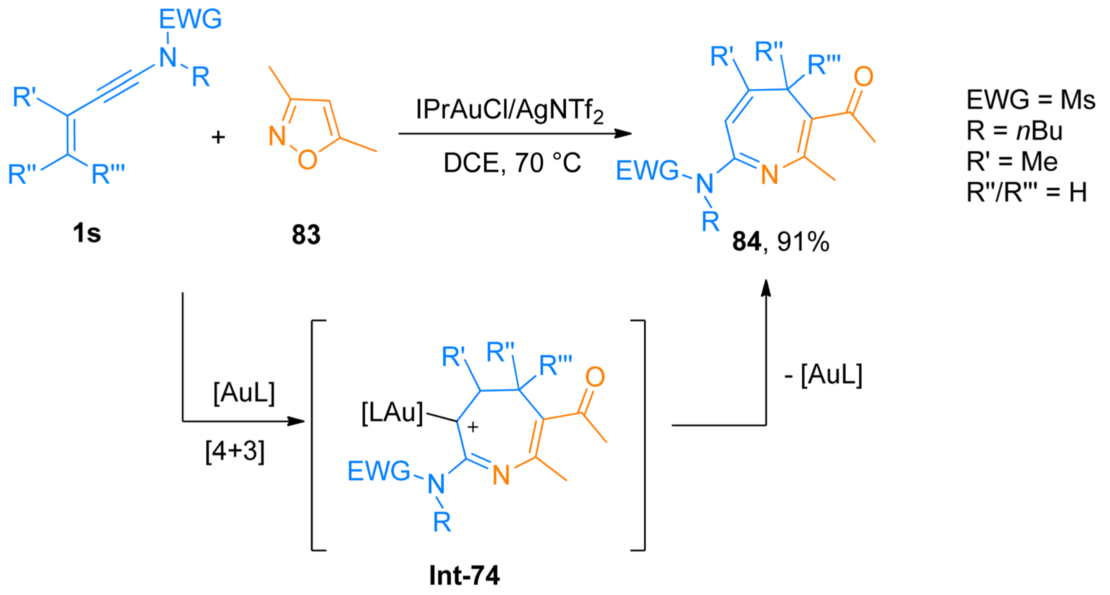
Scheme 39 Synthesis of bicyclic compounds **81** and **82** *via* one-pot Diels–Alder reaction of ynamide **1r**.

tetrahydroisoindoledione **81** (1 example, 78% yield) and hexahydroindole/octahydroquinoline **82** (2 examples, 51–54% yields). Intermolecular Diels–Alder reaction proceeded by treating allenamide **79** with *N*-phenylmaleimide **80** using dichloroethane solvent at 60 °C and the temperature was further raised to 100 °C to afford **81** in 78% yield (Scheme 56). While the intramolecular Diels–Alder reaction furnished **82** *via* the treatment of **79** with butylated hydroxytoluene (BHT) using mesitylene solvent at 180 °C (Scheme 39). The developed methodology afforded excellent (3*E*)-selectivity for distal (attached with β-carbon) carbon–carbon double bond along with good regioselectivity. In contrast, Brønsted acid-catalyzed reaction was associated with poor regio and stereo-selectivity.[87]

2.5. [4 + 3]-cycloaddition

2.5.1. Synthesis of 4*H*-azepines *via* [4 + 3]-cycloaddition.

Giri *et al.* (2018), developed [4 + 3]-cycloaddition reaction of 3-en-1-ynamides and isoxazoles to yield 4*H*-azepines using the gold catalyst. The reaction involved the 6π electrocyclization of



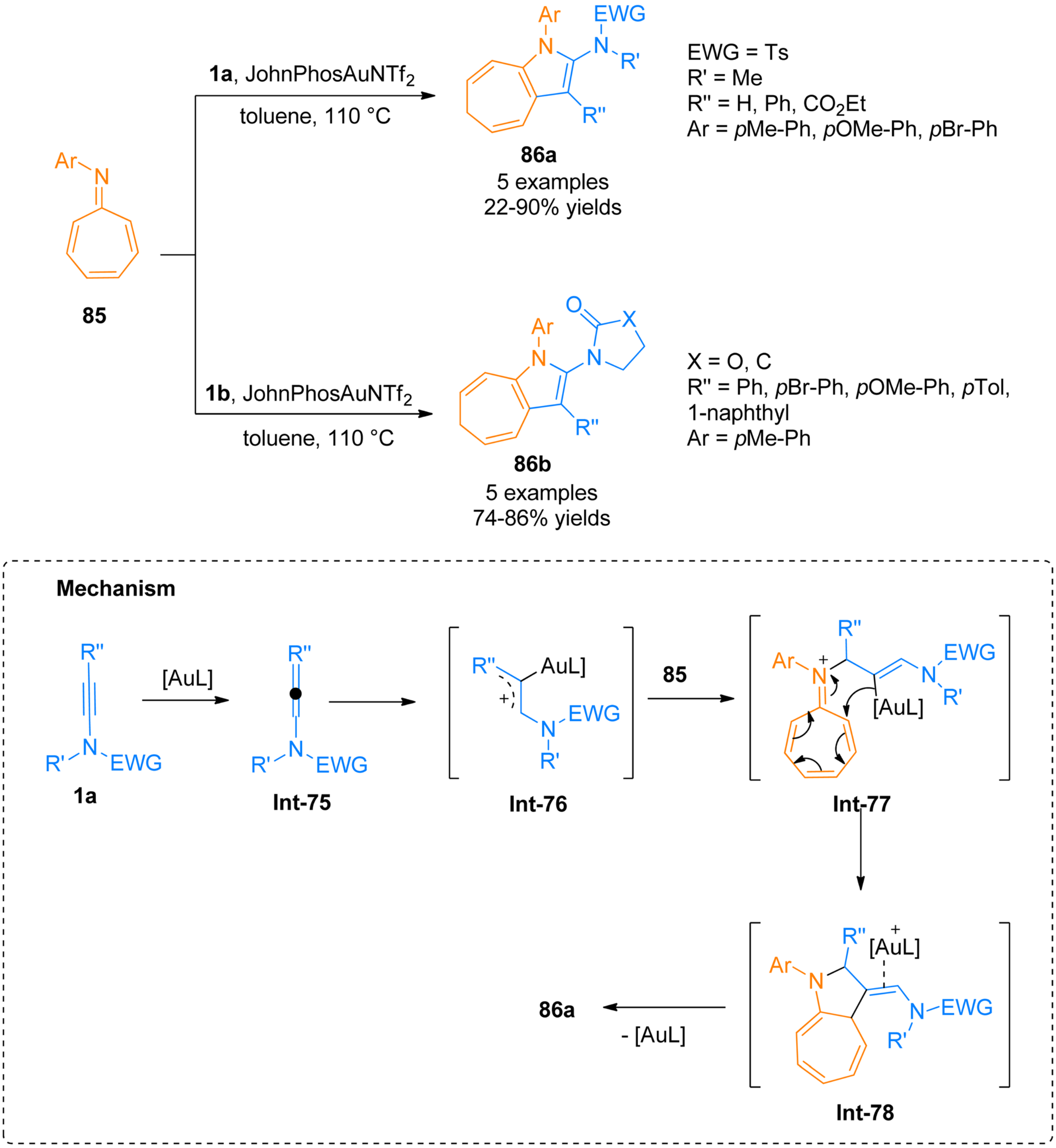
Scheme 40 Synthesis of 4*H*-azepines **84** *via* [4 + 3]-cycloaddition of ynamides **1s** and substituted isoxazoles **83**.

in situ generated gold stabilized 3-azaheptatrienyl cation **Int-74** to access 4*H*-azepines. The developed methodology employed a range of ynamides and substituted isoxazoles to afford the products in a favorable yield range using IPrAuCl/AgNTf$_2$ (10 mol%) catalyst and dichloroethane solvent at 70 °C (23 examples, 16–91% yields). Among the synthesized series compound **84** was afforded in 90% yield by [4 + 3]-cycloaddition of ynamide **1s** and functionalized isoxazole **83** (Scheme 40). The reaction could be extended to construct other valuable scaffolds such as highly substituted pyridine derivatives using Zn(OTf)$_2$.[70]

2.6. [8 + 2]-cycloaddition

2.6.1. Synthesis of cycloheptapyrroles *via* [8 + 2]-cycloaddition.

High-order cyclization reactions are useful tools for the construction of medium sized rings. 8-Azaheptafulvenes is the most reliable partner to undergo the [8 + *n*]-cycloaddition reaction, more specifically the [8 + 2]-cycloaddition reaction provided an efficient route to access cycloheptapyrrole core that is pervasive in several bioactive compounds. [8 + 2]-cycloaddition of 8-azaheptafulvenes is of considerable interest



Scheme 41 Synthesis of 2-amido-1,4-dihydrocycloheptapyrroles **86a**/**86b** *via* [8 + 2]-cycloaddition of ynamides **1a** and **1b** with 8-aryl-8-azaheptafulvenes **85**, respectively.

to yield *in situ* generated intermediates[88–90] and to achieve high enantioselectivity.[91] Rodríguez *et al.* (2021), described [8 + 2]-cycloaddition reaction of ynamides **1a**/**1b** and azaheptafulvenes **85** to furnish 2-amido-1,4-dihydrocycloheptapyrroles **86a**/**86b** in a regioselective manner. This transformation was carried out using gold catalyst JohnPhos $AuNTf_2$ (5 mol%), and toluene solvent at 110 °C (Scheme 41). The reaction mechanism involves the initiation with the construction of electrophilic intermediate **Int-75** and **Int-76** by the coordination of gold-cation intermediate to triple bond of ynamide **1a**, followed by nucleophilic attack of 8-azaheptafulvene **85** to generate **Int-77**. The subsequent cyclization of **Int-77** afforded **Int-78** that undergo elimination of gold catalyst to realize the target products **86a** (5 examples, 22–90% yields) and **86b** (5 examples, 74–86% yields).[92]

2.7. [2 + 2 + 1]-cycloaddition

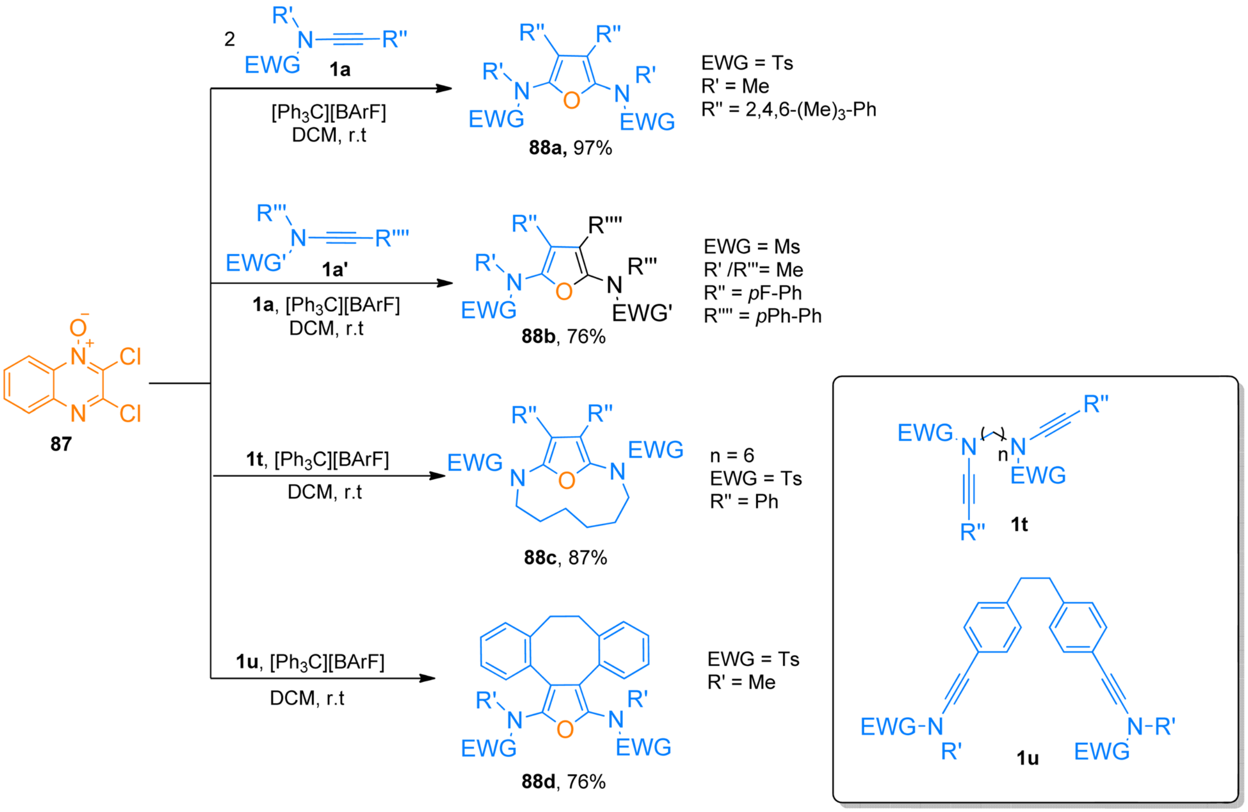
2.7.1. Synthesis of furans *via* [2 + 2 + 1]-cycloaddition.

Jin *et al.* (2019), described trityl promoted oxidative [2 + 2 + 1]-cycloaddition of ynamides and quinoxaline *N*-oxide to construct highly substituted furan rings. This facile and convergent methodology with mild reaction conditions yielded symmetric as well as unsymmetric products (28 examples, 60–97% yields). The reaction mechanism involves the activation of the alkyne core using carbocation catalyst $[Ph_3C][BArF]$ (2 mol%) and dichloromethane solvent at room temperature. While the quinoxaline *N*-oxide prevented the over-oxidation of ynamides. The quinoxaline *N*-oxide **87** underwent cycloaddition with two equivalents of ynamide **1a** to afford the furan derivative **88a** with the highest yield of 97%. While to access **88b** (76%) two different ynamides **1a** and **1a′** were involved in cycloaddition with **87**. The methodology also works for intramolecular macrocyclization of di-ynamides to realize macro-cyclic furan frameworks (9 examples, 20–87% yield). The macrocyclic products **88c** (87%) and **88d** (76%) were furnished by cycloaddition of **87** with di-ynamides **1t** and **1u**, respectively (Scheme 42).[93]

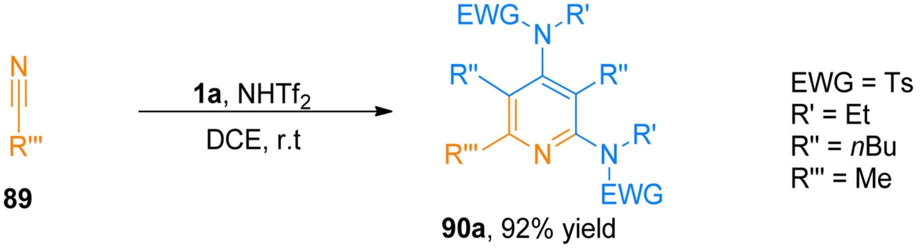
2.8. [2 + 2 + 2]-cycloaddition

2.8.1. Synthesis of pyridines *via* [2 + 2 + 2]-cycloaddition.

The construction of 2,4-diaminopyridine frameworks using a low-valent metal catalyst is a challenging task.[94,95] Wang *et al.* (2016), disclosed a novel synthetic route to access highly substituted pyridines by following a metal-free, $HNTf_2$ (10 mol%) promoted [2 + 2 + 2]-cycloaddition of ynamide and nitrile using dichloroethane solvent under nitrogen atmosphere at room temperature. Brønsted acid-catalyzed mild intermolecular cycloisomerization reaction sequence proceeded to achieve fully substituted pyridines because of the low nucleophilicity of the counter ion NTf_2. The reaction sequence offered complementary excellent chemoselectivity as compared to gold-catalyzed synthesis and high regioselectivity (28 examples, 63–92% yields). Among the synthesized series the product, **90a** was



Scheme 42 Synthesis of highly substituted furan rings **88a–b** and macro-cyclic furan derivatives **88c–d** *via* [2 + 2 + 1]-cycloaddition of ynamides **1a**, **1a′**, **1t**, and **1u** with 2,3-dichloroquinoxaline-*N*-oxide **87**.



90a, 92% yield

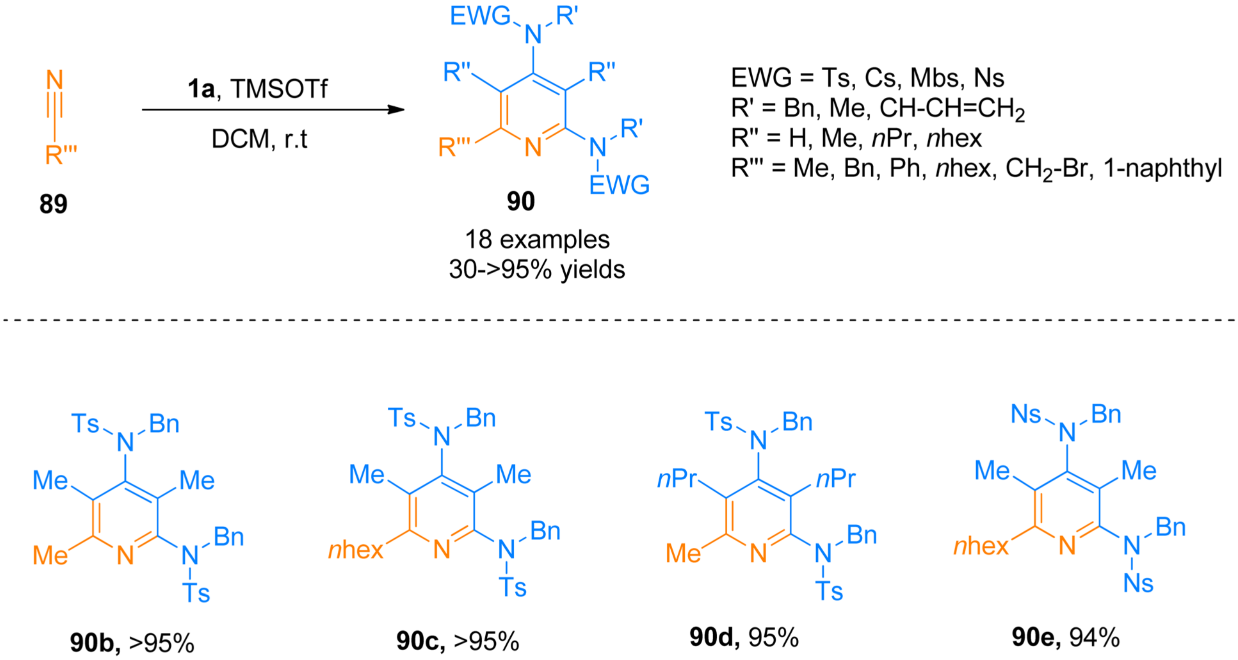
Scheme 43 Synthesis of 2,4-diaminopyridines **90a** *via* [2 + 2 + 2]-cycloaddition of ynamide **1a** with substituted nitrile **89**.

achieved with the highest yield of 92% by HNTf$_2$-catalysed cycloaddition reaction of ynamide **1a** and nitrile **89** (Scheme 43).[96]

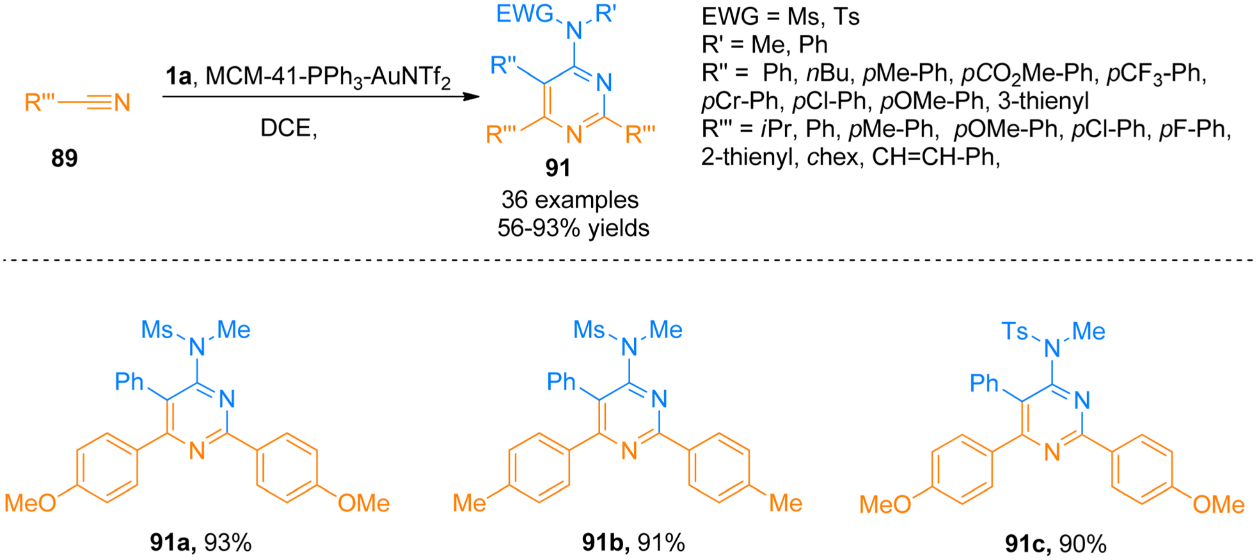
Similarly, Zhang *et al.* (2016), presented [2 + 2 + 2]-cycloaddition reaction of ynamides that provided a metal-free and straightforward route to afford 2,4-diaminopyridines. This novel protocol allowed the concomitant construction of carbon–carbon as well as the carbon–nitrogen bond between ynamide **1a** and nitrile **89**. The developed reaction exhibited moderate substrate scope, and afforded products with excellent chemo-selectivity, and high regioselectivity (18 examples, 30 to >95% yields). Developed transformation offers facile access to **90** by TMSOTf (0.5 equiv.) catalyzed cycloaddition reaction of ynamide **1a** and nitrile **89** using dichloromethane at room temperature (Scheme 44).[97]

2.8.2. Synthesis of pyrimidines *via* [2 + 2 + 2]-cycloaddition. 4-Aminopyrimidines are biologically active scaffolds that have considerable importance in pharmaceutical chemistry. These scaffolds are biologically active cores in numerous natural, pharmaceutical and agrochemical products. Moreover, these cores also serve as precursors to realizing the construction of versatile products. Previously reported intermolecular [2 + 2 + 2]-cycloaddition reactions of alkyne with nitriles promoted by metal catalysts were limited to the synthesis of pyridines only rather than pyrimidines.[98,99] Karad and Liu (2014), for the first time, described an intermolecular [2 + 2 + 2]-cycloaddition between ynamides and two discrete nitriles to construct monomeric 4-aminopyrimidines (27 products with 45–93% yields).[98] One of the drawbacks of the developed transformation realizing the synthesis of 4-aminopyrimidines was the use of expensive catalysts. To overcome this problem, a metal-free TfOH-mediated [2 + 2 + 2]-cycloaddition was designed and realized by Chen *et al.* (2016) (32 examples, 36–97% yields).[100]

Further, Liu *et al.* (2018), developed a highly efficient novel [2 + 2 + 2] annulation reaction between ynamide **1a** and nitriles that provided a general and powerful tool to access a variety of tetra-substituted pyrimidines or monomeric amino-pyrimidines. This reaction presented the first reported example of gold(I) promoted cycloaddition for the synthesis of pyrimidines **91** using mild conditions that presented an alternative to classical synthetic transformations. The presented atom economical protocol afforded the product **91** (36 examples, 56–



Scheme 44 Synthesis of 2,4-diaminopyridines **90** *via* [2 + 2 + 2]-cycloaddition of ynamides **1a** with substituted nitrile **89**.



Scheme 45 Synthesis of substituted pyrimidines **91** by [2 + 2 + 2] cycloaddition of substituted nitrile **89** and ynamide **1a**.

93% yields) using MCM-41-immobilized phosphine gold(I) complex (MCM-41-PPh$_3$-AuNTf$_2$, 5 mol%) catalyst, mild reaction conditions (80 or 30 °C), and dichloroethane. The gold catalyst used in this annulation reaction is recoverable and reusable for up to 8 runs without any substantial loss of catalytic activity. The developed methodology is tolerant to a range of functional groups yielding a wide variety of tetrasubstituted pyrimidines (Scheme 45).[101]

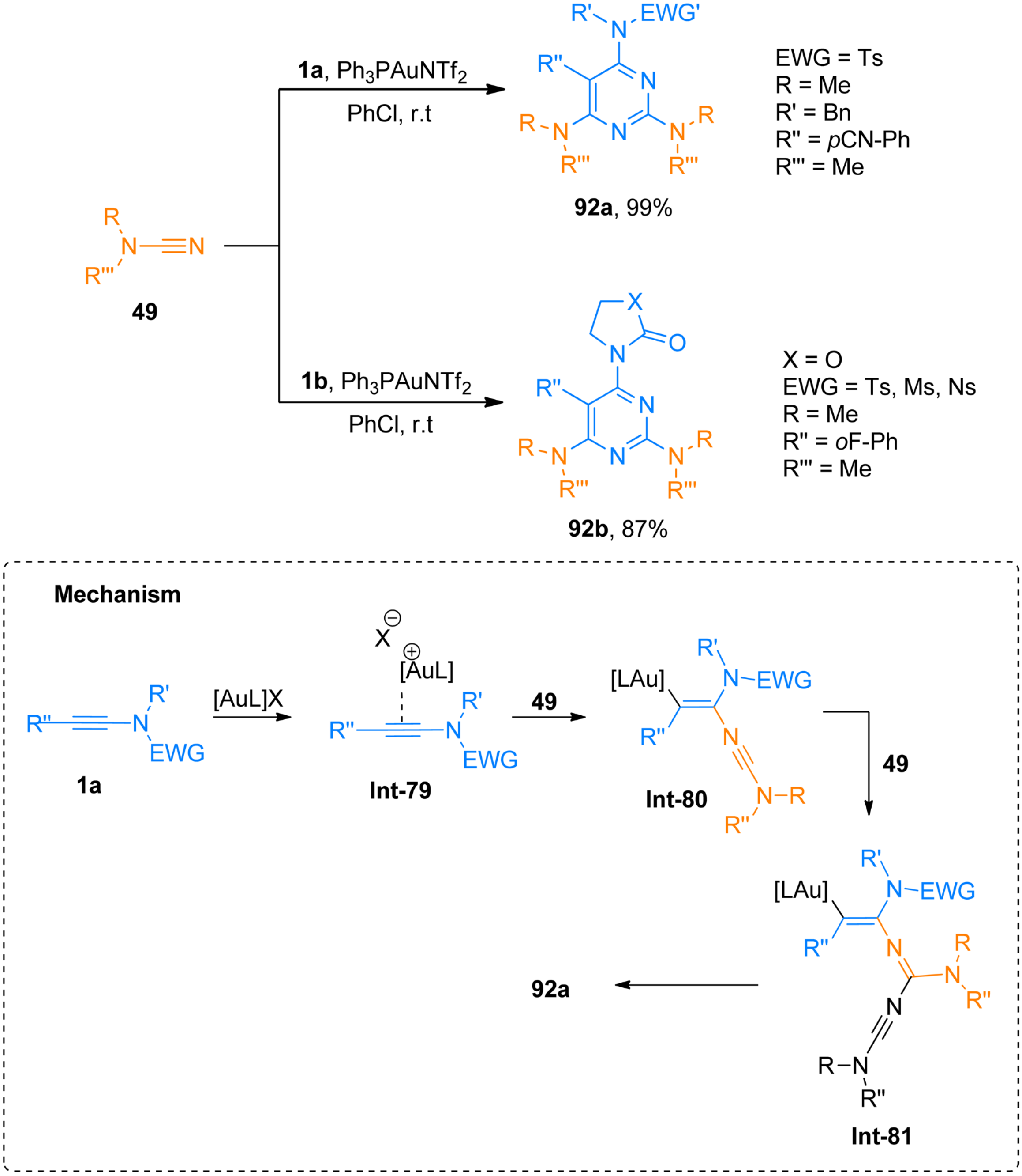
Theoretical and computational studies with the help of DFT calculations were undertaken by Liang *et al.* (2016), on the novel [2 + 2 + 2]-cycloadditions between ynamide and two nitrile species promoted by gold catalyst.[102] The reaction performed by the Liu group[101] was taken as a model reaction in which ynamide **1a** and nitrile underwent cycloaddition to afford 4-aminopyridine using PPh$_3$Au$^+$ X$^-$ (5 mol%) (X = NTf^{2-}, SbF$_6^-$, OTf$^-$) catalysts in dichloroethane solvent at 75 °C. The study involved the explanation of the possible mechanism involved in transformation and the part that the electron withdrawing group attached to N of ynamide **1a** plays in the reaction. The study confirmed that gold-ynamide species **1a** induced dimerization of two nitriles to construct the target product while the catalyst alone was unable to do so. The EWG attached to the N of alkyne resulted in the stabilization of the electron pair on the nitrogen atom while the electron-donating group did not favor the reaction. The study provided a comprehensive understanding of the catalytic [2 + 2 + 2]-cycloaddition reaction that may be helpful for the design of further reactions.[102]

Dubovtsev *et al.* (2020), described the interaction between ynamide and cyanamide reaction during a gold catalyzed cycloaddition that demonstrated condition-dependent mechanistic selectivity. The [2 + 2 + 2]-cycloaddition proceeded *via* formation of **Int-79** to **Int-81** using kinetically controlled conditions of Ph$_3$PAuNTf$_2$ (5 mol%) catalyst and PhCl at room temperature to afford 2,4,6-triaminopyrimidines (19 examples, 35–99% yields). The methodology was well-tolerated by a range of substrates and dialkyl, diaryl, and heterocyclic amino-functional groups could be incorporated into the target pyrimidine framework. The developed methodology offers the advantages of mild reaction conditions, regioselectivities, and versatile products *via* post-functionalization. Among the synthesized series, the compounds **92a** and **92b** were obtained in the highest yields of 99% and 87% *via* the cycloaddition of cyanamide **49** with **1a** and **1b**, respectively (Scheme 46).[61]

2.8.3. Synthesis of 2-amino-α-carbolines. Zhang *et al.* (2019), presented a [2 + 2 + 2]-cycloaddition of ynamides with alkyne-cyanamides and ynamide-nitriles in the metal-free environment to yield amino substituted α-carbolines and δ-carbolines, respectively. The developed efficient methodology provided an environment-friendly synthetic route with wide functional group compatibility for the highly regioselective construction of carboline derivatives in a promising yield range. This TMSOTf (0.2 equiv.) catalyzed cycloaddition reaction in dichloromethane at room temperature is the first method to realize the synthesis of 2-amino-α-carbolines (26 examples, 35–99% yields) and 3-amino-δ-carbolines (27 examples, 40–99% yields) *via* cycloaddition. Among the series of 2-amino-α-carbolines, compound **94** was accessed in 99% yield by cycloaddition of ynamide **1a** and alkyne-cyanamide **93.** While from the series of 3-amino-δ-carbolines, compound **96** obtained in 99% yield *via* cycloaddition of ynamide **1a** and ynamide-nitrile **95** (Scheme 47).[103]

2.9. [5 + 1] and [5 + 2]-cycloaddition

2.9.1. Synthesis of oxazines and oxazepines *via* [5 + 1] and [5 + 2]-cycloadditions. Jadhav *et al.* (2018), described gold-catalyzed ligand controlled chemoselective [5 + 1] and [5 + 2] annulation reactions between ynamides **1a** and 1,2-benzisoxazoles **97**. Using **L1**-AuCl/AgNTf$_2$ catalyst (5 mol%) using dichloroethane solvent at room temperature, aryl-substituted ynamides **1a** underwent [5 + 1]-cycloaddition reaction and

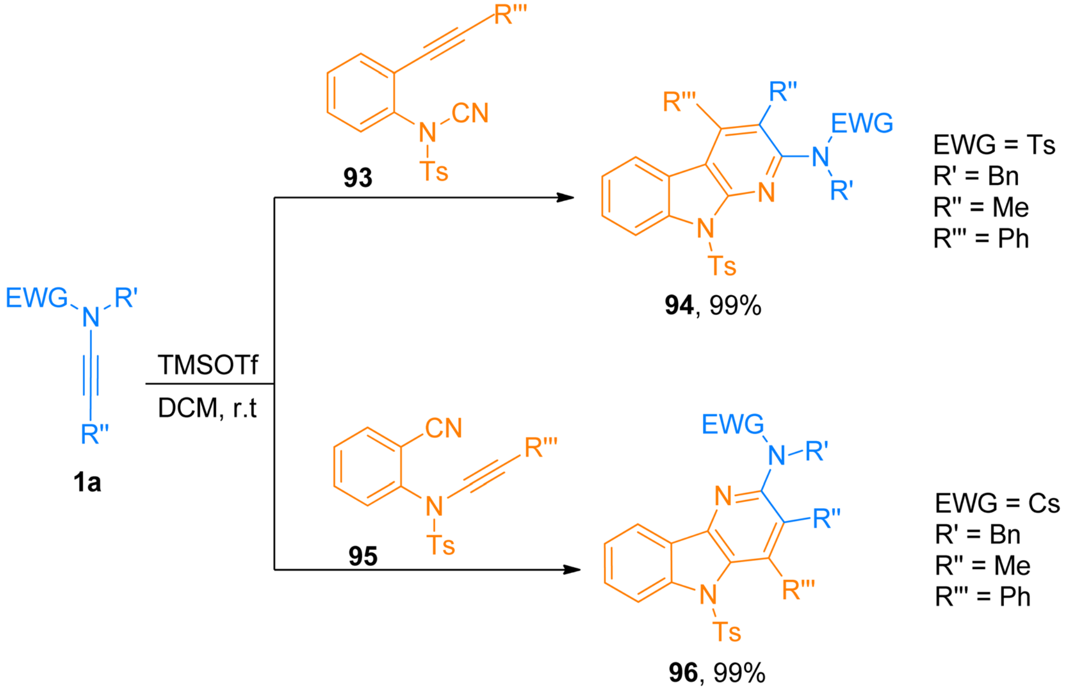


Scheme 46 Synthesis of 2,4,6-triaminopyrimidines **92a** and **92b** *via* [2 + 2 + 2]-cycloaddition of cyanamides **49** and ynamides **1a** and **1b**, respectively.

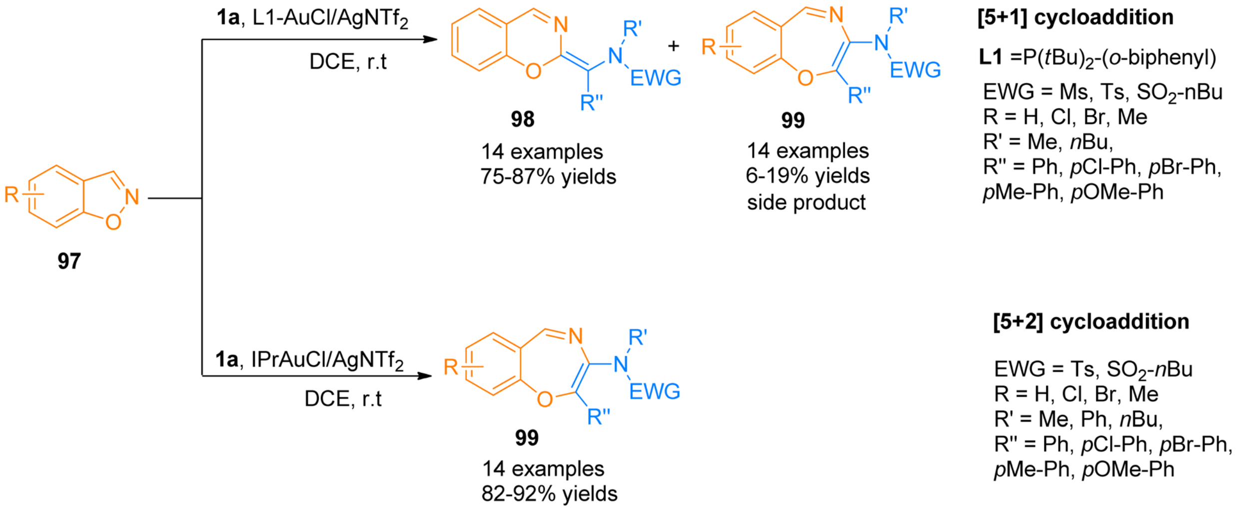
yielded six-membered heterocycles **98** as the major products (14 examples, 75–87% yields) along with seven-membered heterocycles **99** as side products. While the chemoselectivity could be switched to [5 + 2]-cycloaddition reaction by using IPrAuCl/AgNTf$_2$ (5 mol%) catalyst and dichloroethane solvent at room temperature to yield benzo[*f*][1,4]oxazepines **99** (14 examples, 82–92% yields) (Scheme 48). However, for some of the ynamides, chemoselectivity remained unaffected by the change in the gold catalyst. The suggested mechanism for the reaction involves the construction of a common intermediate that underwent two distinct types of *N*–*O* cleavage to afford gold carbenes that yielded final products either by [5 + 1] or [5 + 2]-cycloaddition reaction.[104]

2.10. [5 + 2 + 1]-cycloaddition

2.10.1. Synthesis of oxygen-bridged tetrahydro-1,4-oxazepines *via* [5 + 2 + 1]-cycloaddition. Zhao *et al.* (2018), presented [5 + 2 + 1]-cycloaddition of ynamides, isoxazoles, and water catalyzed by Brønsted acid that yielded oxygen-bridged tetrahydro-1,4-oxazepine derivatives. The Tf$_2$NH (15 mol%)



Scheme 47 Synthesis of 2-aminocarbolines **94** and 3-aminocarbolines **96** *via* [2 + 2 + 2]-cycloaddition of ynamide **1a** with alkyne-cyanamide **93** or ynamide-nitrile **95**.

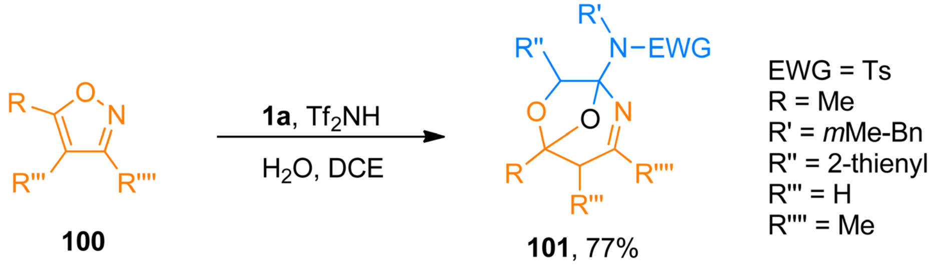


Scheme 48 Synthesis of six-membered heterocycles **98** and seven-membered heterocycles **99** *via* [5 + 1] and [5 + 2]-cycloaddition of ynamide **1a** and 1,2-benzisoxazole **97**.

catalyzed transformation provides an atom economical synthesis of the oxygen-bridged cycloadducts with distinct selectivity than gold-catalyzed reactions using H_2O and dichloroethane solvent at −10 °C or −20 °C. The oxygen of the bridge originates from water. The reaction exhibited good substrate scope with promising yields (27 examples, 40–77% yields). Among the series of oxygen-bridged tetrahydro-1,4-oxazepines, this novel protocol provided access to product **101** (77% yield) by [5 + 2 + 1]-cycloaddition of ynamide **1a**, isoxazole **100**, and water (Scheme 49).[105]

2.11. Sydnone alkyne cycloaddition

2.11.1. Synthesis of pyrazoles *via* sydnone alkyne cycloaddition. Sydnones are one of the most important scaffolds belonging to meso-ionic heteroaromatic compounds that take part as 1,3 dipoles during cycloaddition with alkynes.[106,107] Such cycloaddition reactions require electron-deficient dienophiles, high temperature, and long reaction time for better yields, however, the regioselectivity of the pyrazole products usually depends on precursors.[108] Wezeman *et al.* (2017) reported improved sydnone-alkyne cycloaddition with significant



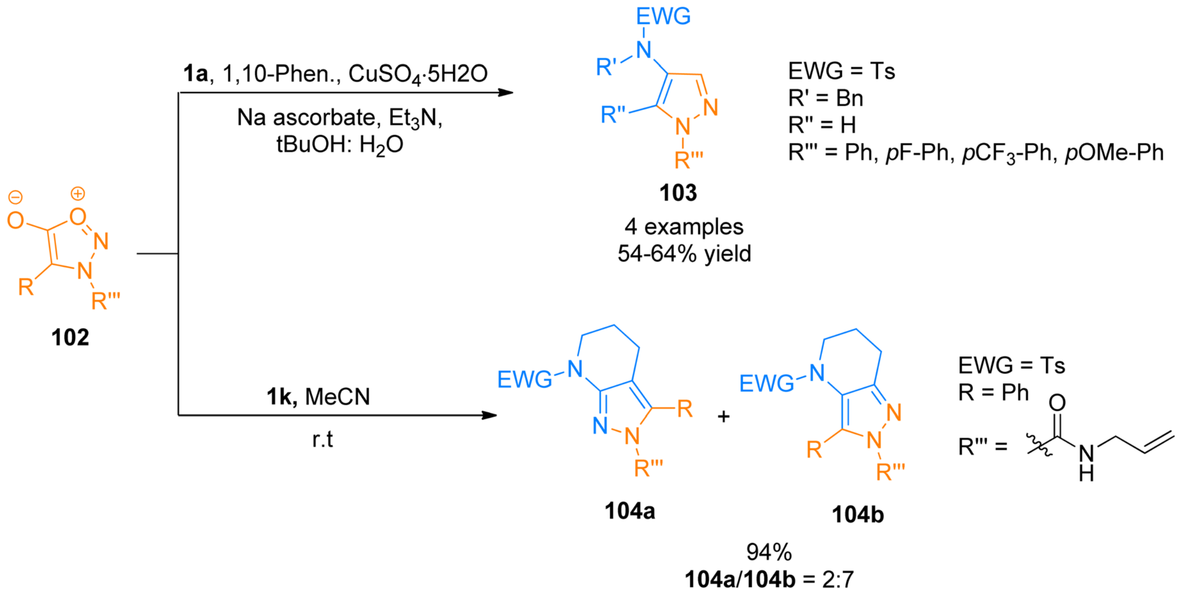
Scheme 49 Synthesis of tetrahydro-1,4-oxazepine derivatives **101** *via* [5 + 2 + 1]-cycloaddition of ynamide **1a**, and isoxazole **100**.

substrate scope and functional group tolerance. 4-Aminopyrazoles **103** (4 examples, 54–64% yield) were accessed *via* copper-mediated cycloaddition of aliphatic ynamides **1a** and sydnones **102** using $CuSO_4 \cdot 5H_2O$, 1,10-phenanthroline, sodium ascorbate, Et_3N, and *t*BuOH : H_2O (1 : 1). Moreover, a mixture of 4,5,6,7-tetrahydro-2*H*-pyrazolo[*x*,*y*-*b*]pyridine isomers was accessed from the reaction of sydnones with strained ynamide **1k** *via* copper-free sydnone alkyne cycloaddition in acetonitrile solvent at room temperature (8 examples, 47–94% yields). Strained ynamides **1k** generated *in situ via* reaction of *N*-Ts-azacyclohexyne with CsF. The isomers products **104a** and **104b** were afforded by strain-promoted *in situ* generated ynamide **1k** and syndone **102** in 2 : 7 with an overall yield of 94% (Scheme 50).[109]

2.12. Applications

2.12.1. Synthetic applications. During the last decade, extensive work on ynamides revealed their attractive synthetic features and broad application spectrum that considerably stimulated the development of the asymmetric synthesis of N-heterocycles.[110–118] In addition to this, the synthetic applications of the developed methodologies for the total synthesis of natural products with biological and optoelectronic properties have been achieved.[119–121] Further the application of the transformations could be extended for the synthesis of biologically active and pharmaceutical molecules *via* late-stage functionalization.[52,56,64,98,100,130]

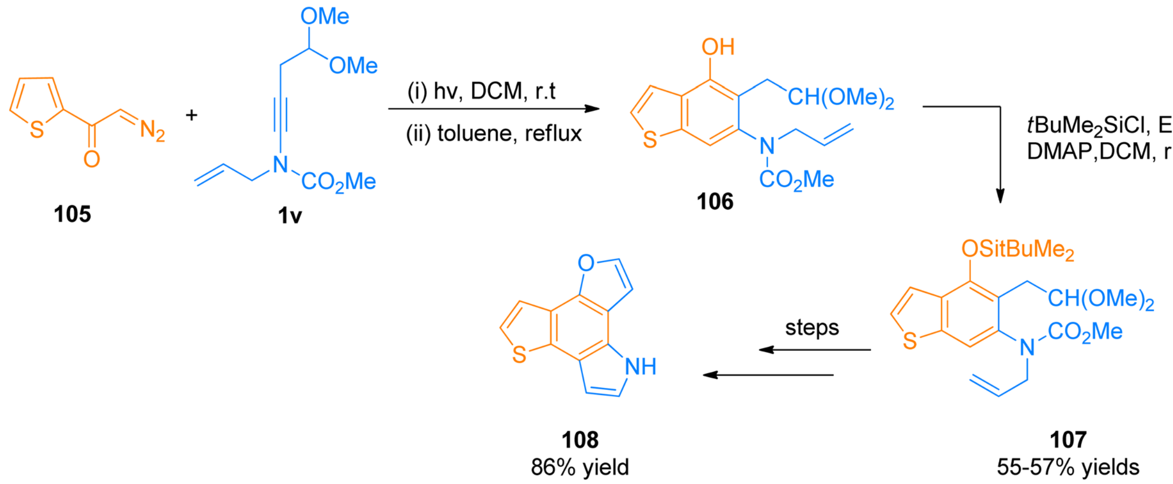
2.12.1.1. Total synthesis of furo[2,3-g]thieno[2,3-e]indole (FTI). Synthesis of FTI containing tetracyclic system was carried out by Forneris *et al.* (2018). Photochemically induced benzannulation of ynamide and α-diazo ketone afforded functionalized benzothiophene that acts as a building block for the construction of N and O-containing heterocyclic rings. The powerful methodology involved the *in situ* realization of vinyl ketene intermediate by the electrocyclic ring opening or photochemical Wolff rearrangement of cyclobutenone or α-diazo ketone precursor, respectively. The benzannulation sequence includes four discrete pericyclic reactions. Vinyl ketene intermediate reacted with highly substituted benzene in a regioselective [2 + 2]-cycloaddition, 4π-electron electrocyclic ring-opening, and 6π-electrocyclization manner to afford vinylcyclobutenone intermediate, dienylketene intermediate, and tetracyclic aromatic benzannulation product respectively.[122]



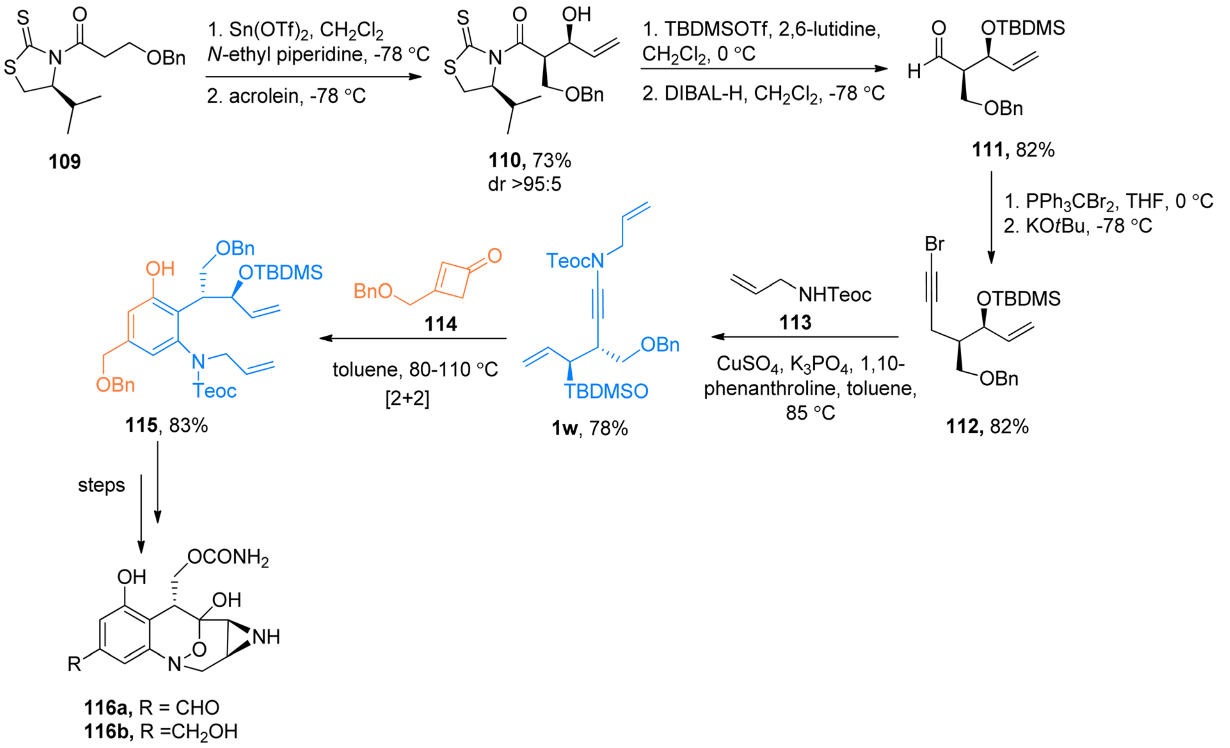
Scheme 50 Synthesis of 4-aminopyrazoles **103** and 4,5,6,7-tetrahydro-2*H*-pyrazolo[*x*,*y*-*b*]pyridine **104a** and **104b** *via* sydnone-alkyne cycloaddition of aliphatic ynamides **1a** and **1k** with sydnones **102**.

The synthetic transformation involves the benzannulation of ynamide **1v** and diazo ketone **105** *via* regioselective [2 + 2]-cycloaddition, 4π-electron electrocyclic ring-opening, and 6π-electrocyclization reaction sequence in two steps. The reaction was carried out by irradiation of the degassed solution in dichloromethane at room temperature followed by reflux in toluene as solvent. The benzannulation product **106** was subjected to column chromatography for purification before the next reaction. In the next step, the phenolic hydroxyl group of compound **106** underwent protection by TBDMS using $t\text{BuMe}_2\text{SiCl}$, Et_3N, 4-DMAP, and dichloromethane solvent at room temperature to furnish silyl ether derivative **107** in 55–57% overall yield starting from **106.** Further, the colorless FTI **108** was afforded by passing through several steps such as oxidative cleavage *via* modified Lemieux-Johnson conditions, deprotection of silyl ethers, and one-pot double cyclization (Scheme 51).[122]

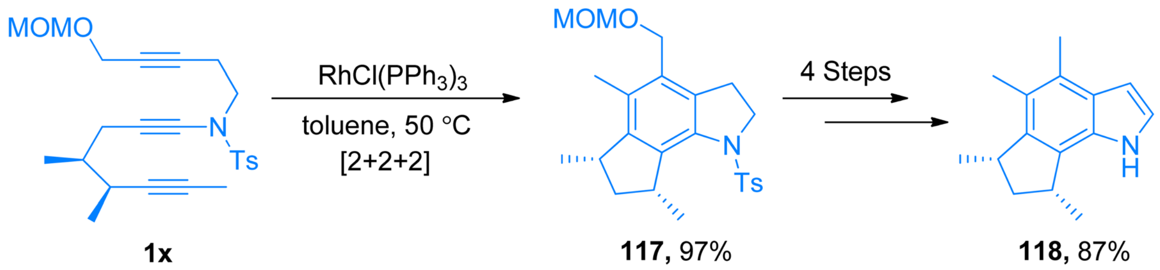
2.12.1.2. *Total synthesis of anticancer agents (+)-FR66979 and (+)-FR900482.* Mak *et al.* (2011) carried out the total synthesis of benzo-fused N-heterocycles **116a** and **116b** with anticancer activities *via* the benzannulation strategy. The ynamide intermediate **1w** was synthesized in a four-step sequence starting



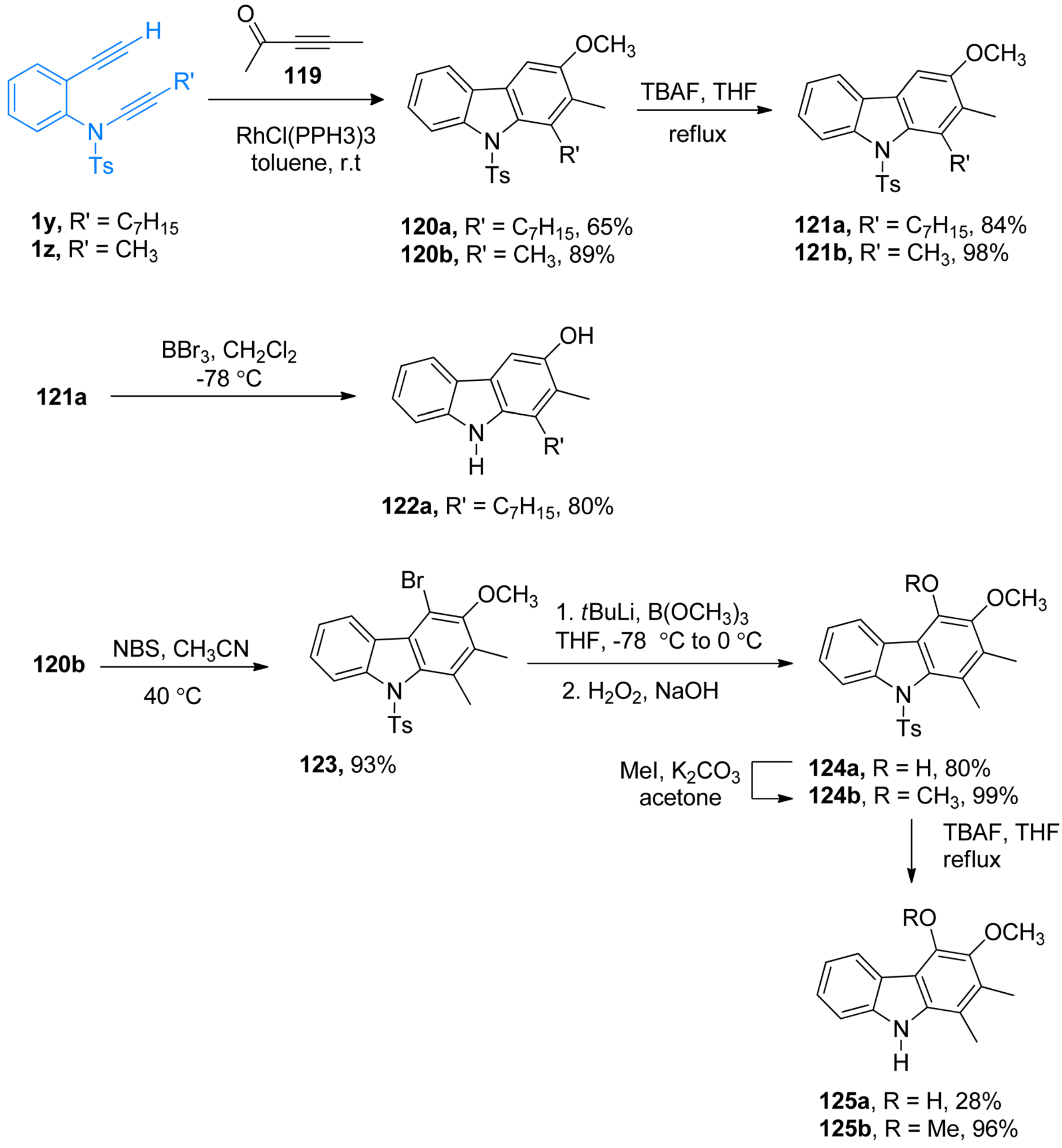
Scheme 51 Synthesis of FTI **108** *via* [2 + 2]-cycloaddition ynamide **1v** with diazo ketone **105**.



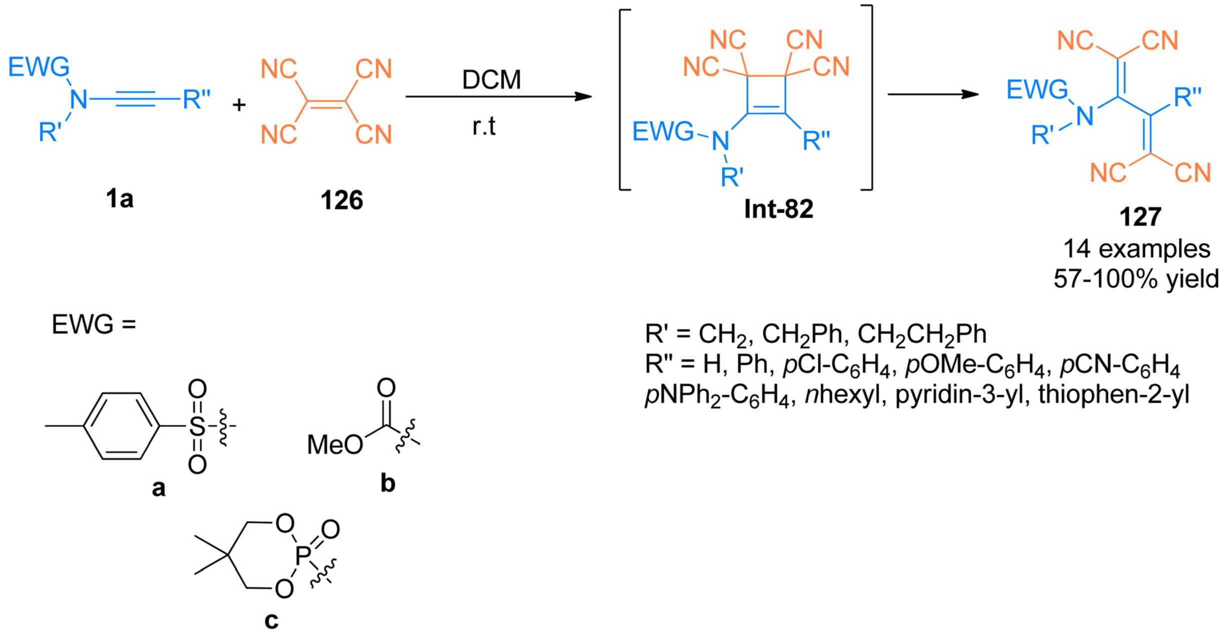
Scheme 52 The total synthesis of the anticancer agents **116a** and **116b** *via* [2 + 2]-cycloaddition of ynamide **1w** and cyclobutenone **114**.



Scheme 53 Synthesis of (−)-herbindole A **118** *via* intramolecular [2 + 2 + 2]-cycloaddition of ynamide **1x**.

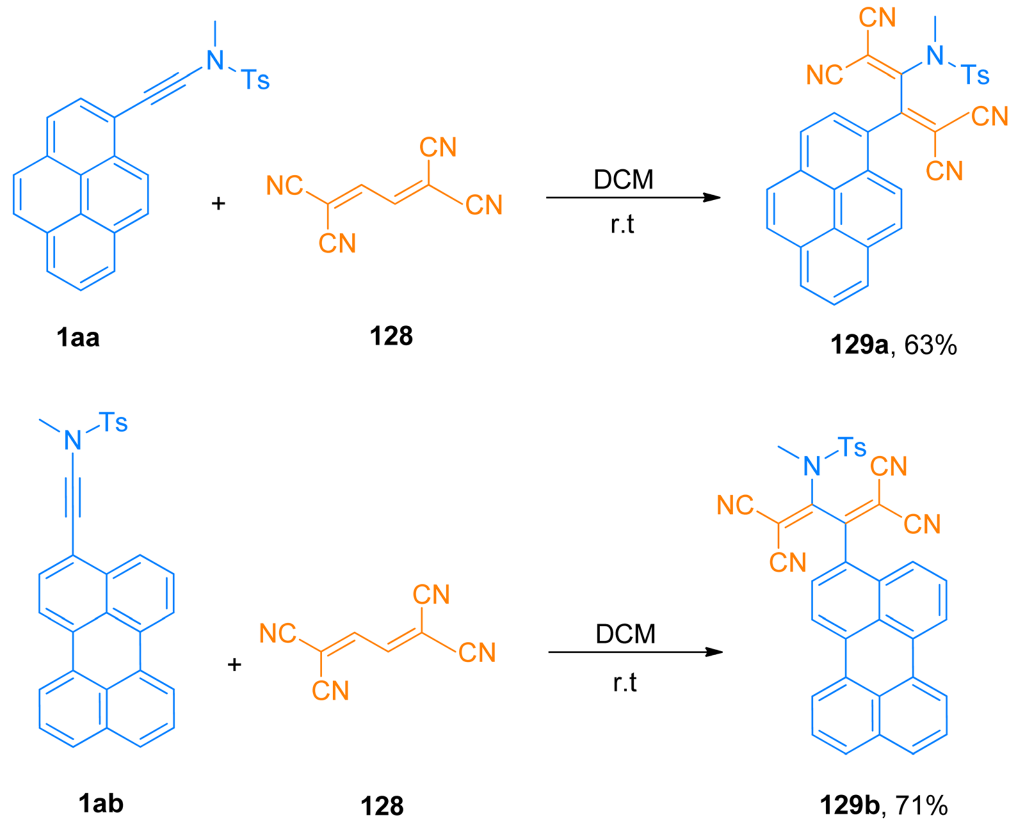


Scheme 54 Synthesis of 4-deoxycarbazomycin B **121b**, carazostatin **122a**, carbazomycin B **125a**, and carbazomycin A **125b** *via* [2 + 2 + 2] cycloaddition of ynamides **1y**/**1z**.



Scheme 55 Synthesis of tetracyanobutadiene **127** by [2 + 2]-cycloaddition of ynamide **1a** and tetracyanoethylene **126**.

from **109.** The compound **109** was derived from (*S*)-valinol in two steps. The ynamide **1w** underwent a pericyclic cascade reaction with cyclobutenone **114.** The reaction sequence involves the steps of 4π-electrocyclic ring opening, [2 + 2]-cycloaddition, and 4π-electrocyclic ring opening followed by 6π-electrocyclization to yield **115.** The compound **115** further yield anticancer agents (+)-FR66979 **116a** and (+)-FR900482 **116b** over several steps (Scheme 52).[123]



Scheme 56 Synthesis of tetracyanobutadiene derivatives **129a** and **129b** *via* [2 + 2]-cycloaddition of between pyrene/perylene substituted ynamide **1aa** and **1ab** and tetracyanobutadiene **128**, respectively.

2.12.1.3. Total synthesis of herbindoles. Saito *et al.* (2012) demonstrated the total synthesis of the herbindoles by taking the sulfonynamide **1x** as a starting material. The ynamide **1x** underwent intramolecular [2 + 2 + 2]-cycloaddition in the presence of $RhCl_3(PPh_3)_3$ catalyst at 50 °C to yield indole derivative **117** (97% yield). The indole derivative further yield (−)-herbindole A **118** (87% yield) in four steps (Scheme 53).[124]

2.12.1.4. Synthesis of 4-deoxycarbazomycin B, carazostatin, carbazomycin A/B. Alayrac and Witulski (2021) synthesized a series of natural alkaloids (4-deoxycarbazomycin B **112b**, carazostatin **112a**, carbazomycin B 125a, carbazomycin A **125b**). The key step in the transformations is the chemoselective and regioselective rhodium-catalyzed [2 + 2 + 2] cycloaddition reaction between ynamides **1y**/**1z** with 1-methoxypropyne **119**. The interplay of stereo-electronic effects allows efficient the introduction of four rings substituents in a carbazole ring within a single step (Scheme 54).[125]

2.12.1.5. Synthesis of tetracyanoethylene derivatives for optoelectronic devices. In recent years tetracyanoethylene (TCNE) and tetracyanobutadiene (TCBD) derivatives have attracted considerable interest due to their exclusive optoelectronic properties such as second and third-order linear optical response and photoluminescence in the near-infrared region.[126,127]

Previously, [2 + 2]-cycloaddition reaction between tetracyanoethylene (TCNE) and alkynyl-transition metal complexes for the synthesis of tetracyanobutadiene (TCNB) have been studied extensively.[128,129] Betou *et al.* (2014), reported a novel and efficient [2 + 2]-cycloaddition-retro electrocyclization protocol for the reaction of ynamide **1a** and tetracyanoethylene **126** to generate intermediate species **Int-82**. The species **Int-82** readily underwent ring opening to afford TCNB species **127** with excellent optoelectronic properties. The metal-free transformation was realized under mild reaction conditions. Different types of ynamides were reacted with TCNE at room temperature using dichloromethane as a solvent to attain good to quantitative yields (57–100%) of novel TCNB derivatives. This methodology could further develop novel molecules exhibiting excellent properties for their potential use in optoelectronic devices (Scheme 55).[130]

Bui *et al.* (2020), designed and constructed two tetracyanobutadinene derivatives **129a** (63% yield) and **129b** (71% yield) *via* [2 + 2]-cycloaddition followed by retrocyclization reaction of tetracyanobutadiene **128** with pyrene substituted ynamide **1aa** and perylene substituted ynamide **1ab**, respectively. The reaction proceeded using dichloromethane at room temperature (Scheme 56). Due to panchromatic absorptions, synthesized compounds exhibited Near Infrared (NIR) photoluminescence with a detectable limit of 1350 nm.[131]

3. Conclusion and future outlooks

Ynamides pioneered the recent decade with extensive research, and still, there is a surge of studies reporting improved strategies and novel methodologies involving ynamides in cycloaddition reactions. Several studies were reported in the literature with efficient and facile metal-catalyzed as well as catalyst-free transformations to form complex nitrogen-containing frameworks with excellent yields from readily available substrates. The perfect balance of stability and reactivity makes ynamides ideal substrates to carry out a wide array of synthetic transformations *via* cycloaddition. Despite the realization of a wide variety of heterocyclic paradigms, still, certain limitations and challenges need to be considered in future research.

The gold catalysts as well as the Brønsted acid catalyst promote the cycloaddition of the ynamide with other reaction partners in a quite similar manner *via* α-addition (chemoselectivity). However, inverted regioselectivity to achieve cycloadducts of high synthetic and medicinal value is highly desirable. Hence, the catalytic systems need to be further explored to achieve the β-addition. Similarly, the area of enantioselective cycloaddition of the ynamides to realize the synthesis of asymmetric products is still under development for which the catalytic systems and chiral ligands should be employed for the enantioselective realization of heterocycles/carbocycles.[132]

In addition to the above, several studies proposed the mechanism of the transformation by isotope labeling experiments, and kinetic as well as theoretical mechanistic studies that help understand the mechanistic grounds of catalytic systems during the reactions. But still, there is great room for theoretical as well as practical investigation of the reaction mechanisms to better understand the reactivity and rational design of novel routes for ynamide cycloadditions. Because some of the studies suggested mechanisms of the transformations based on the previously reported mechanism without controlled experiments and theoretical grounds for the specific reaction.

This review recapitulates the recent state-of-the-art advances in the field of cycloaddition reactions unveil the synthetic potential of ynamides and we hope that it will help readers to further explore the reactivity of ynamides for facile and efficient future strategies.

Data availability

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Author contributions

Ramsha Iftikhar: conceptualization, data collection, writing – original draft, visualization.

Aqsa Mazhar, Muhammad Saqlain Iqbal: writing – original draft, writing – review, and editing.

Faiza Zahid Khan: english proofreading, writing – review, and editing.

Syed Hassan Askary, Hifza Sibtain: writing – review, and editing.

Conflicts of interest

The authors have no conflict of interest to declare.

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