ChemInform Abstract: Propargyl Vinyl Ethers as Heteroatom-Tethered Enyne Surrogates: Diversity-Oriented Strategies for Heterocycle Synthesis

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Propargyl vinyl ethers as heteroatom-tethered enyne surrogates: diversity-oriented strategies for heterocycle synthesis

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This article presents recent progress in the conversion of propargyl vinyl ethers into heterocyclic scaffolds and how this goal can be reached in a diversity-oriented approach. The article also includes examples of transformations of propargyl vinyl ethers where the propargyl vinyl ether moieties are formed *in situ*. Furthermore, related reactions transforming propargyl vinyl amines to heterocycles are discussed.

1. Introduction

Large numbers of bioactive organic compounds are composed of heterocyclic molecules. Functionalized heterocycles are well-known to be utilized in the fields of pharmaceutical industry, food industry, nutritional products development, bio-engineering, *etc.*[1] For example, nine out of thirteen essential vitamins contain at least one heterocyclic ring. Furthermore, antitumor activities of an increasing number of small heterocyclic compounds are revealed.[2] This leads to a situation where the development of powerful and straight-forward methodologies for heterocycle syntheses is an old but still popular and ever-ongoing research area. Diversity-oriented approaches to heterocyclic compounds are particularly attractive since branching reaction pathways have potential to rapidly evolve both molecular complexity and structural diversity of products by altering the skeletal arrays.[3] To this end, a single small molecule precursor is subjected to varying reaction conditions that enable selective activation modes and, thus, lead to structurally distinct heterocyclic products.

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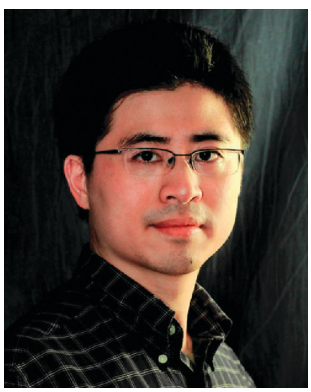

Zhi-Bin Zhu

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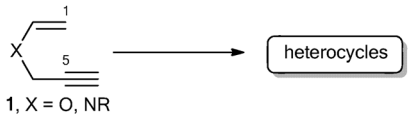
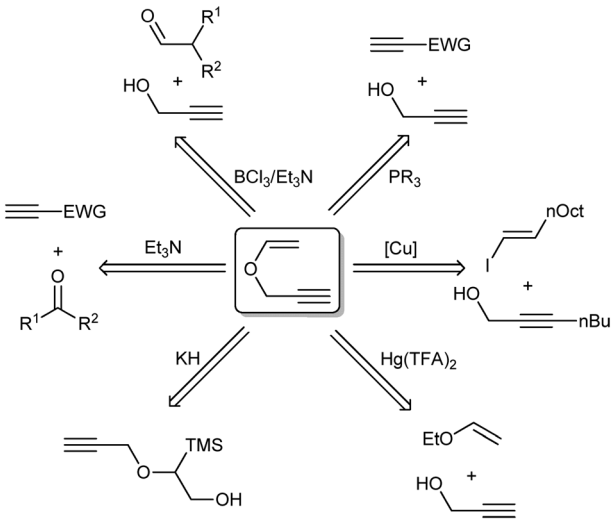


Scheme 1 Heterocycles from propargyl vinyl ethers/amines.

Currently, reactions of heteroatom-tethered enynes (or related systems) are the basis for quite powerful strategies in the field of diversity-oriented heterocycle synthesis. For instance, during the past few years, ring-closing metathesis (RCM) of enynes was widely applied to heterocyclic ring formation.[4] Moreover, following the recent trend of transition-metal-catalyzed enyne cycloisomerization reactions,[5] numerous heterocycle syntheses of great value were developed based on the cycloisomerization of heteroatom-tethered enynes. In particular, propargyl vinyl ethers and their derivatives, which are also recognized as a class of 1,5-enynes, were appreciated as starting materials in heterocycle syntheses. Depending on the reaction conditions, the choice of catalyst and/or the exact nature of the substrate, propargyl vinyl ethers can undergo cyclization reactions *via* distinct pathways through selective activation of the unsaturated system.[6] As summarized in Scheme 1, our goal is to show how propargyl vinyl ethers **1** (or their corresponding amines) have emerged as a versatile starting point for the rapid and flexible access to various heterocycles of interest. The use of propargyl aryl ethers for the synthesis of heterocycles is also discussed in a brief way. This review is not intended to be comprehensive, but from a personal perspective, it covers those features that are fundamental to control the selective generation of the desired heterocyclic scaffolds. We believe that propargyl vinyl ethers have the potential to become the universal starting material for all kinds of five- and six-membered heterocycles.

At this stage, it should be noted that the synthetic value of propargyl vinyl ethers **1** is particularly outstanding since they are readily accessed by use of a variety of simple and highly convenient methods as summarized in Scheme 2.[6] For example, triethylamine-catalyzed reaction of activated alkynes with carbonyl compounds affords poly-substituted activated propargyl vinyl ethers *via* a cascade process through propargyl alcohol intermediates.[7] The reaction of propargyl alcohols and aldehydes was also reported to be promoted by boron trichloride and trimethylamine.[8] An example of copper-catalyzed C–O bond coupling between substituted propargyl alcohols and vinyl iodides is promising to become one of the most general methods to afford propargyl vinyl ethers.[9] However, currently one of the most universal methods to obtain propargyl vinyl ethers is the simple conjugate addition of propargyl alcohols to α,β-unsaturated alkynoic acid esters by employing trialkylphosphines (or trialkylamines) as organocatalysts; this method gives rise to propargyl vinyl ethers with electron-withdrawing substituents at the vinyl side.[10] The synthesis of simple propargyl vinyl ethers with no additional substituents at the vinyl moiety typically works well when combining ethyl vinyl ethers and propargyl alcohols in the presence of Hg(II) salts.[11] Alternatively, ether formation through elimination of trimethylsilanol from 2-(prop-2-yn-1-yloxy)-2-(trimethylsilyl)ethanol was utilized.[12] Notably, analogous propargyl vinyl amines are obtained in a similar manner.[13] While this list of methods towards substituted propargyl vinyl ethers is not complete, it supports the impression that this class of compounds is easily accessed with a broad spectrum of substituents.



Scheme 2 Synthesis of propargyl vinyl ethers.

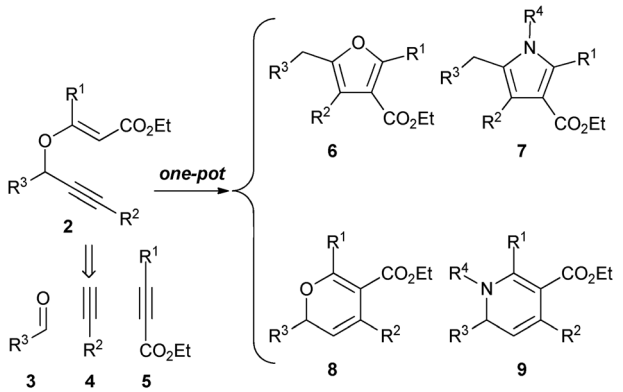
2. Propargyl vinyl ethers as starting materials

2.1 Transition-metal catalyzed reactions

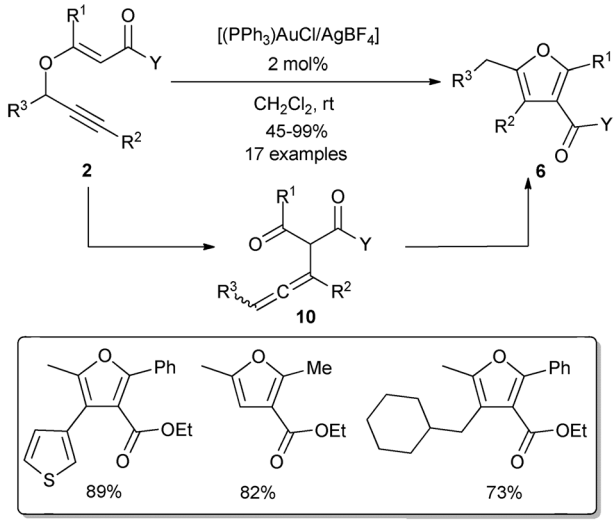
In the past decades, the transition-metal catalyzed skeletal reorganization of unsaturated frameworks has become a fantastic concept to access heterocyclic compounds. Owing to their exceptional ability to activate π-systems, and especially alkynes,[14] toward intermolecular and intramolecular nucleophilic attack, strategies involving π-activation[15] by soft noble metal cations (such as Au^{I}, Au^{III}, Ag^{I} and Pt^{II}) have found increasing popularity.[5,16] While being operationally simple and convenient to perform (in most cases, neither air nor humidity needs to be excluded), such skeletal rearrangements provide a diverse and atom-economical[17] route to functionalized heterocycles.

Recently, we presented a series of studies that were aimed to become a unified approach to five- and six-membered heterocycles. Starting from acceptor substituted propargyl vinyl ethers **2** (which are accessed from the corresponding aldehyde **3**, and alkynes **4** and **5**), highly substituted furans **6**,[18] pyrroles **7**,[19] 2*H*-pyrans **8**[20] and 1,2-dihydropyridines **9**[21] can be obtained in an efficient and diversity-oriented way by choosing specific catalysts and reactants (Scheme 3).

In 2005, we reported the first part of this series dealing with the furan synthesis.[18] Though initially a transition-metal catalyzed direct 5-*exo* cyclization of **2** was planned, it was found instead that a catalytic version of a propargyl-Claisen rearrangement[22] of **2** takes place first giving access to the

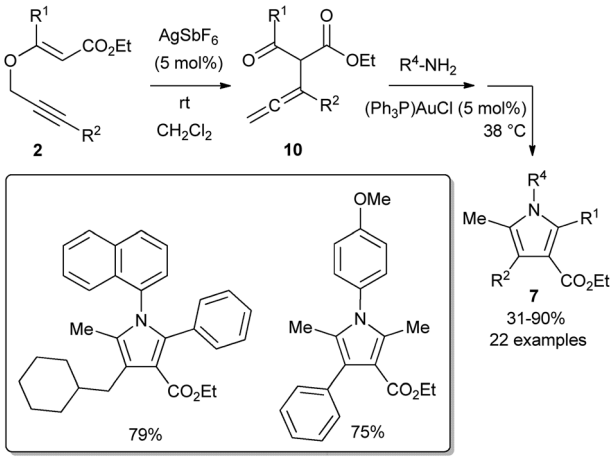


Scheme 3 Unified approach to five- and six-membered heterocycles.



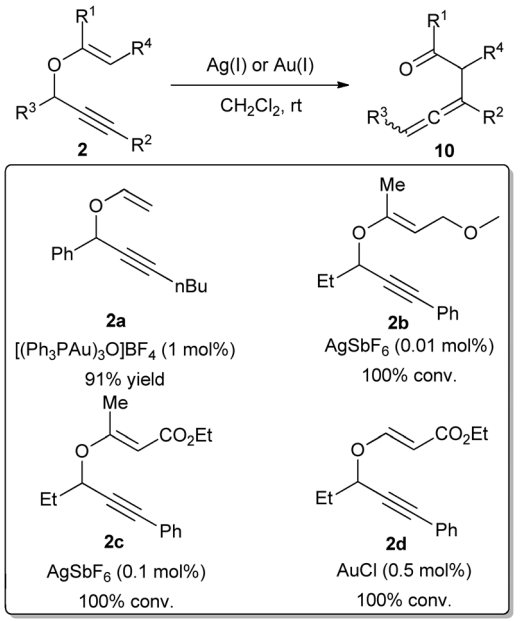
Scheme 4 Synthesis of furans **6** *via* allenylcarbonyl intermediates.

allenylcarbonyl intermediate **10** (Scheme 4). The catalyst system used for this rearrangement also promotes the cycloisomerization of **10** to tetrasubstituted furans **6**. The overall cascade proceeds at ambient temperature and under neutral conditions; typical cationic gold species such as $(PPh_3)AuCl/AgBF_4$ were found to be the most effective precatalysts to trigger both steps of the reaction cascade. $PtCl_2$ as another general alkyne activator also proved effective to promote the formation of **6**, albeit in only moderate yields. A special precaution to exclude air and moisture from the reaction mixture was not necessary. It is important to note that more acidic gold(III) complexes failed to give the desired furans in high yields, most likely due to the C–O cleavage in the propargyl vinyl ether starting materials. Several observations merit note. For example, the reaction of the *Z*-stereoisomer of propargyl vinyl ether **2** was marginally slower compared to that of the analogous *E*-isomer affording the same product. Therefore, mixtures of *E*/*Z*-stereoisomers could also be employed as starting substrates, a fact that is of particular importance since the formation of **2** from alkynoic esters **5** is high-yielding but variable with respect to stereoselectivity. The active gold species is formed *in situ* from $(PPh_3)AuCl$ and $AgBF_4$ by anion exchange.[23] While $(PPh_3)AuCl$ itself was unreactive, the use of $AgBF_4$ led to a clean rearrangement to allene **10** with no subsequent cyclization to furan **6** at room temperature (*vide infra*). A variety of acceptor substituted propargyl vinyl ethers were surveyed for this transformation. Gratifyingly, this type of gold(I)-catalyzed reaction demonstrates a remarkable functional group tolerance, and the acceptor substituents at the 3-position do not necessarily have to be esters. By utilizing this protocol, trisubstituted furans are also accessible in good to excellent yields (R^1 = H or R^2 = H). Further experiments indicated that heterocyclization forming furans with substituents other than methyl at the 5-position ($R^3 \neq H$) was slow under the influence of the standard catalyst system. As discussed below, other reaction conditions are successful to overcome this limitation by accessing these types of furans.

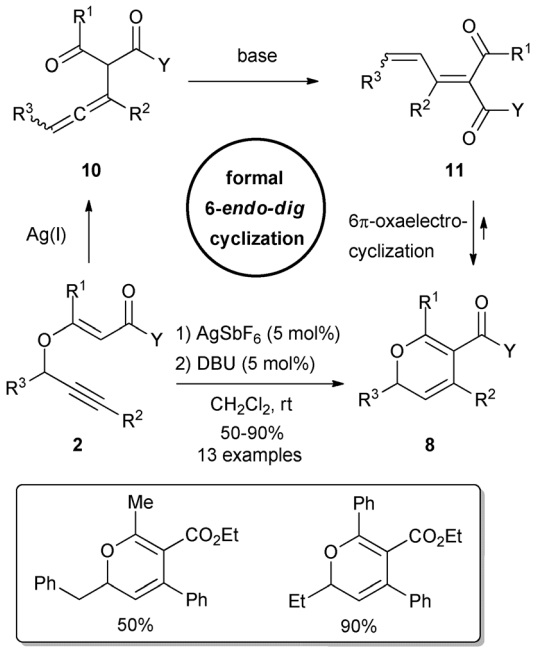


Scheme 5 Synthesis of pyrroles **7** *via* allenylcarbonyl intermediates.

In analogy to this furan synthesis, the concept of combining a catalyzed propargyl-Claisen rearrangement with a subsequent heterocyclization was then expanded to the synthesis of pyrrole derivatives **7**.[19] As shown in Scheme 5, the one-pot process starts with the propargyl-Claisen rearrangement, and, after formation of the corresponding allenylcarbonyl compound **10**, subsequent amine condensation and heterocyclization takes place to afford tetra- and pentasubstituted pyrroles **7** with high diversity in moderate to good yields. To this end, a silver(I)-catalyst, a primary amine, and a gold(I)-catalyst were added sequentially to the reaction mixture. When performing these steps simultaneously, treatment of a preformed mixture of the amine and **2** with a variety of transition-metal complexes gave only traces of the desired pyrroles **3** (<5% yield). The multi-metal-catalyzed one-pot process showed an excellent scope with regard to R^1 and R^2. Amines with R^4 being aryl and heteroaryl substituents are easily incorporated into the heterocyclic core, while the reaction with aliphatic amines (R^4 = Me, ^{i}Pr, Bn) did not provide the corresponding pyrroles **7**. As in the case of the furan synthesis discussed above, a major limitation stems from the fact that the five-membered heterocycles are produced best when the 5-position bears a methyl group. This limitation was at least partially reduced by the finding that selective IBX-oxidation of the C5-methyl group at the benzylic position of furan **6** and pyrrole **7** is possible,



Scheme 6 Allene formation by Ag(I)- and Au(I)-catalysts.



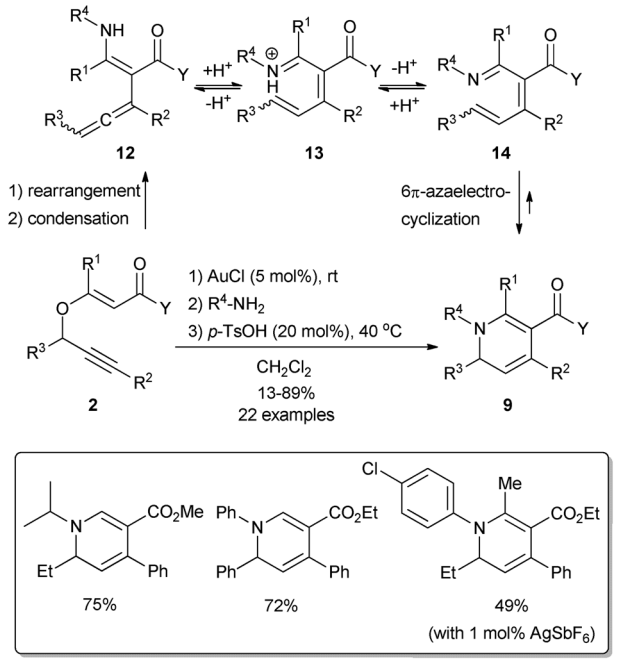
Scheme 7 Synthesis of 2*H*-pyrans **8** *via* allenylcarbonyl intermediates.

thus providing an additional aldehyde functionality at this position.[24]

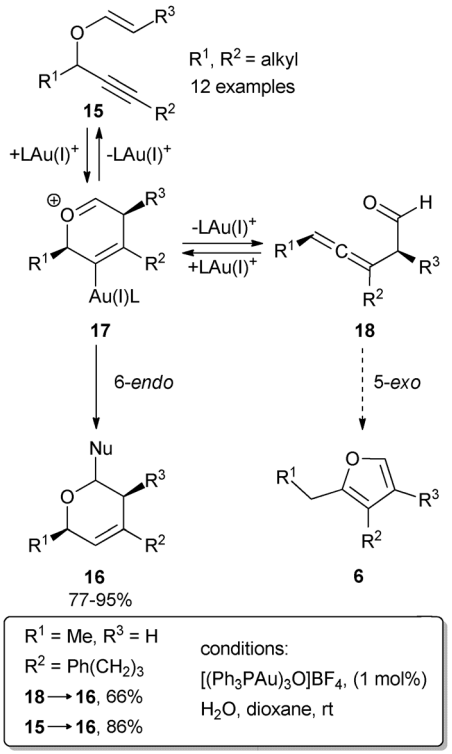
Since the catalyzed propargyl-Claisen rearrangement was key in both cascade processes, the central aspects of the catalysis of this formal [3,3]-sigmatropic rearrangement are summarized in Scheme 6. As shown in the seminal studies of Toste and Sherry, propargyl vinyl ethers with an unsubstituted vinyl moiety (*e.g.* **2a**) are rearranged best by use of the gold(I) oxo complex $[(Ph_3PAu)_3O]BF_4$; the resulting allenes are formed in outstanding yields.[22a] In the course of our studies on the catalysis of this rearrangement step, we put the focus on subtle changes in the vinylic moiety. It was found that rearrangement of propargyl vinyl ethers with donor substituents at C2 (Me: **2b** and **2c**) at room temperature produce a diastereomeric mixture of the corresponding allenes in a remarkably clean reaction if silver(I) salts are employed in catalytic amounts to promote the reaction. By far the best catalyst was $AgSbF_6$, which provided the rearrangement products rapidly in CH_2Cl_2 (without the formation of cyclization products as the corresponding furans).[18] On the other hand, AuCl as the less active gold(I) species became the better choice to promote the rearrangement of C2-unsubstituted propargyl vinyl ethers as **2d**.[21]

The catalyzed rearrangement of propargyl vinyl ethers developed into a crucial element in our attempts to access six-membered heterocycles from the very same starting materials that can be converted into furans and pyrroles. To establish a cascade sequence for the synthesis of stable 2*H*-pyran-5-carboxylates **8** from propargyl vinyl ethers **2**, a formal 6-*endo* cyclization of allenylcarbonyl intermediate **10** was obligatory. However, in our hands, transition-metal catalysis favored the competing 5-*exo* cyclization in most cases. To this end, a one-pot sequential catalyst system consisting of $AgSbF_6$ and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was adopted. Following the formation of **10** promoted by silver(I), a base-catalyzed double bond isomerization was assumed, and the sequence concludes with a 6π-electrocyclic ring-closure of 1-oxatriene intermediates **11** to give the 2*H*-pyrans **8** in 50–90% yields (Scheme 7).[20] The overall process can be considered an equivalent to a propargyl-Claisen rearrangement/6-*endo-trig* cyclization domino reaction. With regard to the double bond isomerization, DBU was found to be the most efficient catalyst among various nitrogen-containing organic bases and potassium *tert*-butoxide. Of note, the substitution pattern results in the exclusive formation of the cyclic 2*H*-pyrans **8** in most cases, without the isolation of furan **6** or acyclic oxatrienes **11**.

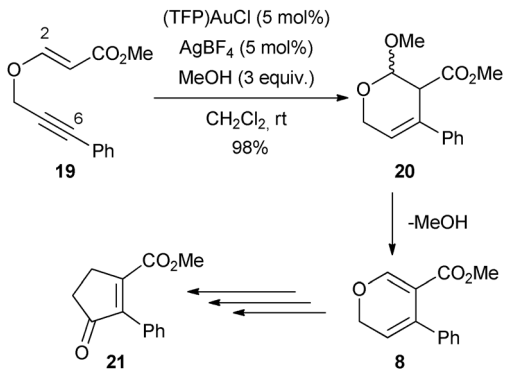
By incorporating an external amine into this formal 6-*endo-dig* cyclization, the strategy would be extended towards the synthesis of 1,2-dihydropyridines and, thus, would provide a convenient and flexible entry into the class of 6-membered nitrogen-containing heterocycles. Following this consideration, Xu *et al.* reported a highly useful sequence to 1,2-dihydropyridines catalyzed by gold- and silver-salts in 2010; therein, tosyl amide and propargyl vinyl ethers with mostly terminal alkynes were reacted.[25] Our own studies on the synthesis of 1,2-dihydropyridines **9** from propargyl vinyl ether **2** led to the finding that, while the direct 6-*endo* cyclization with transition-metal catalysts was less successful, catalytic amounts of *p*-TsOH can be utilized to ensure the heterocyclization.[21] As summarized in Scheme 8, the overall strategy towards 1,2-dihydropyridines from propargyl vinyl ethers is composed of a metal-catalyzed propargyl-Claisen rearrangement followed by a condensation step with a primary amine and subsequent tautomerization to azatriene **14** in the presence of *p*-TsOH. Formation of the heterocycle then proceeds through 6π-electrocyclization to terminate the sequence. This mechanism was supported by the observations that (i) complete loss of chirality was observed when starting with enantiopure substrates, and (ii) condensation product **12** was isolated in the absence of proton acid catalysts. Regarding the scope, both aliphatic amines and



Scheme 8 Synthesis of 1,2-dihydropyridines **9** *via* allenylcarbonyl intermediates.



Scheme 9 Gold(I)-catalyzed synthesis of dihydropyrans **16**.

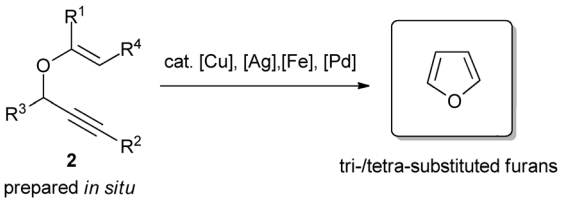


Scheme 10 Gold(I)-catalyzed synthesis of dihydropyran **20**.

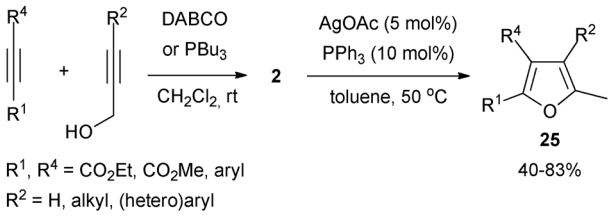
aromatic amines were efficiently incorporated into the heterocyclic core. The cyclization steps worked particularly well when propargyl vinyl ethers were subjected to the reaction conditions that do not bear additional substituents at C2 (*e.g.* R^1 = H); as discussed above (Scheme 6), AuCl was utilized to catalyze the starting sigmatropic rearrangement in an efficient manner. With propargyl vinyl ethers having a methyl group at C2, silver salts were used for the rearrangement step; however, the subsequent condensation–cyclization sequence was low-yielding in these cases.

Three important trends were set to further broaden the value of the above-discussed concept that utilizes a combination of catalyzed propargyl-Claisen rearrangement and heterocyclization to access various classes of heterocycles: (i) cationic intermediates can be trapped by nucleophiles, (ii) oxidative processes are possible through metal carbene intermediates, and (iii) propargyl vinyl ethers can be generated *in situ* through base catalysis. The effect of nucleophiles on the heterocycle formation is discussed first with the breakthrough work of Toste *et al.* on the preparation of dihydropyrans **16** from 1,3-disubstituted propargyl vinyl ether **15** (Scheme 9).[26] Simply by adding oxygen nucleophiles such as water to the gold-catalyzed reaction mixture, the ring size could be altered. Instead of furan formation, the 6-*endo* cyclization was observed using gold catalysis and wet dioxane as solvent. Dihydropyran **16** was obtained stereoselectively from allene **18** as well as from propargyl vinyl ether **15**. For both pathways promoted by $[(Ph_3PAu)_3O]BF_4$, it is assumed that product formation proceeds through cationic intermediate **17**. Moreover, stereoselective entries into spiroketals were provided by replacing water with a pendant alcohol as an intramolecular nucleophile. It should be noted that only dihydropyrans with alkyl substituents for R^1, R^2 and R^3 were accessed while the corresponding systems with aryls and heteroaryls were not investigated. By utilizing tris-2-furylphosphine (TFP) as a low σ electron-donating ligand,[27] Pour *et al.* successfully expanded the scope of the Toste protocol.[28] In the presence of methanol as an external nucleophile and (TFP)AuCl/$AgBF_4$ as a catalytic system, the cyclization of acceptor-substituted propargyl vinyl ethers **19** to the corresponding *trans*-predominated dihydropyran **20** was possible (Scheme 10). These conditions appear to be quite general for acceptor-substituted propargyl vinyl ether substrates with no additional substituent at C2, thus tolerating a range of (hetero)aryl and alkyl substituents at C4 and C6. The authors also demonstrated the further acid-promoted conversion of **20** into cyclopentenone **21** by elimination of methanol and subsequent modifications.

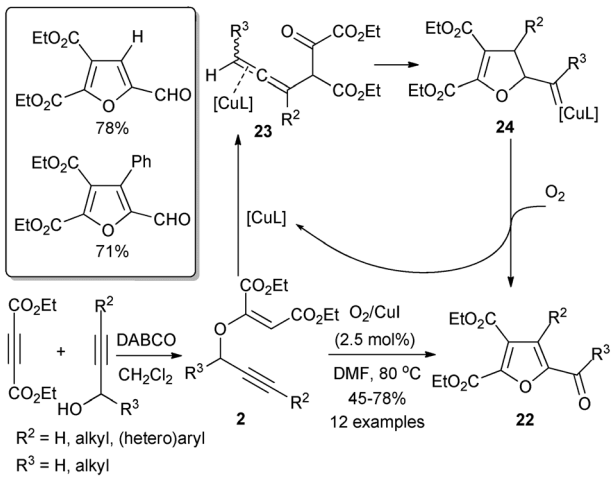
In a great series of studies, Jiang *et al.* demonstrated that, besides gold and silver catalysts, other transition-metal based



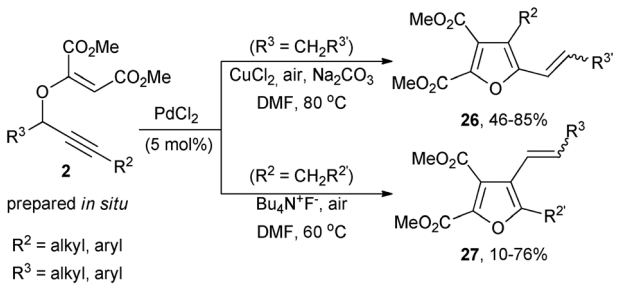
Scheme 11 Transition-metal catalyzed furan formation from propargyl vinyl ethers prepared *in situ*.



Scheme 13 Ag(I)-catalyzed formation of furans **25**.



Scheme 12 Cu(I)-catalyzed formation of furans **22** through oxidative cascades.



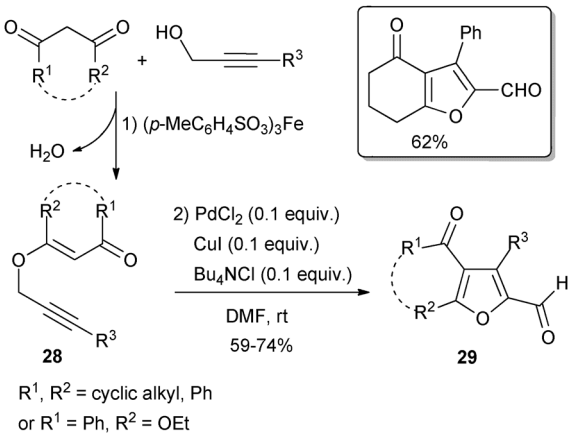
Scheme 14 Pd(II)-catalyzed furans formation from propargyl vinyl ethers.

catalysts such as copper,[29] iron,[30] silver,[31] and palladium[32] can serve in the synthesis of different tri- or tetra-substituted furans from acceptor-substituted propargyl vinyl ethers (Scheme 11). Analogous to the examples discussed above, the five-membered heterocycles are generated through a sequence of propargyl-Claisen rearrangement followed by heterocyclization. Of importance in most of these cases, propargyl vinyl ethers **2** were not employed as starting materials, instead, they were prepared *in situ* from acceptor activated alkynes and propargyl alcohols under base catalysis.

A striking example is shown in Scheme 12 where enyne **2** was prepared *in situ* from alkynols and diethyl but-2-ynedioate in the presence of catalytic amounts of DABCO in dichloromethane. After changing the solvent, treatment of **2** with CuI under atmospheric oxygen pressure generated furan **22** in dry DMF at 80 °C in moderate to good yields.[29] As illustrated by the authors and of primary importance, susceptible furan-2-carbaldehyde products were formed without further oxidation to the corresponding acid. It was further shown that these products were not formed in the absence of oxygen pressure, a hint that the oxygen atom of the carbonyl group originated from dioxygen. A possible mechanism including direct carbene oxidation was proposed, according to which, upon copper activation of the alkyne, propargyl-Claisen rearrangement to allene **23** takes place first. The authors then propose that **23** is converted to copper carbene intermediate **24**. Subsequent dehydrogenation and carbene oxidation through oxygen metathesis results in furan **22** as the final product. Continuing their studies, Jiang *et al.* found that replacement of CuI with an iron complex as simple as $Fe(ClO_4)_3$ hydrate provided identical furans **22** in 53–83% yields.[30] Of note, this oxidative cascade tolerates 5-aryl-2,4-pentadiyn-1-ol (R^2 = ethynylaryl) as the starting substrate to provide an entry into alkyne-substituted furans.

In Scheme 13, a non-oxidative variant of this strategy towards furans is shown. Again, propargyl vinyl ethers are formed *in situ* by use of electron-deficient alkynes (but-2-ynedioates, ethyl 3-phenylpropiolate or aryl alkynyl ketones) and primary propargyl alcohols. Simple alkyl groups (Me, Et) as well as a range of electron-rich and electron-poor aryl groups were successfully attached at the propargyl alcohol part (R^2). Treatment of **2** with catalytic amounts of AgOAc and PPh_3 in hot toluene then directly provided the cyclic furan products **25** in moderate to good yields.[31] This result demonstrates that under forcing conditions, propargyl vinyl ethers can be both rearranged and cyclized by use of silver catalysts. On the other hand, the reactions discussed in Schemes 4–8 have in common that, under silver catalysis at room temperature in dichloromethane, propargyl vinyl ethers **2** only undergo propargyl-Claisen rearrangement without further cyclization.[21]

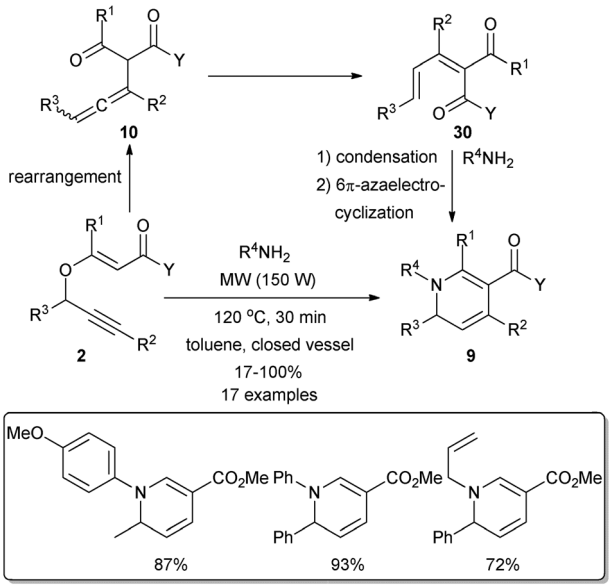
In another variant, Jiang *et al.* reported a one-pot protocol where the propargyl vinyl ether system **2** was once more generated *in situ* by DABCO-mediated reaction of alkynols and diethyl but-2-ynedioates, but heterocycle formation was achieved upon treatment with $PdCl_2$ as catalyst (Scheme 14).[32] It was found that, by employing $CuCl_2{\cdot}2H_2O$ and Na_2CO_3 as additives, 5-vinyl-substituted furans **26** were obtained in DMF at 80 °C under aerobic conditions (19 examples). The alkene was formed with great diastereoselectivity (E/Z > 90/10) over a broad range of substrates. However, for the construction of 4-vinyl-substituted furans **27**, a combination with phase-transfer catalysts such as tetra-*n*-butylammonium fluoride (TBAF) was used. While substrates with R^3 = Me or Et were transformed in



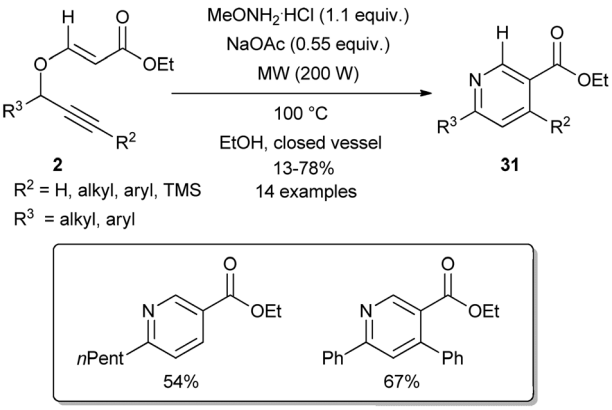
Scheme 15 Pd/Cu co-catalyzed synthesis of α,γ-dicarbonyl furans **29**.

high yields, substrates with R^3 = aryl or H provided the desired furan **27** in significantly lower yields. The mechanism most likely involves the intermediary formation of the common allenylcarbonyl compound **10** followed by a sequence of isomerization, cyclization and β-H elimination.

Most methods that involve *in situ* generation of propargyl vinyl ethers **2** make use of the base-mediated addition of propargyl alcohols onto acceptor-substituted alkynes, as discussed above. However, electron-deficient propargyl vinyl ethers **28** can also derive from cyclic β-diketones and propargyl alcohols.[33] This very reaction was recently utilized by Jiang *et al.* for the *in situ* generation of **28** followed by treatment with catalytic amounts of a mixture of $PdCl_2$, CuI, and tetra-*n*-butylammonium chloride in DMF at room temperature. The overall reaction proceeds oxidatively and, thus, nicely affords 2,4-dicarbonyl-substituted furans **29** in 59–74% yields with remarkable functional group tolerance (Scheme 15).[34] As shown by recent advancements in the field,[35] one can expect further variants on the protocols for the synthesis of heterocyclic targets *via in situ* preparation of propargyl vinyl ethers.



Scheme 16 Microwave-assisted formation of 1,2-dihydropyridines **9** from propargyl vinyl ethers (MW = microwave).



Scheme 17 Microwave-assisted formation of nicotinic acid derivatives **31** from propargyl vinyl ethers.

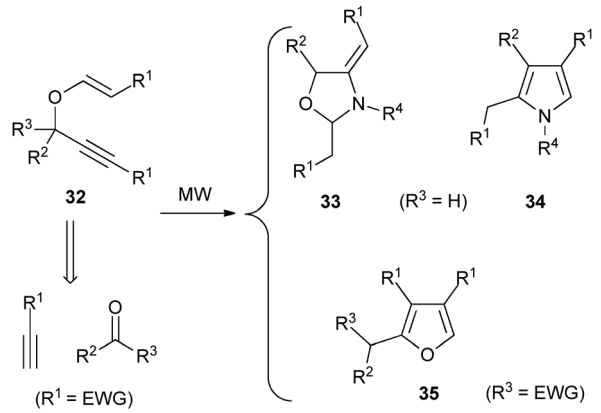
2.2 Thermal reactions

Thermally induced, catalyst-free reactions benefit from the fact that they occur under environmentally benign conditions in the absence of potentially toxic metals. In particular, organic synthesis in the fields discussed in this article might gain profit from microwave-assisted reactions since, in many cases, sluggish transformations are accelerated, yields are enhanced, and reproductivity is highly reliable.

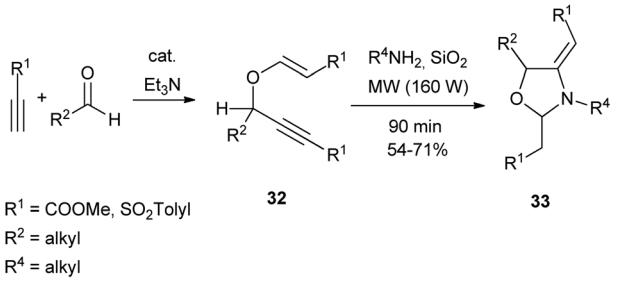
In a great series of studies, García-Tellado, Tejedor *et al.* demonstrated how microwave-assisted domino reactions are a perfect tool to create heterocycles from propargyl vinyl ethers **2** in a flexible way. For example, the microwave-(MW)-assisted domino access to 1,2-dihydropyridines[36] and nicotinic acid derivatives[37] was reported in 2010. As in the case of the transition-metal catalyzed reactions, the thermal pathway proceeds through key allenylcarbonyl intermediate **10** that undergoes reorganization. Under microwave irradiation conditions, thermally allowed prototropic rearrangement leads to the formation of oxatrienes **30**. Subsequent condensation with an external primary amine and 6π-aza-electrocyclization then furnished 1,2-dihydropyridines **9** (Scheme 16).[36] With respect to R^2 and R^3, the scope is excellent; however, substrates with R^1 = H react best while R^1 = Me results in low yields.

Of unique nature, this strategy also provided access to substituted alkyl nicotinates **31** when a primary amine armed with a good leaving group (*e.g.* methoxyamine hydrochloride) was employed (Scheme 17).[37] The reaction was performed in the presence of sodium acetate in ethanol under microwave irradiation. The reaction conditions accepted a diverse range of alkyl and aryl substituents providing **31** in 13–78% yields.

Likewise, García-Tellado *et al.* examined analogous 1,6-diacceptor substituted propargyl vinyl ethers **32**, which are readily accessed from alkynes with R^1 being an electron-withdrawing group and aldehydes,[7] under microwave irradiation conditions. It was found that tetrasubstituted 1,3-oxazolidines **33**, pyrroles **34**[38,39] and trisubstituted furans **35**[40] can be easily synthesized in a transition-metal free manner (Scheme 18).



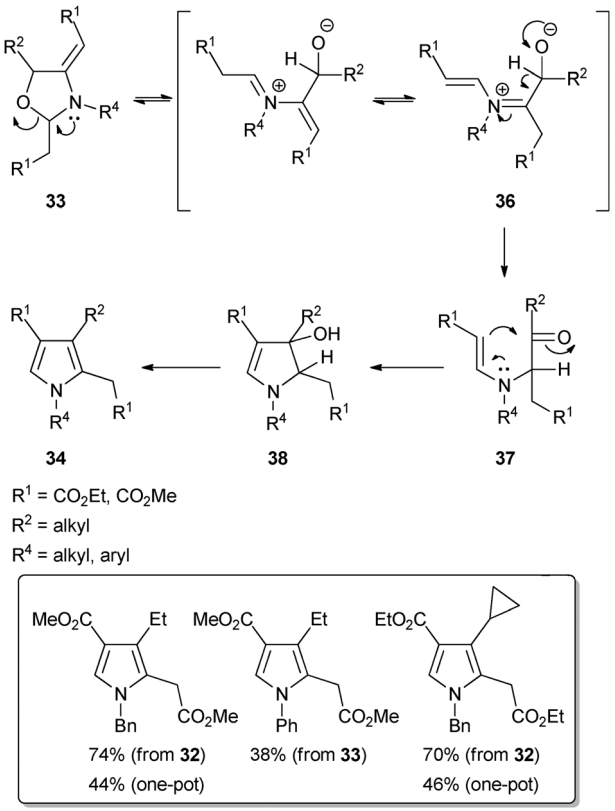
Scheme 18 Microwave-assisted formation of various heterocycles from di-/triacceptor-activated propargyl vinyl ethers **32**.



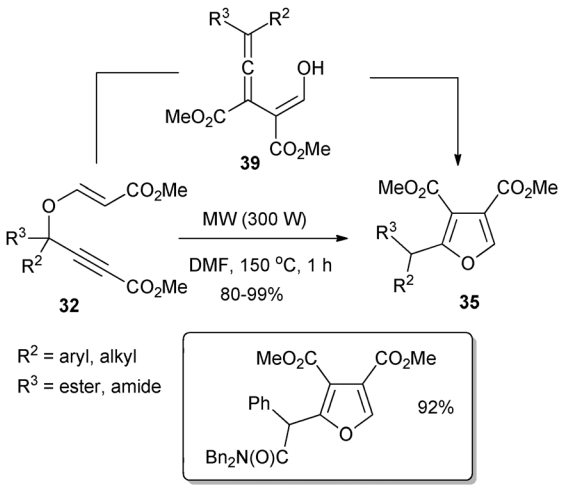
Scheme 19 Microwave-assisted formation of 1,3-oxzolidines **33** from 1,6-diacceptor activated propargyl vinyl ethers **32**.

The synthesis of oxazolidines **33** is composed of two processes linked in an efficient one-pot manner. After the *in situ* formation of propargyl vinyl ethers **32** through action of Et_3N, silica gel and a primary amine are added to the reaction system, and the solvent is removed under vacuum. The reactants loaded on silica are then treated with microwave irradiation (160 W) to afford the desired heterocyclic products **33** in 54–71% yields (Scheme 19).[38,39] The one-pot sequence requires the use of terminal alkynes bearing an electron-withdrawing group (R^1 = EWG). It should be noted that the 1,3-oxazolidine products could also be obtained through a reaction pathway catalyzed by ytterbium triflate.[41] However in both the catalyzed and the thermal set-up, the reaction starts with the selective Michael-type addition of the primary amine onto the activated triple-bond of propargyl vinyl ether intermediate **32**. Heterocyclization with the α,β-unsaturated ester groups (R^1) then gives the five-membered product.

The authors also found that, upon treatment of *in situ* generated **33** with primary amines and silica gel under markedly enhanced microwave irradiation (900 W), pyrroles **34** rather than oxazolidines **33** were obtained in overall 40–50% yields (Scheme 20).[38,39] In this case, even weak nucleophiles such as aniline are able to transform propargyl vinyl ethers **32** into pyrroles **34**. The mechanism of this pyrrole formation likely involves, upon initial formation of oxazolidines **33**, ring-opening, isomerization of iminium ions **36** to afford enamine intermediate **37**, cyclization and terminal dehydration.



Scheme 20 Proposed mechanism for microwave-assisted pyrrole synthesis.

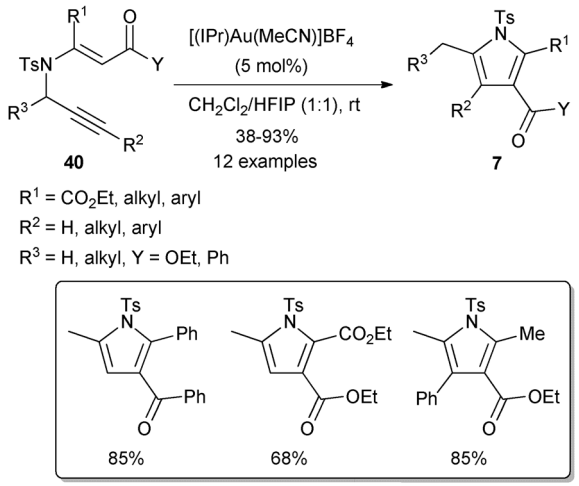


Scheme 21 Microwave-assisted formation of furans **35** from triacceptor-activated propargyl vinyl ethers **32**.

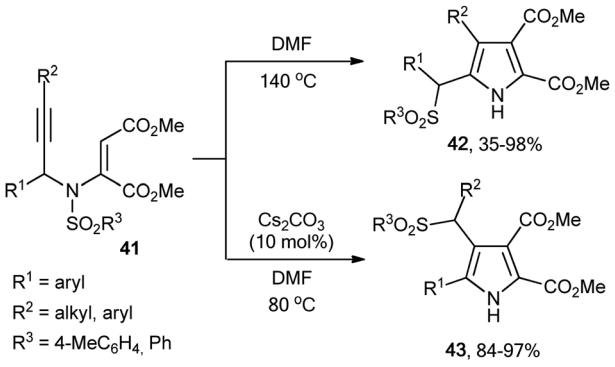
Propargyl vinyl ethers **32** with three acceptor substituents (2 × R^1, R^3) can be synthesized from acceptor-substituted alkynes and α-keto esters through catalysis with DABCO. When these substrates were subjected to microwave irradiation conditions, furans **35** were produced in good yields (Scheme 21).[40] The one-pot synthesis starting directly from the corresponding alkynes and α-keto esters gives the identical products. This domino process is believed to involve a thermal propargyl-Claisen rearrangement that is followed by a 5-*exo* cyclization of allene intermediate **39**.

3. Propargyl vinyl amines as starting materials

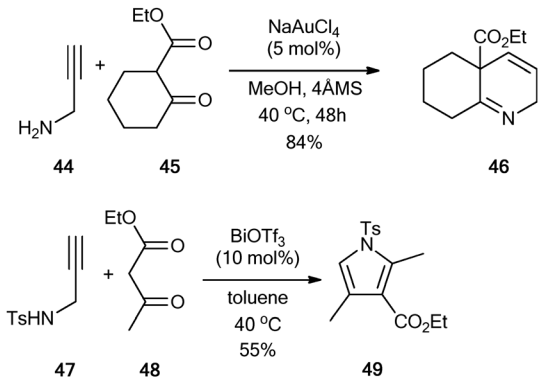
In the previous section, strategies were discussed that are mainly based on an initial propargyl-Claisen rearrangement of propargyl vinyl ether starting materials. Accordingly, oxygen-containing heterocycles are directly accessed while nitrogen-containing heterocycles require an additional amine condensation to install the nitrogen atom. Therefore to access nitrogen-containing heterocycles, it was logical for researchers to begin with propargyl vinyl amines **40** since this substrate class has the nitrogen atom already "pre-installed". Propargyl vinyl amines are readily accessible from the corresponding propargyl *p*-tosylamides and 2-propynoic acid derivatives. As shown in Scheme 22 by Saito *et al.*, the addition of external primary amines was not required for the construction of pyrrole heterocycles.[42] In the presence of the cationic *N*-heterocyclic carbene–gold(I) complex $[(IPr)Au(MeCN)]BF_4$, tosyl-protected pyrroles **7** were formed from **40**. Hexafluoro-2-propanol (HFIP) was used as co-solvent (or sole solvent) to inhibit the competing formation of 1,2-dihydropyridines **9** as undesired byproducts. One can expect that the reaction once again proceeds through an allene intermediate similar to **12**.



Scheme 22 Synthesis of pyrroles **7** from propargyl vinyl amines **40**.



Scheme 23 Synthesis of functionalized pyrroles through the highly regioselective migration of sulfonyl groups.



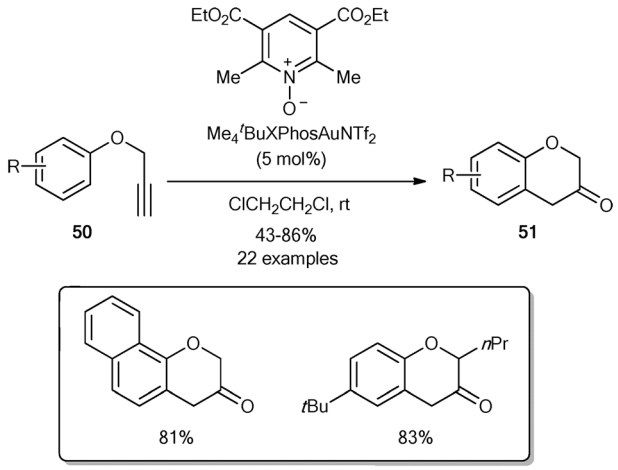
Scheme 24 Synthesis of nitrogen-containing heterocycles through *in situ* generation of propargyl vinyl amines.

In a fully analogous way, Wan *et al.* showed how pyrrole formation can result from either a thermal or a base-promoted cyclization of propargyl vinyl amines **41** (Scheme 23).[43] Under both conditions, a quite unique migration of a sulfonyl group was observed, the regioselectivity of which is perfectly controlled. For example at 140 °C in DMF, a sequence of aza-Claisen rearrangement, cyclization, and N–S bond cleavage leads to an ion pair that subsequently recombines and provides pyrrole **42**. On the other hand, the presence of a base at lower temperatures results in the direct alkyne/allene isomerization while the aza-Claisen rearrangement does not take place. Subsequent cyclization and N–S bond cleavage affords an ion pair that finally leads to pyrrole **43**. It should be noted that the current scope of these transformations appears to be somewhat restricted. While the reactions were shown to work well with R^1 being a range of electron-rich and electron poor aryls, only phenyl, 4-MeC_6H_4, 4-FC_6H_4, and Bu were tested for R^2.

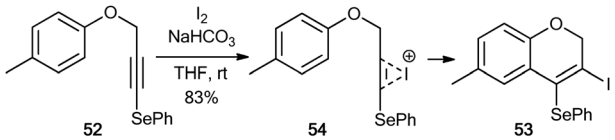
Propargyl vinyl amines can also be accessed by the reaction of propargyl amines such as **44** (or their amides **47**) and 1,3-dicarbonyl compounds such as **48**.[44] In this context, Fañanás *et al.* demonstrated that *in situ* synthesis of propargyl vinyl amines is possible when **44** and **45** are treated with $NaAuCl_4$. Subsequent heterocyclization then provides the six-membered 2,5-dihydropyridine **46** (Scheme 24).[45] A one-pot process of similar ease was developed by Komeyama *et al.* to access pyrrole **49**.[46] In this case, $Bi(OTf)_3$ was used as a Lewis-acid catalyst to trigger both the *in situ* formation of the propargyl vinyl amides and the heterocyclization.

4. Propargyl aryl ethers and propargyl aryl amines as starting materials

Propargyl aryl ethers can be recognized as propargyl vinyl ether analogs as propargyl aryl amines are analogs of propargyl vinyl amines. Therefore, it comes as no surprise that the strategies discussed in the previous sections for the synthesis of monocyclic heterocyclic compounds also have great potential en route to the synthesis of benzoheterocyclic compounds. For example, Saito, Hanzawa *et al.* reported in 2007 how indoles can be synthesized from propargyl vinyl amines *via o*-allenylaniline intermediates through catalysis with $[Rh(cod)_2]OTf$.[47]



Scheme 25 Synthesis of chroman-3-ones **51** through gold-catalyzed oxidation of propargyl aryl ethers **50**.



Scheme 26 Preparation of 3-halo-4-chalcogen-2*H*-benzopyran **53** from propargyl aryl ether **52**.

Recently, Zhang *et al.* developed an oxidative process towards chroman-3-ones, which deviates from the other cyclization strategies by the fact that the site of oxidation is inside the heterocyclic ring (Scheme 25).[48] This valuable transformation became possible when using the sterically demanding gold complex $Me_4{}^tBuXPhosAuNTf_2$ to catalyze the heterocyclization. As stoichiometric oxidants, pyridine *N*-oxides were employed.

Thermal rearrangements and transition-metal-catalyzed alkyne activations are the strategies employed most to trigger the heterocyclization. However, in the cases of propargyl aryl ethers, another mode of activation was used successfully that is the electrophilic alkyne activation. Though several transformations have been reported converting propargyl aryl amines and ethers into heterocyclic products by use of electrophilic iodine sources,[49] we only discuss one archetypical example of this type reported by Zeni *et al.*, which is shown in Scheme 26.[50] As exemplified, propargyl aryl ethers **52** react with electrophiles under cyclization to afford 3-iodo-4-chalcogen-2*H*-benzopyran **53**. To generate the proposed iodonium intermediate **54**, stoichiometric amounts of I_2 or ICl were most effective.

5. Miscellaneous reactions

Finally, we briefly mention a personal selection of heterocycle syntheses that resemble some of the motifs discussed above but do not exactly fit into the previous sections. As propargyl alcohols play an important role in the *in situ* synthesis of propargyl vinyl ethers, it was also established that propargyl alcohols can serve as starting materials for heterocycle syntheses through other key intermediates.[51] For instance, a highly attractive strategy relies on the α-propargylation of 1,3-dicarbonyl compounds with propargyl alcohols. The resulting γ-alkynyl ketones can be cyclized in the presence of trifluoroacetic acid[52] or indium chloride[53] to provide multi-substituted furans. Notably, when adding primary amines, the corresponding pyrroles are generated through amine condensation and subsequent 5-*exo* cyclization.[54] Another furan synthesis is based on unsaturated compounds with leaving groups at the propargylic position, such as propargyl acetates and propargyl halides; furan derivatives are obtained through the action of triphenylphosphine.[55] When propargyl alcohols having an additional carboxy group attached at the propargylic position are treated with platinum catalysts, 3(2*H*)-furanones are obtained;[56] interestingly, furans can be accessed by simply switching the position of hydroxyl and carboxy groups.[57] Although our focus was on the synthesis of heterocyclic scaffolds, we finally point out that propargyl vinyl ethers are also great substrates for the synthesis of complex carbocycles.[58]

6. Conclusions

Propargyl vinyl ethers (and their amines) are a class of compounds with a unique synthetic value for the synthesis of highly functionalized 5- and 6-membered heterocycles. They are easily accessed with a broad substitution pattern that can be fully transferred to the heterocyclic target compounds. Of utmost attraction, one can achieve a diversity-oriented access to a variety of different heterocyclic skeletons from the very same starting substrate by simply adjusting the exact reaction conditions. Successful protocols in this field are based on transition-metal catalysis and thermal reactions. Mechanistically, propargyl-Claisen rearrangements and direct cyclizations are possible. Further variations are realized by methods that generate the propargyl vinyl ether substrates *in situ*. A group of one-pot protocols aims to incorporate nitrogen into the heterocyclic core by an additional condensation with external amines. In summary, we strongly believe that such a simple class of compounds had hardly ever been transformed into a so great diversity of heterocycles. Future research will reveal other elements of how to control the selective formation of the target heterocycles. One can expect that the scope and the diversity reached will be even further expanded over the next years. Thus, we imagine that the overall strategy might soon be ready for applications in, for example, compound screening and combinatorial approaches toward heterocycles.

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