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Haloalkynes: A Powerful and Versatile Building Block in Organic Synthesis

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CONSPECTUS: Inspired by the need for green and sustainable chemistry, modern synthetic chemists have been seeking general and practical ways to construct complex molecules while maximizing atom economy and minimizing synthetic steps. Over the past few decades, considerable progress has been made to fulfill these goals by taking advantage of transition metal catalysis and chemical reagents with diverse and tunable reactivities. In recent years, haloalkynes have emerged as powerful and versatile building blocks in a variety of synthetic transformations, which can be generally conceived as a dual functionalized molecules, and different reaction intermediates, such as σ-acetylene–metal, π-acetylene–metal, and halovinylidene–metal complexes, can be achieved and undergo further transformations. Additionally, the halogen moieties can be retained during the reaction processes, which makes the subsequent structural modifications and tandem carbon–carbon or carbon–heteroatom bond formations possible. As a consequence, impressive effort has been devoted to this attractive area, and some elegant work has been done over the past several years.

This Account highlights some of the recent progress on the development of efficient and practical synthetic methods involving haloalkyne reagents in our laboratory and in others around the world, which showcase the synthetic power of haloalkynes for rapid assembly of complex molecular structures. The focus is primarily on reaction development with haloalkynes, such as cross-coupling reactions, nucleophilic additions, and cycloaddition reactions. The designed approaches, as well as serendipitous observations, will be discussed with special emphasis placed on the mechanistic aspects and the synthetic utilities of the obtained products. These transformations can lead directly to heteroatom-containing products and introduce structural complexity rapidly, thus providing new strategies and quick access to a wide range of functionalized products including many synthetically useful conjugated cyclic and acyclic structures that have potential applications in natural product synthesis, materials science, and drug discovery. Importantly, most of these protocols allow multiple bond-forming events to occur in a single operation, thereby offering opportunities to advance chemical synthesis and address the increasing demands for economical and sustainable synthetic methods.

We anticipate that a deep understanding of the properties of haloalkyne reagents and the underlying working mechanism can lead to the development of novel catalytic systems to answer the unsolved challenges in haloalkyne chemistry, which, in turn, may be also instructive for other research areas. We hope this Account will help to provide a guideline for researchers who are interested in this fertile area.

1. INTRODUCTION

Haloalkynes are an important class of easily accessible and highly versatile building blocks, which exhibit rich and tunable reactivities particularly in the presence of transition metal catalysts. Due to the sp hybridization of the triple bond and the presence of a halogen atom, haloalkynes exhibit both controllable electrophilic and nucleophilic properties, rendering them highly powerful and versatile synthons. Traditionally, haloalkyne reagents were employed as a source of acetylides via metal–halogen exchange (Scheme 1A). In 1943, Ott[1] discovered that haloalkyne derivatives can be also used as equivalents of electrophilic acetylenic moieties, which would undergo an addition–elimination pathway upon the reaction with nucleophiles. The first enantioselective version was realized by Jørgensen[2] with the employment of a chiral phase-transfer catalyst (Scheme 1B). On the other hand, Boger[3] and Gevorgyan[4] demonstrated that haloalkynes can serve as effective sources of the corresponding X^+ ion or both X^+ and acetylide ions, respectively, under treatment with organolithium species (Scheme 1C,D). However, the potential of haloalkyne reagents became fully apparent with the development of transition metal catalysis. Generally, haloalkynes can be regarded as a dual functionalized molecule in the presence of transition metal catalysts. Under different reaction conditions, several reaction intermediates, such as σ-acetylene–metal complex (Scheme 1, type I), π-acetylene–metal complex (Scheme 1, type II), and halovinylidene–metal complex (Scheme 1, type III) can be achieved and undergo further transformations to construct a

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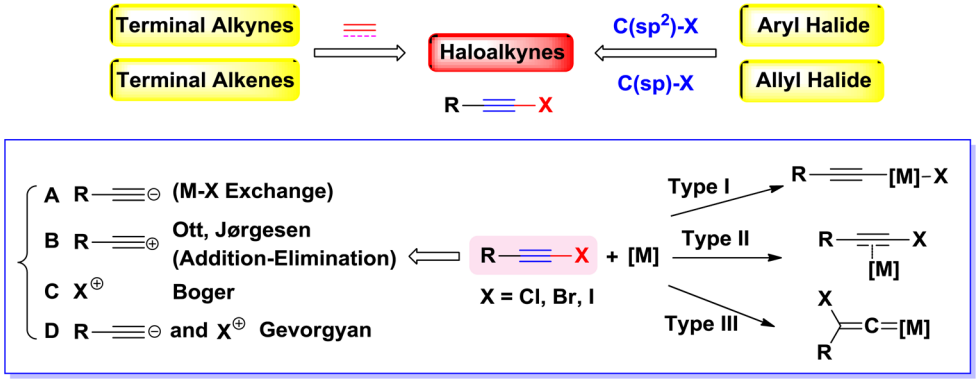
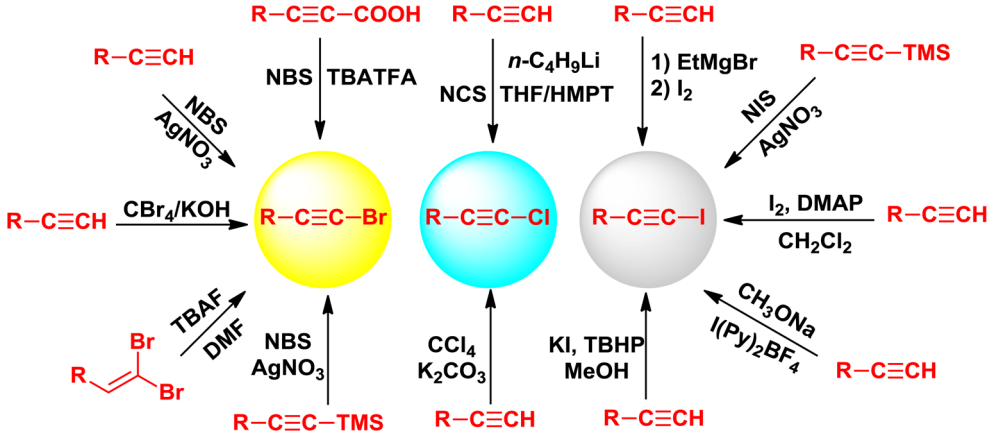
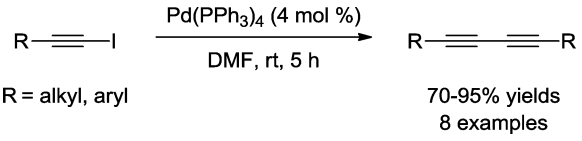
Scheme 1. Potential Reaction Pathways of Haloalkynes in Transition Metal Catalysis



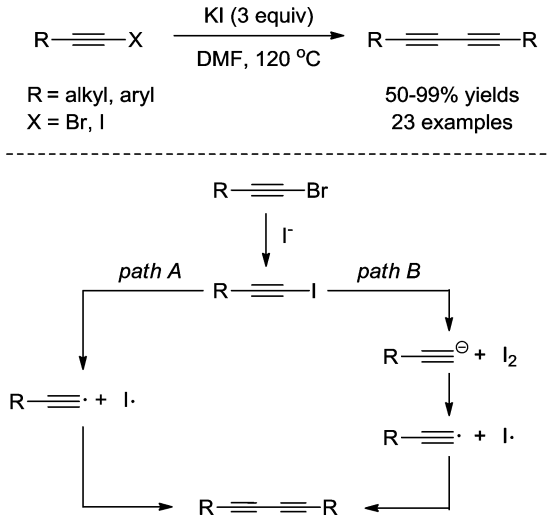
Scheme 2. Preparation Methods for Haloalkynes



Scheme 3. Pd-Catalyzed Homocoupling Reactions of Iodoalkynes



Scheme 4. KI-Mediated Homocoupling Reactions of Haloalkynes



diverse array of useful structures in organic synthesis. Additionally, reactive halogen substituents can be employed for further elaboration, which allows the rapid assembly of structural complexity. As a consequence, impressive effort has been made in this area recently, and many novel chemical transformations involving haloalkynes have been developed.[5]

Developing efficient and selective methods that are critical for ideal and green synthesis[6] is a long-term objective of our group. Our research efforts focus on (i) new oxidation reactions using economical and environmentally benign molecular oxygen (O_2),[7] (ii) compatible catalytic systems with the use of unconventional media that may potentially simplify synthesis and enhance resource utilization, such as water, supercritical carbon dioxide ($scCO_2$),[8] and ionic liquids (ILs),[9] and (iii) new strategies for the construction of carbon−carbon or carbon−heteroatom bonds with high atom- and step-economy. This Account highlights our recent progress on the development and applications of convenient and concise synthetic methods involving haloalkyne reagents. Related works from other groups will be also cited appropriately, aiming to illustrate the potential of haloalkyne chemistry in a wide array of settings including natural-product synthesis, materials science, and bioorganic chemistry.

2. PREPARATION OF HALOALKYNES

Haloalkynes were traditionally accessible through the deprotonation of the corresponding terminal alkynes with a strong base, followed by trapping with a halogenating reagent. Recently, several mild and convenient methods have been developed (Scheme 2),[10] thus increasing the attractiveness of this class of

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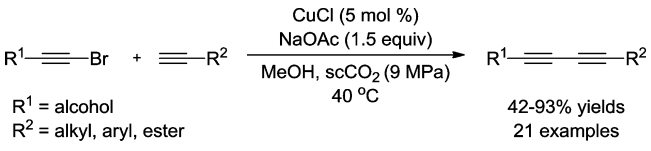
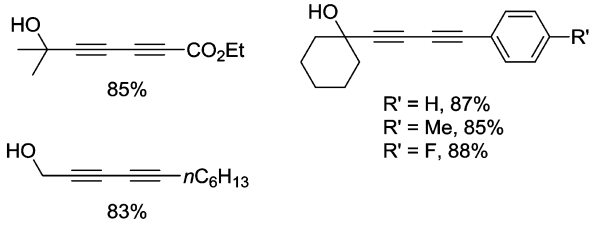
Table 1. Cu-Catalyzed Cross-Coupling Reactions of Bromoalkynes



Selected Examples:



compounds in organic synthesis. Among these, the electrophilic bromination of terminal alkynes with *N*-bromosuccinimide (NBS) and Ag catalyst[11] is one of the most commonly used methods for the preparation of bromoalkynes due to the mild reaction conditions, high efficiency, and simple manipulation.

3. REACTIONS OF HALOALKYNES

In this section, the focus will turn to the recent reaction development of haloalkynes, including cross-coupling reactions, nucleophilic additions, and cycloaddition reactions. These transformations represent a powerful tool for generating molecular complexity quickly. Both our experience and related works from other research groups are described, with a particular emphasis placed on the reaction design and mechanistic investigation.

3.1. Transition Metal-Catalyzed Carbon−Carbon Cross-Coupling Reactions

Carbon−carbon (C−C) cross-coupling reaction is among the most important and useful methods in organic synthesis, providing easy access to a variety of synthetically valuable compounds. Expansion of this reaction to include haloalkyne reagents with controllable steric and electronic characters based on selection of the halogen atom attached to the triple bond, could allow the facile synthesis of skeletons that previously were difficult or impossible to prepare.

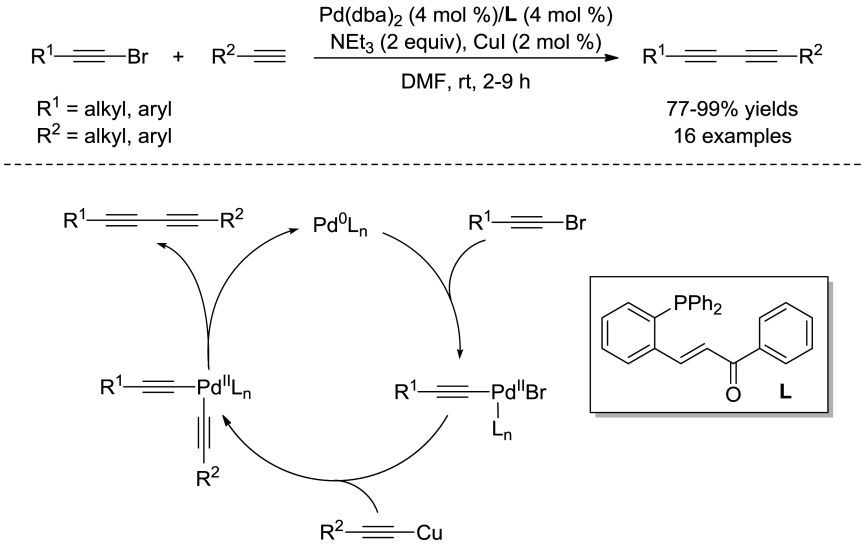
3.1.1. C(sp)−C(sp) Coupling. Conjugated diynes are of vital importance as versatile building blocks in the synthesis of natural products, pharmaceuticals, and functional materials. In 2003, Lee's group[12] reported a convenient method for the construction of symmetrical 1,3-diynes from 1-iodoalkynes in the presence of Pd^0 catalyst without any use of additives or other metal reagents (Scheme 3). This reaction could be performed under an inert atmosphere, thus avoiding side reactions associated with the Glaser coupling reaction that used O_2 as the oxidant.

Considering the environmental and economic impacts, the development of a transition metal-free system for the synthesis of 1,3-diynes is rather attractive. In 2010, our group successfully developed an efficient synthetic approach to 1,3-diynes from haloalkynes under treatment with KI in *N*,*N*-dimethylformamide (DMF) solvent without the addition of oxidant and base (Scheme 4).[13] Generally, iodoalkynes gave symmetrical 1,3-diynes in better yields compared with the corresponding bromoalkynes. Both aromatic and aliphatic alkynyl halides proceeded smoothly in this reaction system, and different functional groups on haloalkyne substrates could be tolerated. As for the reaction mechanism, we proposed the substitution of bromoalkyne with KI first occurred to form the iodoalkyne intermediate, which might undergo two possible pathways for the observed 1,3-diyne product (Scheme 4).

In 2007, we disclosed a mild and environmentally friendly method for the construction of unsymmetrical 1,3-diynes via the Cu-catalyzed Cadiot−Chodkiewicz coupling of bromoalkynes with terminal acetylenes in $scCO_2$ using NaOAc as base (Table 1).[14] As a cosolvent, methanol could promote the dissolution of inorganic salts in $scCO_2$ and accelerate the reaction rate. This new heterocoupling reaction system not only tolerated a range of functional groups to afford diverse unsymmetrically substituted 1,3-diynes, but also avoided the employment of amine. It was discovered that this transformation was sensitive to high reaction temperature and the pressure of $scCO_2$.

Besides Cu catalysis, several Pd-catalyzed conjugated diyne construction methods have been reported.[15] However, the major problem in Pd-catalyzed C(sp)−C(sp) cross-coupling reactions is still the competitive homocoupling process. In 2008, Lei's

Scheme 5. Pd-Catalyzed Cross-Coupling Reactions of Bromoalkynes



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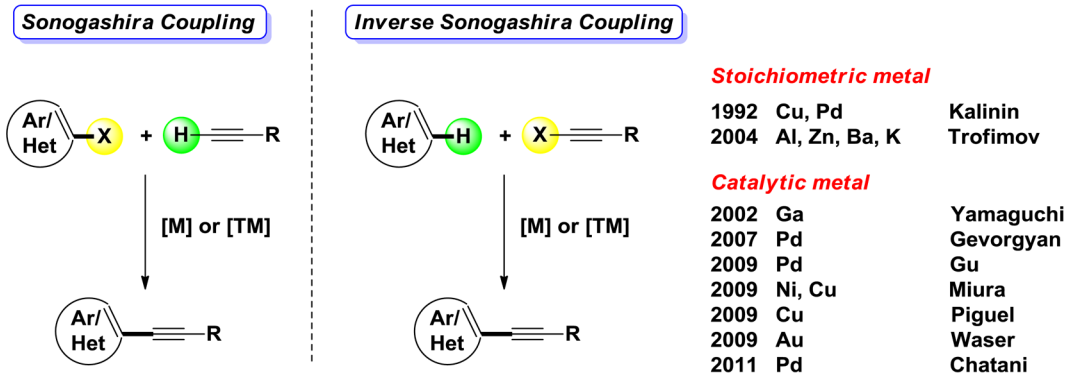
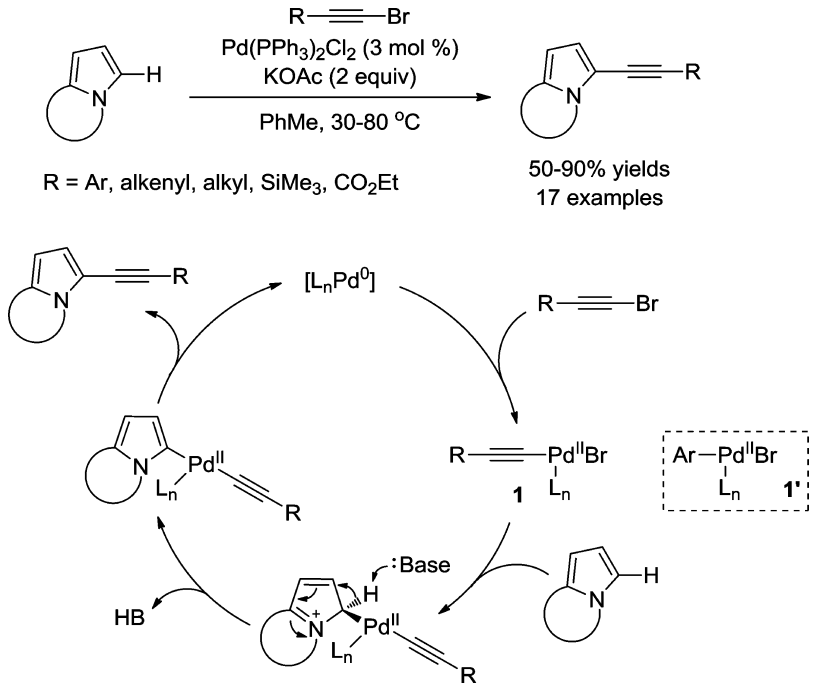
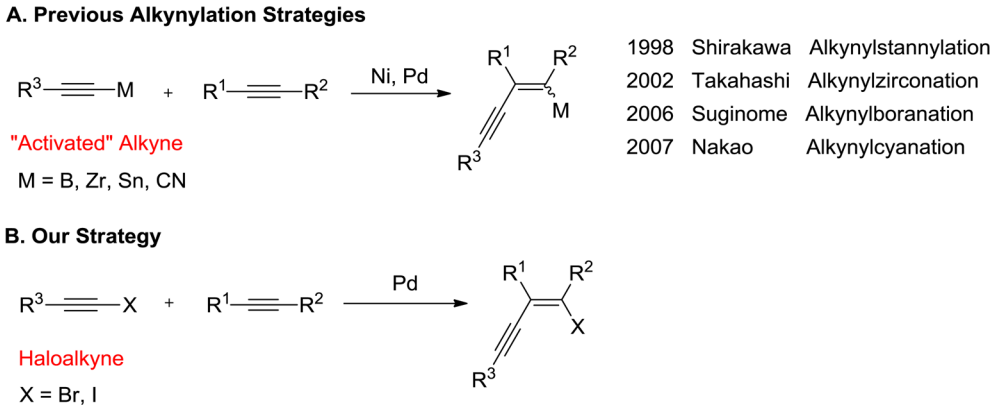
Scheme 6. Development of "Inverse Sonogashira Coupling"



Scheme 7. Pd-Catalyzed Alkynylation of N-Fused Heterocycles



Scheme 8. Strategies for the Conjugated Enyne Synthesis



group[16] described an efficient protocol to synthesize unsymmetrical 1,3-diynes promoted by $Pd(dba)_2$ and a phosphine–olefin ligand **L** with the assistance of the Cu(I) catalyst (Scheme 5). This methodology realized the cross-coupling of a broad range of terminal alkynes and haloalkynes in good to excellent yields with high selectivities. One-pot synthesis of symmetrical and unsymmetrical triynes was also achieved. Mechanistic studies indicated that the phosphine–olefin ligand could facilitate the reductive elimination process in the catalytic cycle, thereby improving the selectivity.

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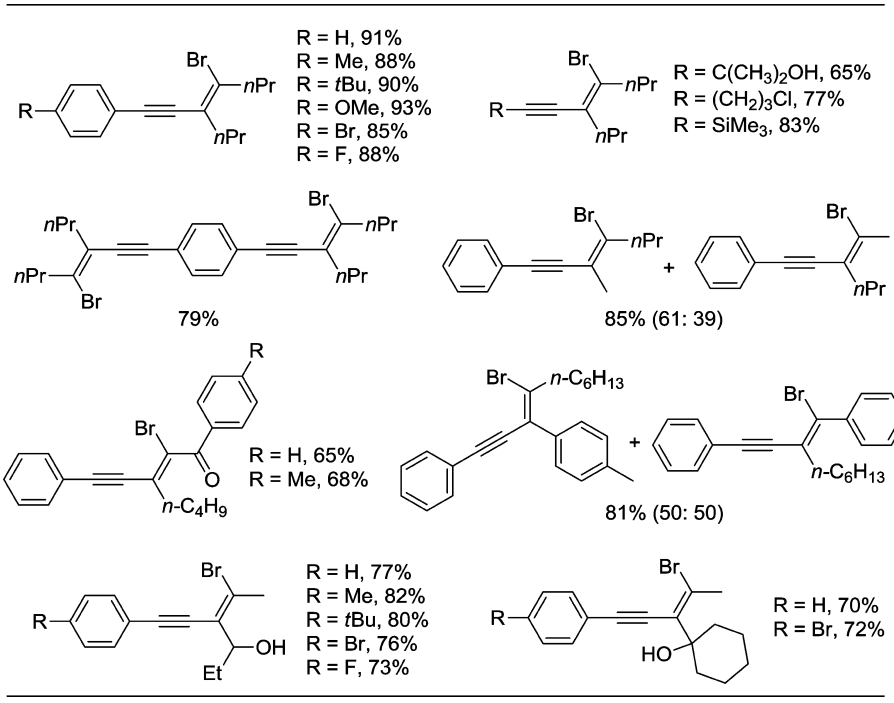
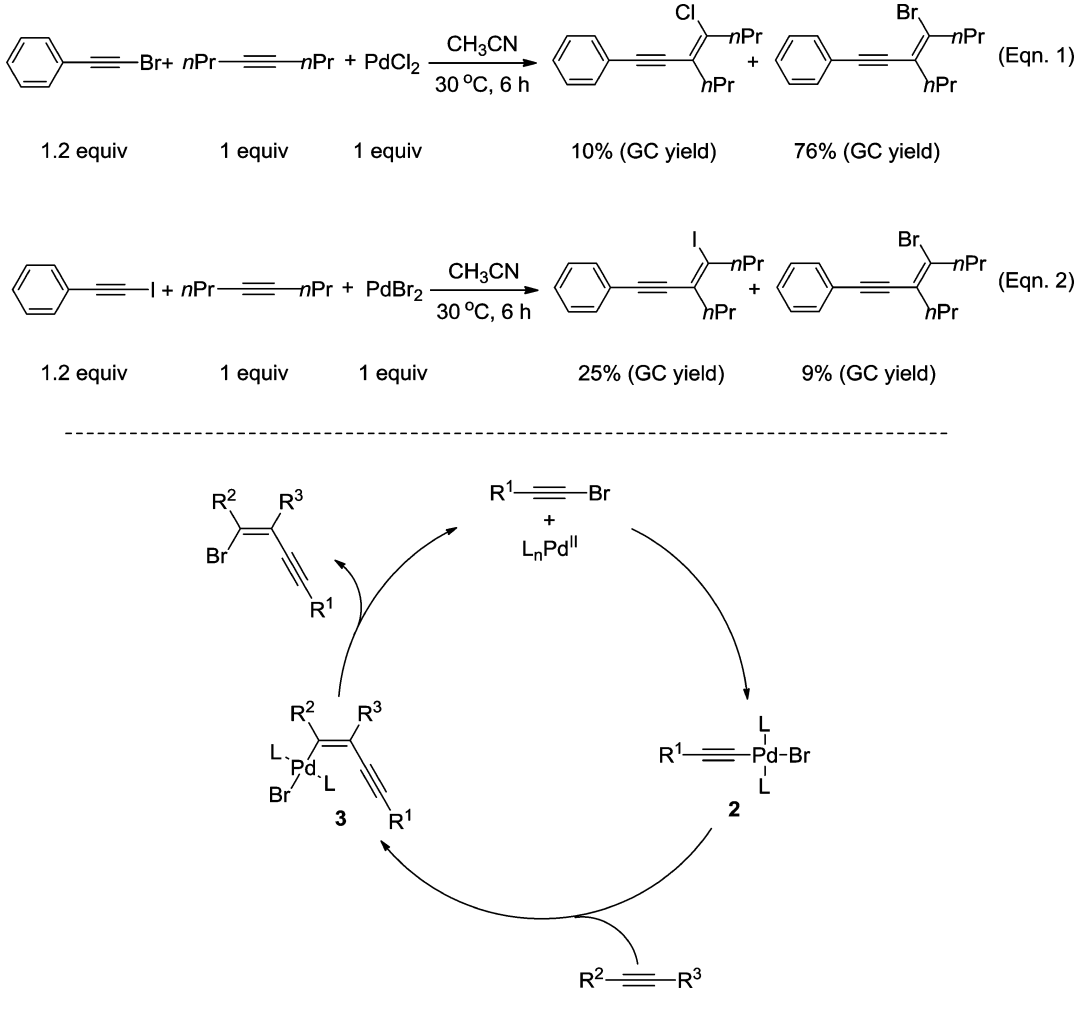
Table 2. Pd-Catalyzed Bromoalkynylation of Alkynes



Scheme 9. Control Experiments and Proposed Catalytic Cycle



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Scheme 10. Pd-Catalyzed Cross-Coupling Reaction for 1,3-Enynes

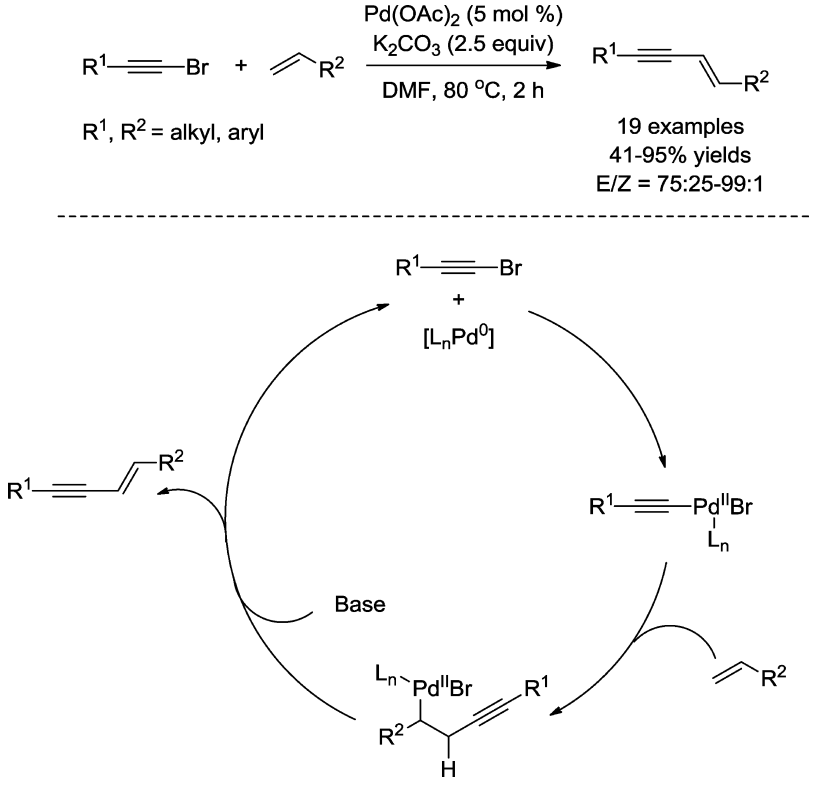
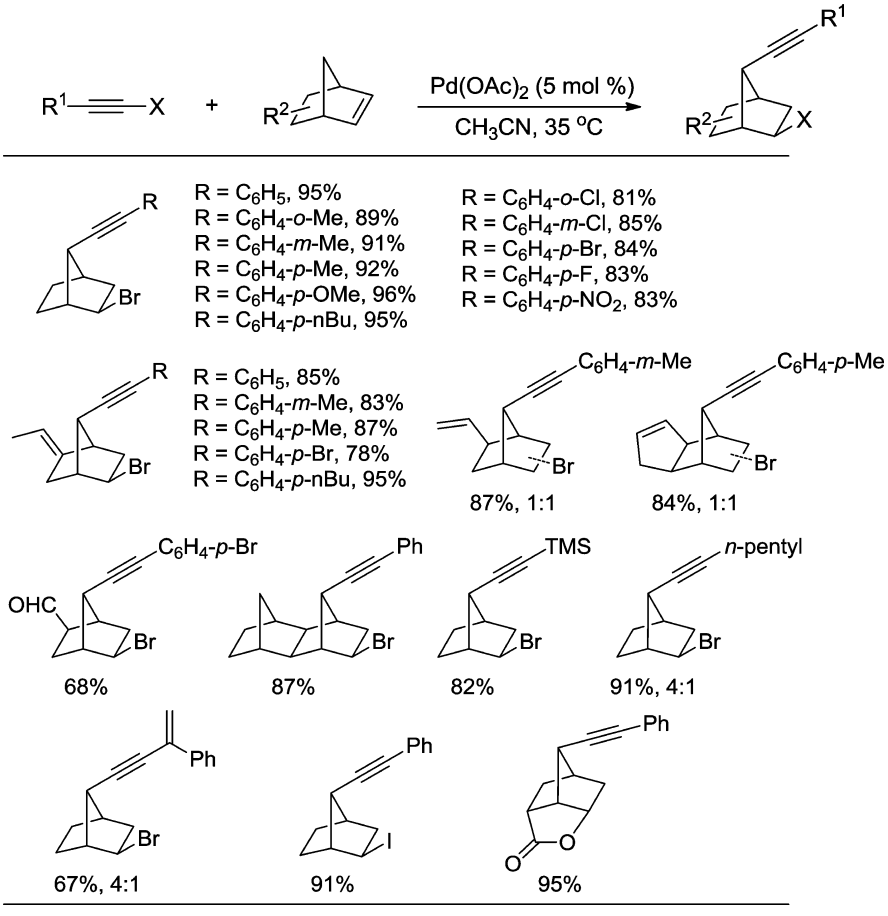


Table 3. Pd-Catalyzed Synthesis of 7-Alkynyl Norbornanes



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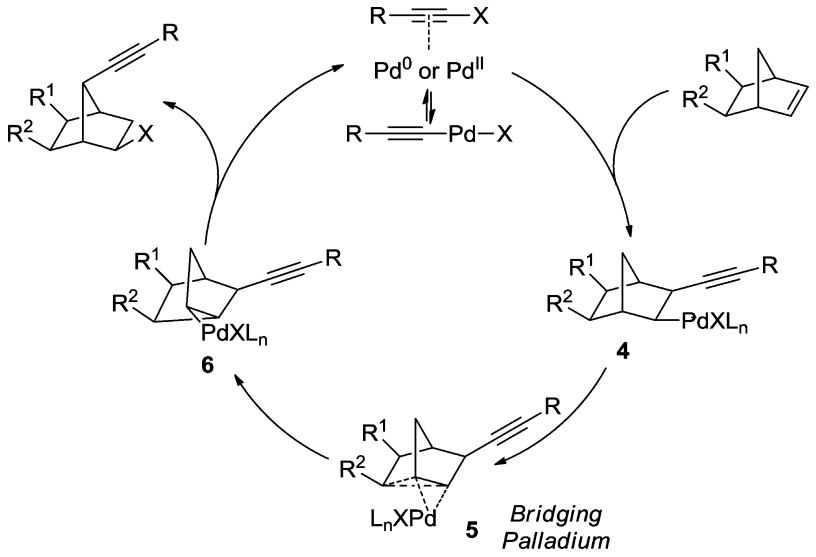
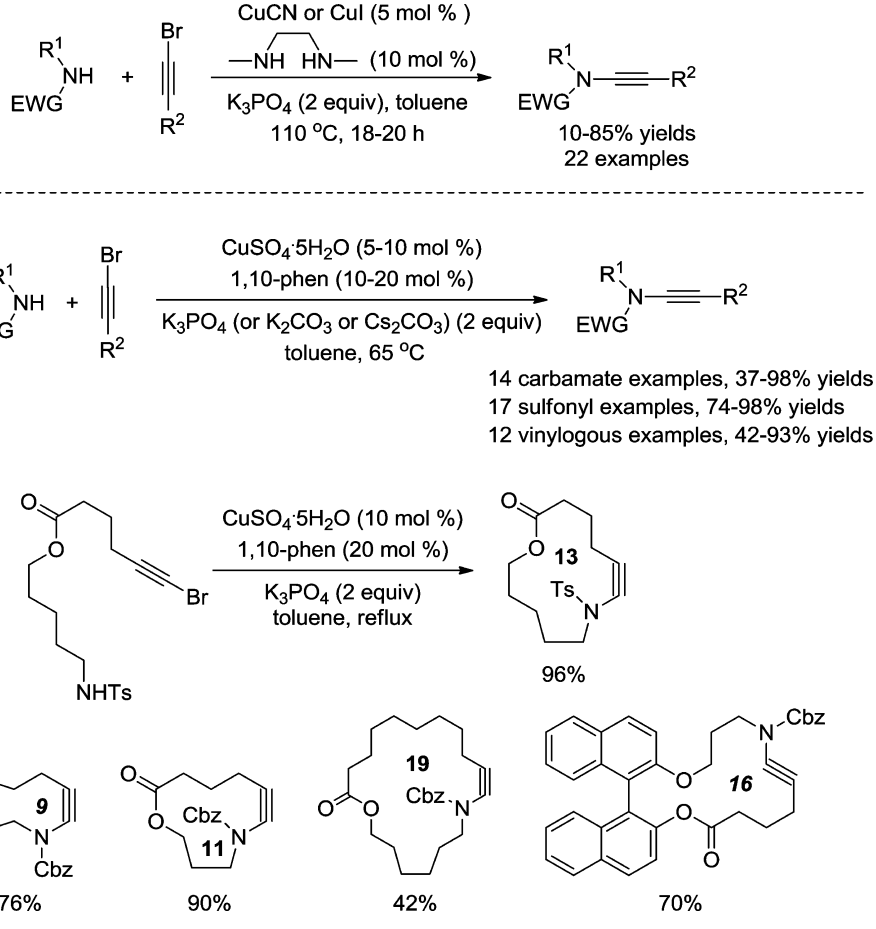
Scheme 11. Plausible Reaction Mechanism

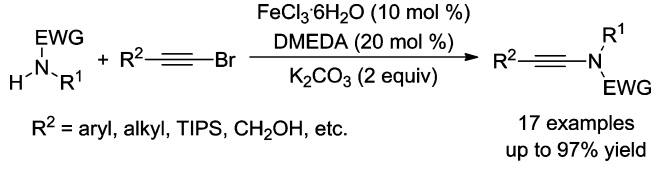


Scheme 12. Cu-Catalyzed Ynamide Formation Reactions



3.1.2. C(sp)–C(sp^2) Coupling. The construction of C(sp)–C(sp^2) bonds plays an important role in the synthesis of various conjugated molecules and biologically active compounds. Among different strategies for achieving this goal, the cross-coupling reaction between vinyl halides and terminal alkynes stands as one of the most widely used methods. Recently, the development of "inverse Sonogashira coupling" has represented a complementary strategy for the construction of aryl/heteroaryl

Scheme 13. Fe-Catalyzed Coupling of Amides and Bromoalkynes



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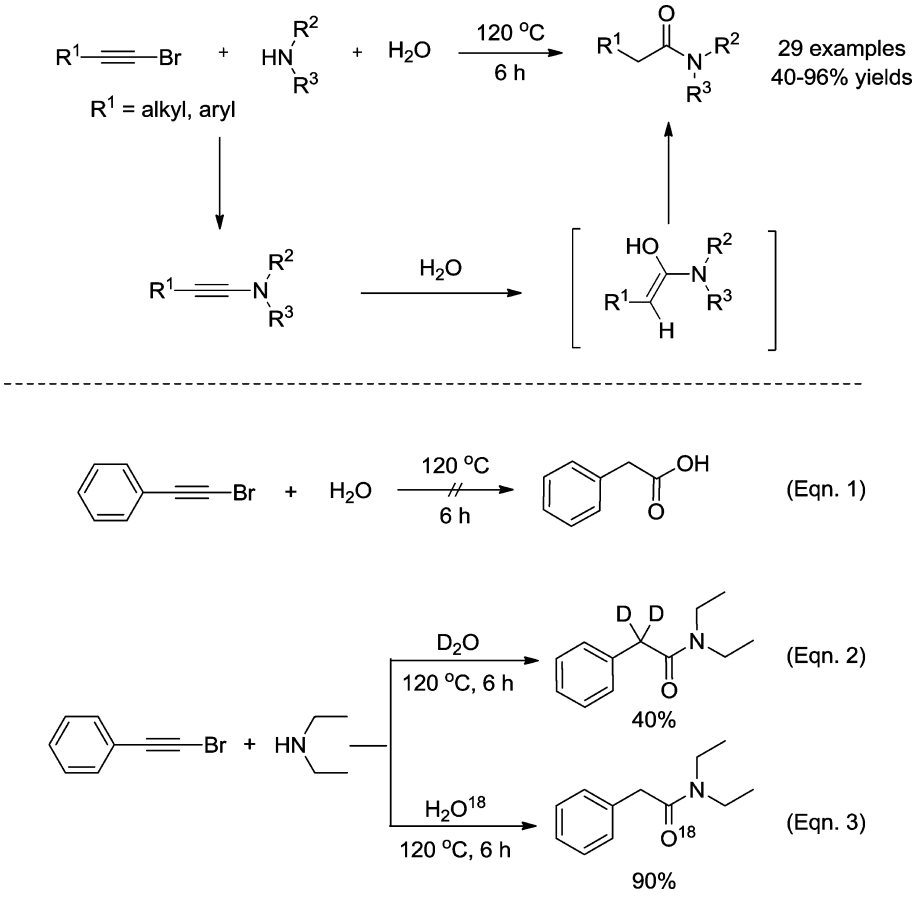
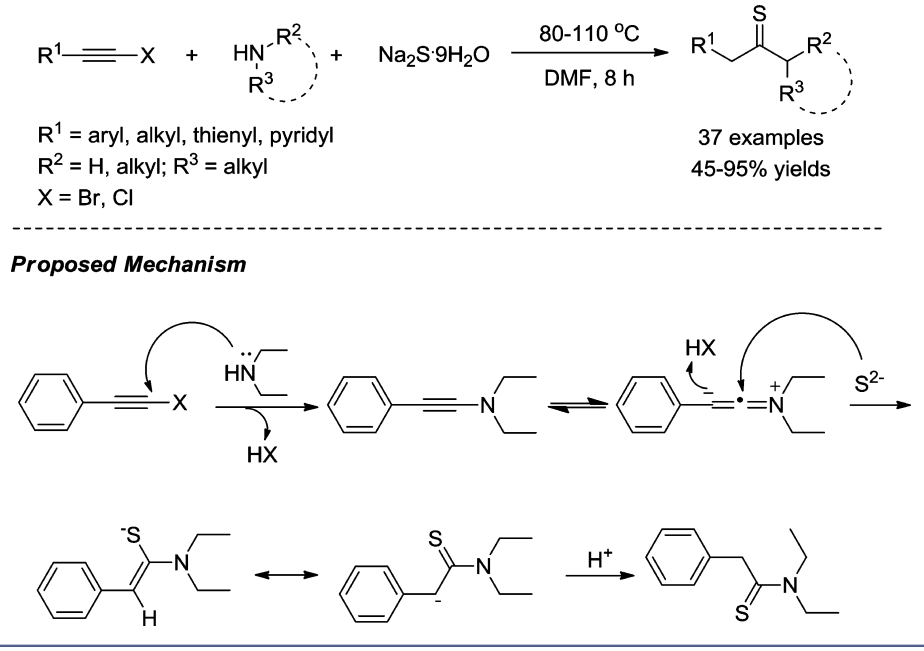
Scheme 14. Multicomponent Reaction for Amides



Scheme 15. Multicomponent Reaction for Thioamides



alkynes involving the direct alkynylation of unreactive C−H bonds with readily available haloalkynes (Scheme 6). Though the first practical example of this type of alkynylation was reported by Kalinin and co-workers using a stoichiometric amount of Cu^{I} salt in 1992,[17] this field did not experience major growth until 2007, when the first example of a transition metal-catalyzed direct alkynylation of electron-rich N-fused heterocycles was disclosed by Gevorgyan's group (Scheme 7).[18] A range of indolizine, pyrroloquinoline, pyrroloisoquinoline, and pyrrolooxazole derivatives could be alkynylated regioselectively with different substituted bromoalkynes under the treatment of Pd catalyst. It is essential for conceptual advance that the alkynylpalladium

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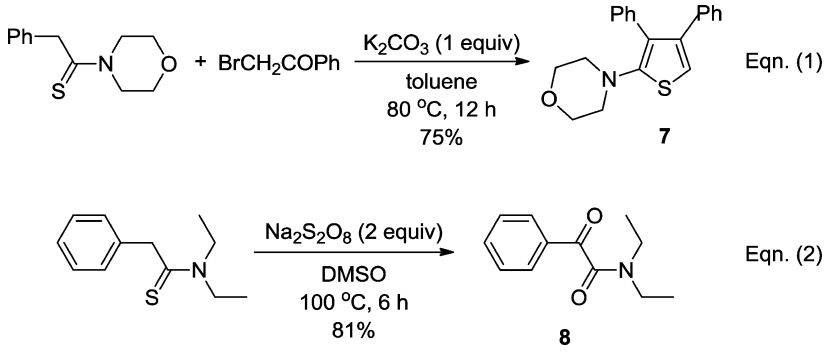
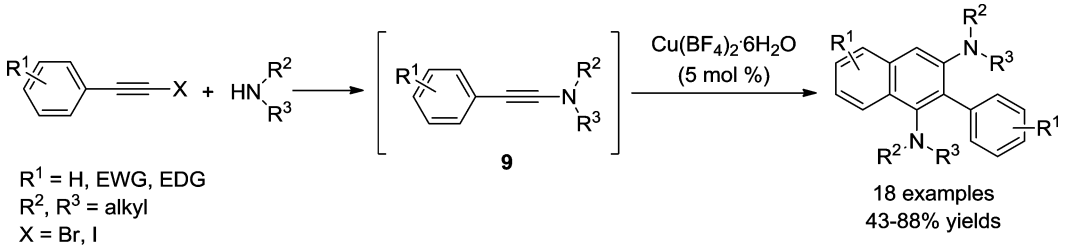
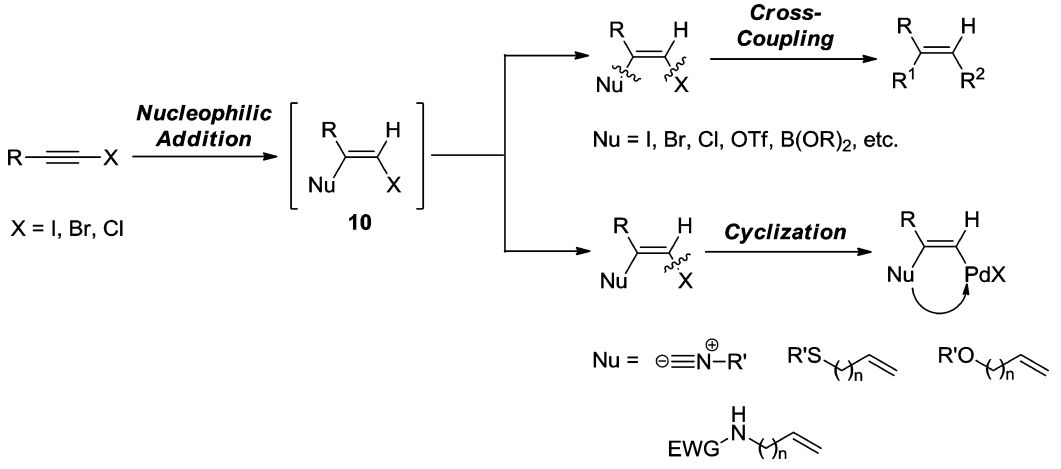
Scheme 16. Synthetic Applications of Thioamides



Scheme 17. Cu-Catalyzed Synthesis of Naphthalene-1,3-diamine Derivatives



Scheme 18. Nucleophilic Additions to Haloalkynes



intermediate **1** showed the similar reactivity to that of arylpalladium species **1′**, which is known to undergo an electrophilic pathway in the process of indolizine arylation. Later, Ni-, Cu-, and Au-catalyzed variations of inverse Sonogashira reactions have been developed independently by Miura,[19] Piguel,[20] and Waser[21] and their co-workers. Recent findings in the field of direct alkynylation reactions with the employment of haloalkyne reagents open up new exciting opportunities for the functionalization of C−H bonds.

Likewise, the development of efficient and practical alkynylation methods for functionalized acyclic enyne compounds is also desirable. In this context, direct addition of an "activated" alkyne to another alkyne is one of the straightforward routes, and several catalytic systems for alkynylcyanation,[22] alkynylstannylation,[23] and alkynylboranation[24] have been reported (Scheme 8A). In 2010, we disclosed a selective Pd-catalyzed intermolecular cross-coupling reaction between haloalkynes and internal alkynes, which afforded a series of halogenated enyne products via a new kind of direct haloalkynylation process (Scheme 8B).[25] Condition screening indicated that Pd^{II} was critical to the product formation, while Pd^{0} just retarded the reaction. Reductive additives and inorganic bases would also slow the transformation; however, organic oxidant or air did not disturb the reaction. This method was found to have a broad substrate scope (Table 2). Generally, symmetrical internal alkynes gave *cis*-addition products exclusively, whereas the regioselectivity of unsymmetrical disubstituted acetylenes was mainly affected by the functional groups in the internal alkynes.

To gain insight into the reaction pathway, control experiments using stoichiometric Pd catalyst were conducted, and the major halogenated products were proven to originate from phenylethynyl halides (Scheme 9, eqs 1 and 2), which indicated that the process should go through an unusual oxidative addition of Pd^{II} species to phenylethynyl bromide rather than a direct halopalladation of alkynes. Thus, this transformation was supposed to be initiated by the oxidative addition of Pd^{II} salt to bromoalkyne, and the Pd^{IV} complex **2** was formed. Then, the addition of **2** to internal alkyne gave the *cis*-alkynyl vinylpalladium intermediate **3**, which

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Scheme 19. Halogenation Reaction of Haloalkynes

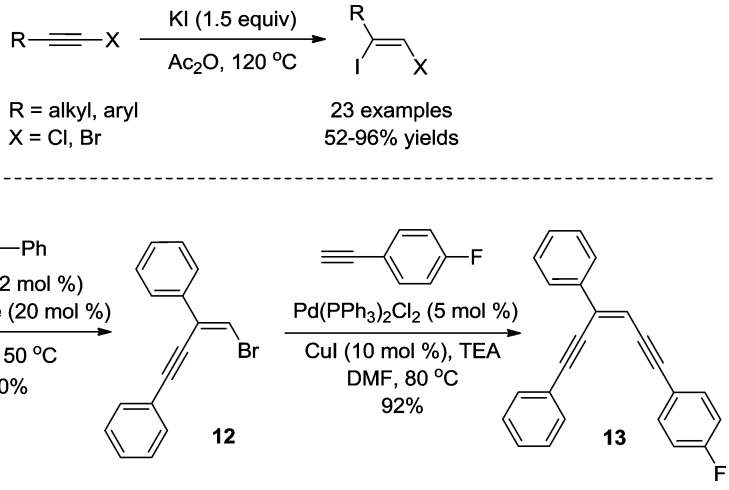
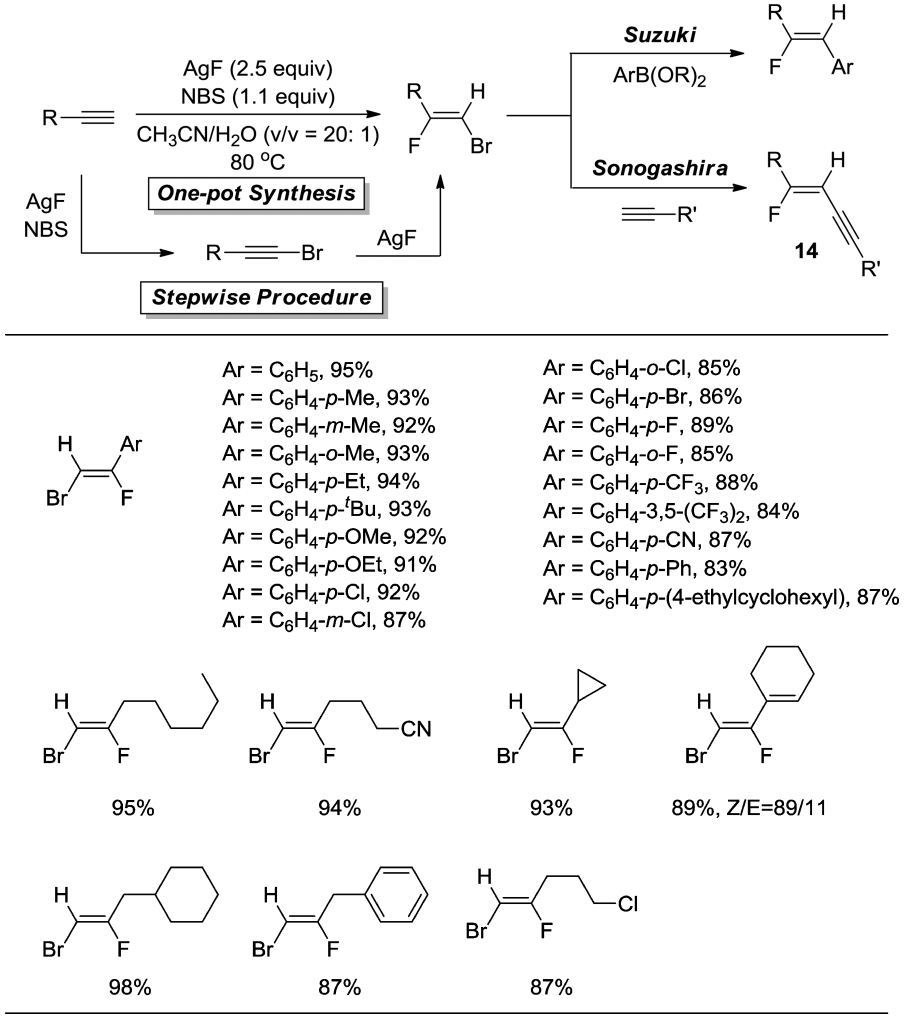


Table 4. Ag-Assisted Bromofluorination Reaction of Terminal Alkynes



underwent a reductive elimination to generate the brominated enyne product and the active Pd^{II} species (Scheme 9).

Our further investigation revealed another efficient procedure for the stereoselective synthesis of conjugated 1,3-enynes by a simple cross-coupling reaction of unactivated alkenes and bromoalkynes (Scheme 10).[26] This method had a good functional group tolerance and the corresponding enyne derivatives could be obtained in good to excellent yields. A plausible reaction mechanism including oxidative addition, Heck cross-coupling and β-H elimination was proposed.

3.1.3. C(sp)−C(sp^3) Coupling. The development of efficient and sustainable procedures for the creation of C(sp)−C(sp^3) bonds continues to be a challenging task in modern organic chemistry.[27] As part of our research programs, subsequent studies

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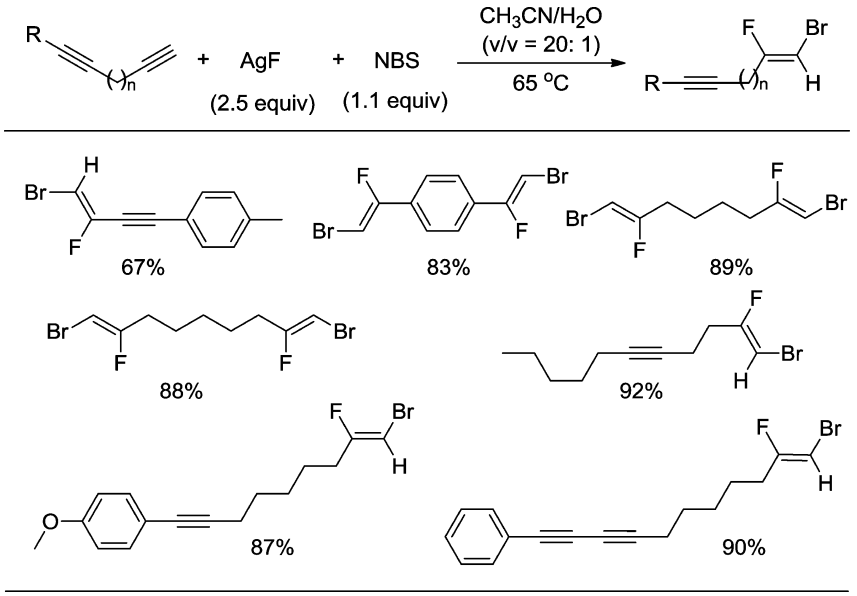
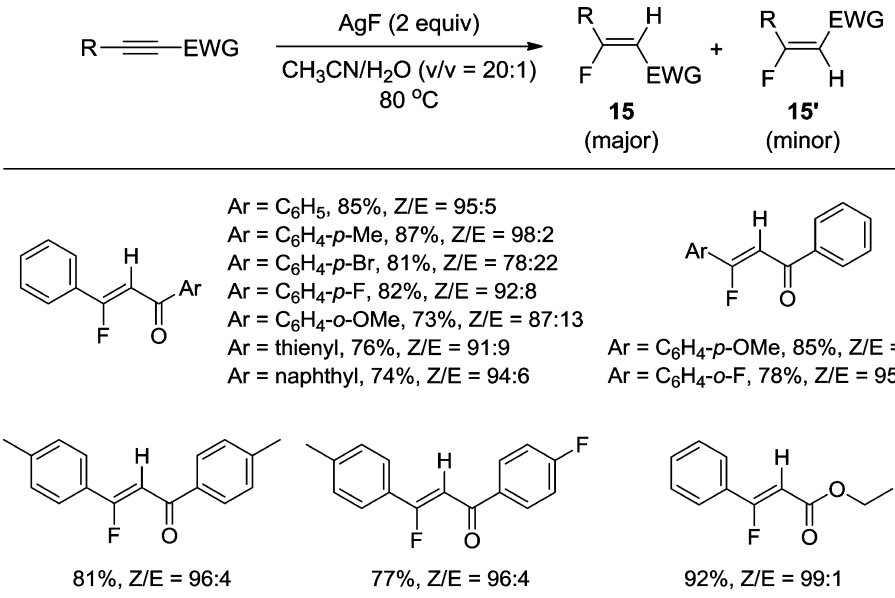
Table 5. Bromofluorination of 1,*n*-Diynes[a]



[a]*Z*/*E* ratio was determined GC or NMR. Unless otherwise noted, *Z*/*E* ratio >95:5.

Table 6. Hydrofluorination of Electron-Deficient Alkynes[a]



[a]*Z*/*E* ratio was determined by GC analysis of the crude product.

on haloalkyne reagents revealed their utilization in complex molecule synthesis. We developed the first example of highly selective Pd-catalyzed intermolecular reaction of haloalkynes and norbornene derivatives, leading to diverse 7-alkynyl norbornane products that could not be easily accessed via traditional methods (Table 3).[28] Our success in the construction of C7-functionalized norbornyl alkynes proved the compatibility of nonclassical norbornonium cation with this catalytic system. The transformation proceeded through the direct cleavage of an alkynyl−halogen bond, followed by the formations of C(sp)−C(sp^3) and C(sp^3)−halogen bonds, featuring excellent atom economy.

Based on previous reports and our experimental results, a tentative pathway is proposed in Scheme 11. Initially, the oxidative addition of Pd^0 or Pd^{II} species to haloalkyne gave a high-valent alkynylpalladium complex, followed by *cis*-insertion to generate intermediate **4**. Subsequently, the bridging Pd complex **5** was formed, and then the Pd catalyst was delivered to the bridged carbon on the same side as the incoming alkyne, which led to the formation of the alkylpalladium halide intermediate **6** with high stereoselectivity. Finally, the reductive elimination generated the brominated product and the active catalyst species.

3.2. Transition Metal-Catalyzed Carbon−Nitrogen Cross-Coupling Reactions

Ynamines and ynamides are modern functional groups with increasing importance that can transfer directly to the nitrogen-containing products, providing access to privileged scaffolds found in natural products and molecules of medicinal interest.[29]

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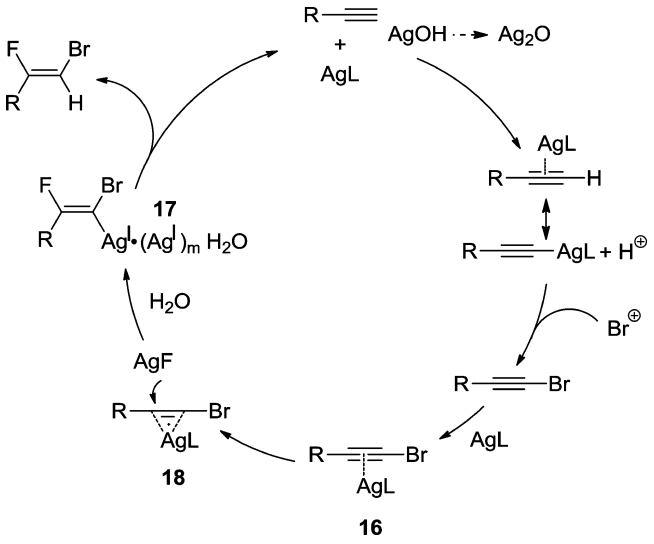
Scheme 20. Proposed Mechanism

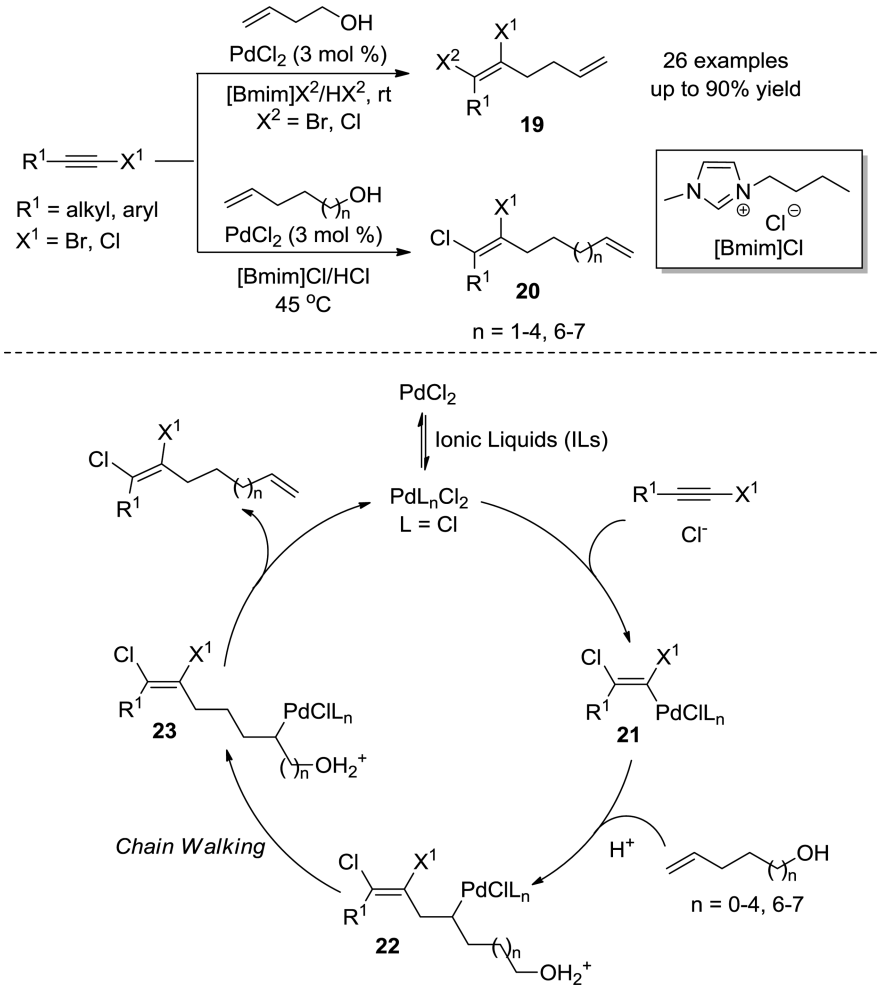


With the development of efficient means of preparation, the field of ynamide chemistry has experienced rapid expansion in the past decade.[30] Especially, the amidative cross-coupling of amines and haloalkynes has emerged as one of the most important protocols. In 2003, Hsung et al.[31] discovered the first Cu-catalyzed ynamide formation reaction, which provided a direct and atom-economical entry to various ynamides (Scheme 12). Later, they developed an improved and more practical catalytic system for ynamide synthesis, with the employment of inexpensive $CuSO_4 \cdot 5H_2O$ and 1,10-phenanthroline as ligand.[32] This process had a good functional group tolerance and was equally effective for intramolecular amidation reactions, which could be applied to the synthesis of unique macrocyclic ynamides that contain ring systems up to 19-membered.[33] In 2009, the first Fe-catalyzed coupling of amides and alkynyl bromides was disclosed by Zhang's group (Scheme 13).[34]

In contrast, although the ynamine chemistry has a long history, the high reactivity often causes much difficulty in the general handling of ynamine compounds.[35] Therefore, a key consideration in developing ynamine chemistry is how to make full use of the active ynamine intermediates where versatility, convenience, and practicality need to be addressed. Our recent work in this area includes reaction development for amides, thioamides, and naphthalene derivatives with the utilization of haloalkyne reagents.

Amides are one of the most important functional groups in polymers, natural products, and pharmaceuticals. Recently, we disclosed a mild and efficient procedure for the construction of amides from bromoalkynes based on the multicomponent reaction employing water as one reacting partner under convenient conditions,[36] which provided secondary and tertiary amides in moderate to excellent yields (Scheme 14). Related

Scheme 21. Pd-Catalyzed Synthesis of Functionalized Dihalo-1,*n*-dienes



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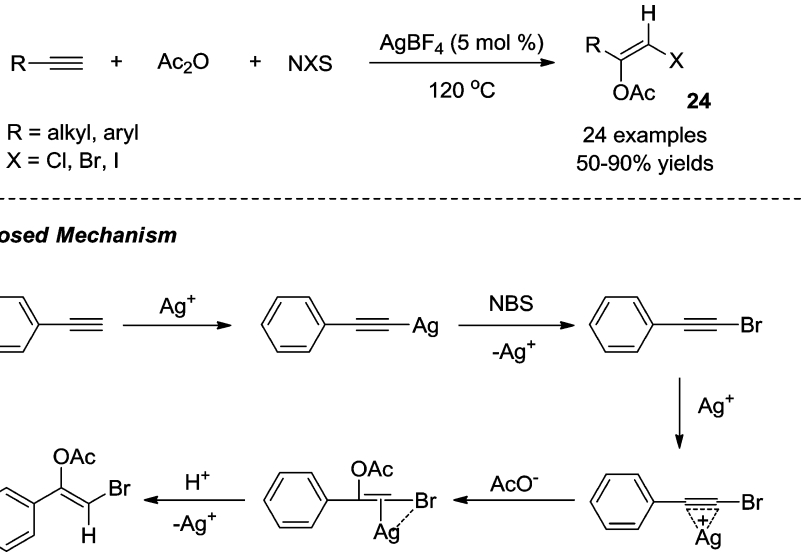
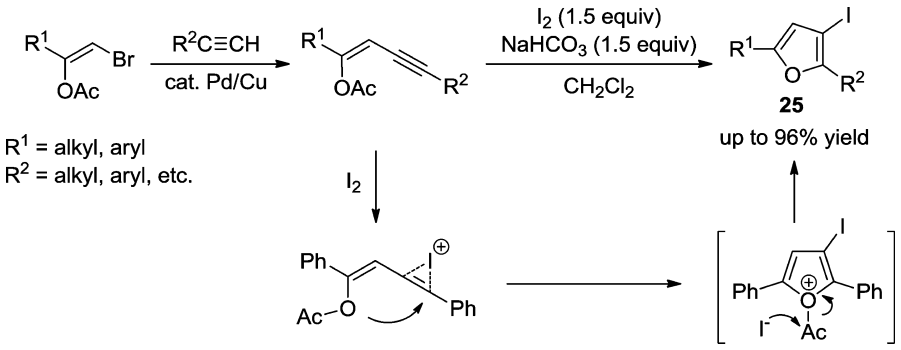
Scheme 22. Ag-Catalyzed Synthesis of (Z)-β-Haloenol Acetates



Scheme 23. Pd/Cu-Catalyzed Synthesis of 3-Iodofurans



control experiments suggested that the alkynyl bromide should first react with amine, and the isotopic labeling study clearly demonstrated that the oxygen atoms of the amide products originated from water (Scheme 14, eqs 1−3). A mechanism involving ynamine formation and nucleophilic addition was thus proposed.

Thioamides are also prevalent structural motifs that are found in many biologically active molecules and synthetic intermediates.[37] However, compared with those for their analogue amides, the synthetic methods for thioamides are rather limited. We reported a highly efficient protocol for thioamide synthesis via a three-component condensation of haloalkynes, amines, and $Na_2S{\cdot}9H_2O$ (Scheme 15).[38] A series of primary, secondary, and tertiary amines, as well as alkynyl bromides, bearing different functional groups could be applied to this method. Moreover, to demonstrate the synthetic utility of this protocol, the newly formed thioamides were employed for further transformations to prepare a series of functional products. For examples, [3 + 2] cycloaddition successfully delivered the substituted thiophene **7** (Scheme 16, eq 1), while oxidation with $Na_2S_2O_8$ afforded the α-ketoamide derivative **8** in good yields (Scheme 16, eq 2).

Also, we discovered the first Cu-catalyzed one-pot domino synthesis of naphthalene derivatives from haloalkynes and amines (Scheme 17).[39] Mechanistic studies suggested that two consecutive processes, including the formation of ynamine intermediates **9** from haloalkynes with amines and the subsequent dimerization of ynamines **9**, should be involved in this transformation. Though the substrate scope was relatively limited, this method was one of the useful additions to the application of haloalkynes and paved a new way for the development of ynamine chemistry.

3.3. Nucleophilic Additions

The development of efficient and sustainable methods for the synthesis of heteroatom-containing olefins is an important task in contemporary catalysis research. Nucleophilic addition of haloalkynes to construct C(sp^2)−heteroatom bonds represents a series of reactions with significant synthetic value. Recently, we and other groups have demonstrated that different kinds of nucleophiles, including halide ions, acetates, isocyanides, phenols, thiols, imidazoles, and sulfonamides, could easily undergo nucleophilic addition to haloalkynes and generate the corresponding 2-haloalkenes **10**, which have been utilized in the construction of polysubstituted alkenes and heterocycle derivatives (Scheme 18).

3.3.1. Halogen Nucleophiles. Halogenated alkenes are one of the most versatile intermediates in organic synthesis and are often employed for transition metal-catalyzed cross-coupling reactions. However, the traditional preparation methods for dihaloalkenes usually have some limitations, such as poor selectivity and difficult purification. In 2010, we presented the first example of a facile two-step synthesis of (*Z*)-2-halo-1-iodoalkenes from simple terminal alkynes in moderate to

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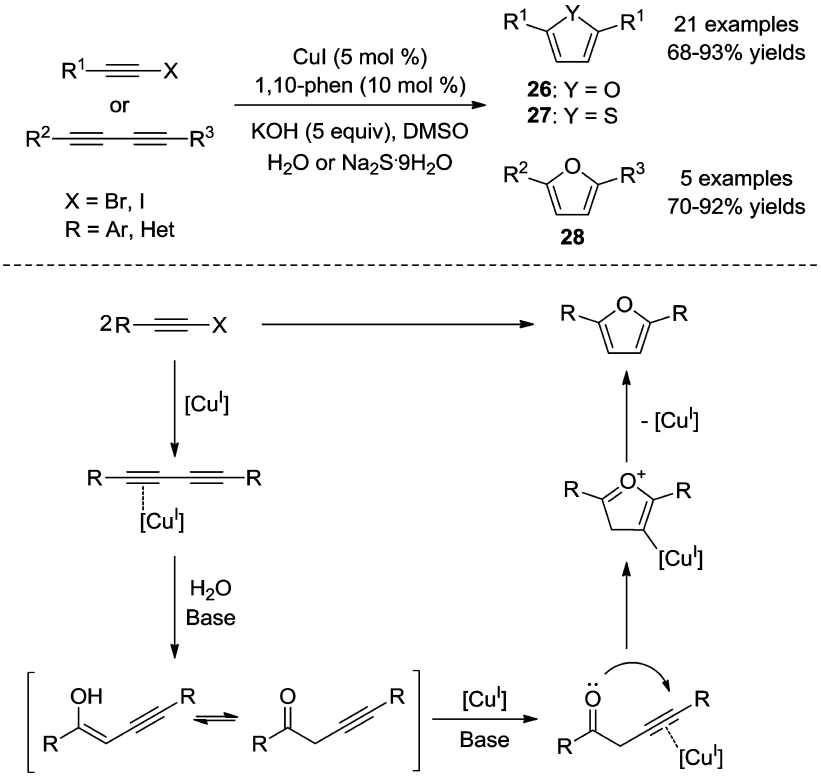
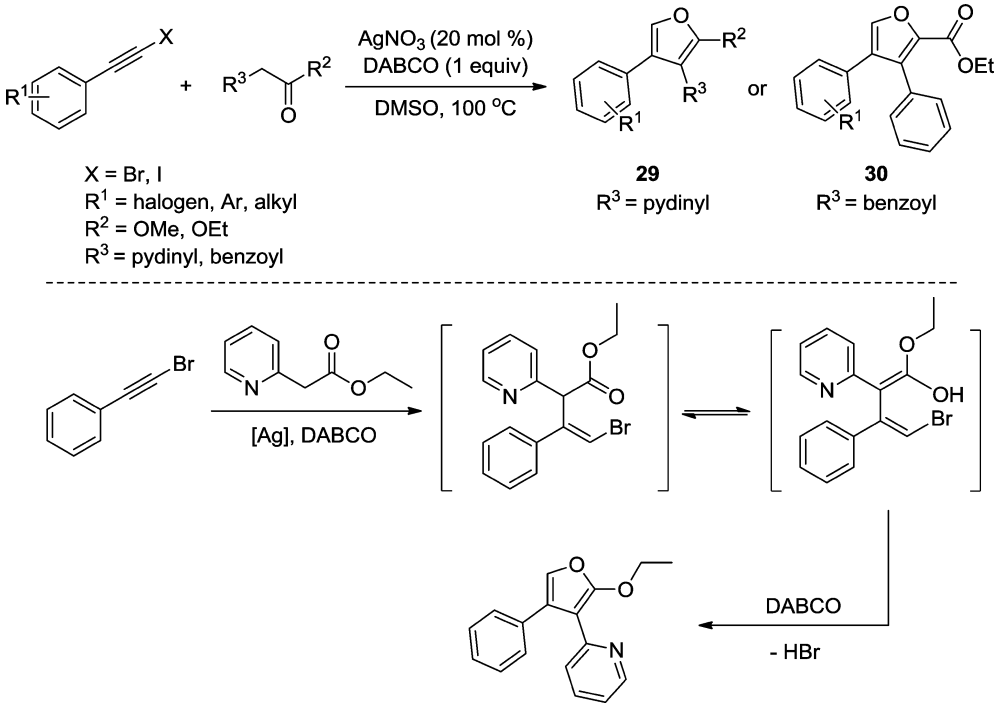
Scheme 24. Cu-Catalyzed Synthesis of 2,5-Disubstituted Furans and Thiophenes



Scheme 25. Ag-Catalyzed Synthesis of 2,3,4-Trisubstituted Furans



excellent yields with high regio- and stereoselectivities (Scheme 19).[40] In addition, the useful halo-iodoalkene product **11** could be readily transformed to the conjugated (*Z*)-haloenyne **12** and asymmetrical (*Z*)-enediyne **13** in good yields via a selective Sonogashira cross-coupling process.

Although our ongoing studies on this subject have provided a diverse set of haloalkene derivatives, it is still a challenging issue to incorporate the fluorine atom into the final olefin products by transition metal catalysis. We discovered a silver-assisted regio- and stereoselective bromofluorination reaction of terminal alkynes (Table 4).[41] It should be noted that the stereoselective functionalization of bromide moiety was successfully achieved via Sonogashira or Suzuki coupling reactions. Thus, the present synthetic strategy would be applicable to access the 1-fluoro-1,3-enyne

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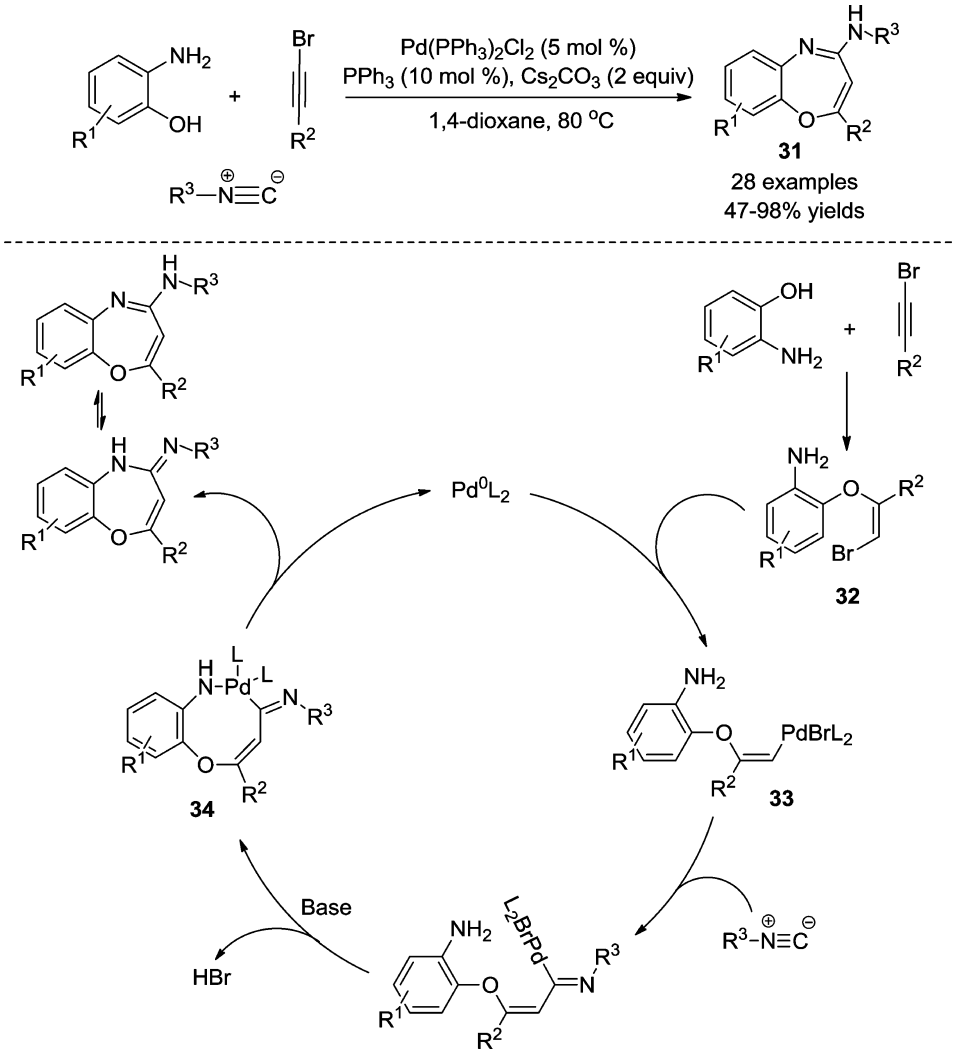
Scheme 26. Pd-Catalyzed Cascade Reaction for 4-Amine-benzo[*b*][1,4]oxazepines



compounds **14** that exist in many organic materials and biologically active products.

Interestingly, the bromofluorination of 1,*n*-diynes was also realized using this reaction system (Table 5). It was found that the electron-rich internal C−C triple bond was tolerated under the optimized conditions. Furthermore, we successfully extended this methodology to other internal electron-deficient alkynes and obtained the corresponding "HF" cross-addition products **15** and **15′** (Table 6).

A possible mechanism is proposed in Scheme 20. The bromoalkyne intermediate was first formed by the Ag-promoted bromination of terminal alkynes. Subsequently, the Ag cation was attacked by the triple bond of bromoalkyne to give a π-complex **16**, which was then converted to the corresponding vinylsilver intermediate **17** by *trans*-addition of AgF to bromoalkyne. Protonation of **17** afforded the final product and silver oxide. The high regio- and stereoselectivities were supposed to originate from the back-side attack of the fluoride anion (**18** to **17**), and the bromide atom was regarded as both an activating and a regio-directing functional group. However, another mechanism involving nucleophilic addition of fluoride to bromoalkyne providing vinylsilver intermediate **17** could not be excluded.

With haloalkyne reagents and unactivated alkenes as the starting materials, we also developed a series of Pd-catalyzed intermolecular cross-coupling reactions in ionic liquids (ILs) for the stereoselective synthesis of functionalized 1,*n*-dienes **19** and **20**.[9,42] The ionic liquids not only acted as a solvent in the reaction but also provided excess halide ions to control the *Z*/*E* selectivity. A tentative chain-walking mechanism for this transformation is proposed in Scheme 21. Pd complex was initially formed *in situ* in ILs and vinylpalladium intermediate **21** was generated by *trans*-halopalladation of the alkyne moiety in a polar solvent system in the presence of excess halide ions. Subsequently, **21** underwent alkene insertion to generate the alkylpalladium species **22**, followed by rapid β-H elimination and reinsertion to change the position of the metal on the alkyl chain, affording the intermediate **23**. Finally, a β-heteroatom elimination gave the observed dihalo-1,*n*-diene product.

3.3.2. Oxygen Nucleophiles. The β-haloenol acetate skeletons are of great significance in organic synthesis and pharmaceutical chemistry.[43] However, there are very few catalytic methods for building the OC═CX bond in one step from simple terminal alkynes. Recently, our group has presented the first example of Ag-catalyzed highly regio- and stereoselective alkyne difunctionalization reaction to afford the (*Z*)-β-haloenol acetate derivatives **24** (Scheme 22).[44] And we further developed a two-step approach for the synthesis of 2,5-disubstituted 3-iodofurans **25** involving the Sonogashira cross-coupling of terminal alkynes

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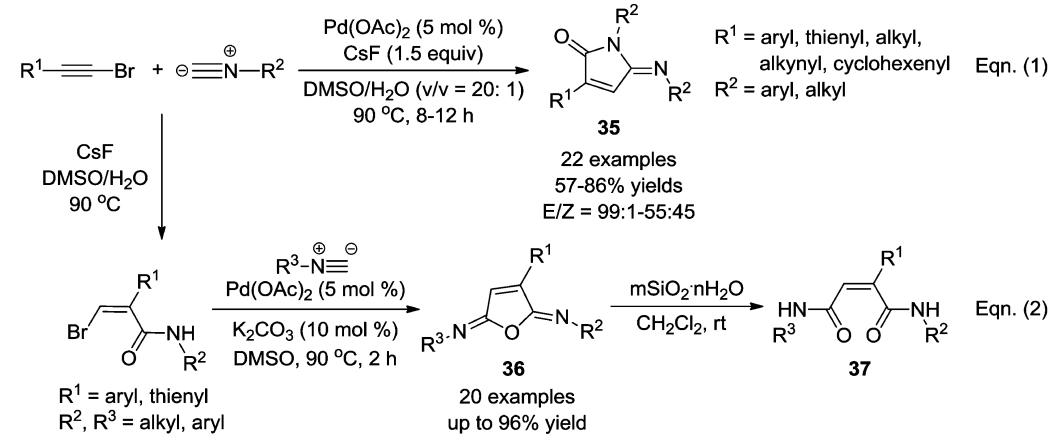
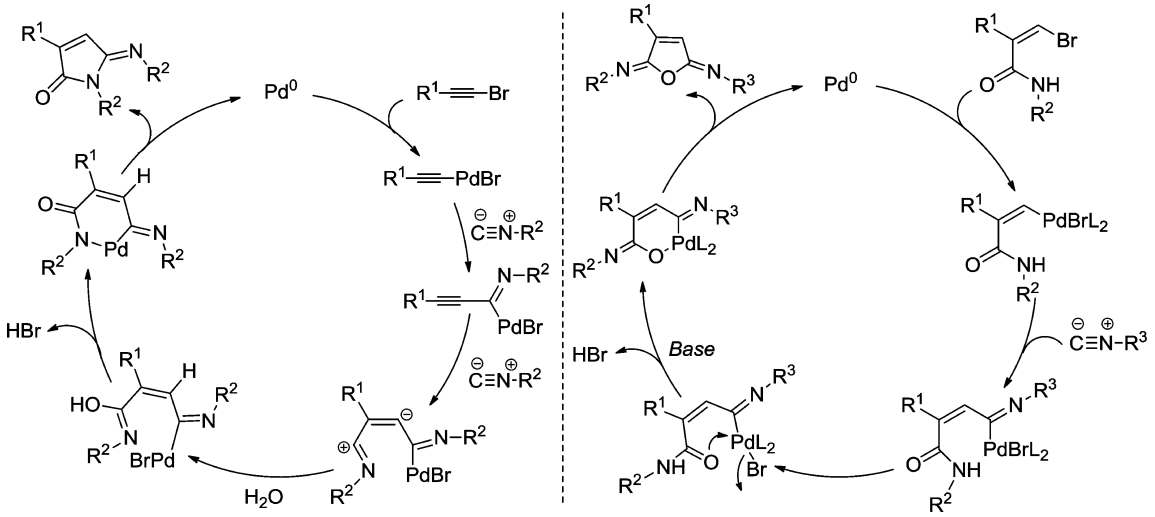
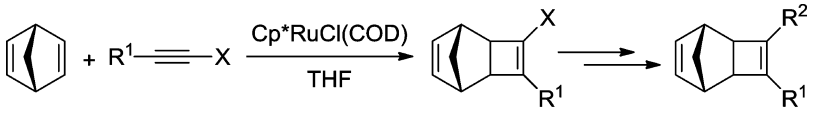
Scheme 27. Pd-Catalyzed Synthesis of 5-Iminopyrrolones and 2,5-Diimino-furans



Proposed Catalytic Cycles



Scheme 28. Ru-Catalyzed [2 + 2] Cycloaddition between Norbornadiene and Haloalkynes



and (*Z*)-*β*-haloenol acetates, followed by iodocyclization process (Scheme 23).[45]

Later, a regioselective synthesis of 2,5-disubstituted furans and thiophenes **26**−**28** using Cu catalyst from haloalkynes in one-pot procedure has been reported by our group and a plausible mechanism for this transformation is also illustrated (Scheme 24).[46] Under the treatment of Cu catalyst, 1,3-diyne was first generated by the homocoupling of haloalkyne, followed by the single alkyne hydration and enol−ketone equilibrium. Then the nucleophilic attack of carbonyl oxygen to the Cu-activated alkyne moiety might lead to the formation of the resonance stabilized oxonium ion, which could easily transfer to the furan product with the regeneration of Cu^{I} catalyst. We also developed an efficient method for the construction of 2,3,4-trisubstituted furans **29** and **30** via a sequential Ag-catalyzed nucleophilic addition and cyclization reaction of haloalkynes (Scheme 25).[47] This transformation exhibits a good aryl group tolerance and provides the corresponding products with high yields and regioselectivity.

Besides furans, *N*-heterocycles represent a long sought after target due to their wide applications in the synthesis of natural products, pharmaceuticals, and agrochemical products. Among these, benzoxazepine derivatives, an important kind of seven-membered ring, are the core scaffolds with remarkable biological activities and pharmaceutical interests.[48] In 2012, we disclosed a robust route for the synthesis of substituted 4-amine-benzo[*b*]-[1,4]oxazepines **31** in a rapid and convenient manner. This Pd-catalyzed cascade reaction of *o*-aminophenols, bromoalkynes, and isocyanides went through a selective C−O and C−N bond

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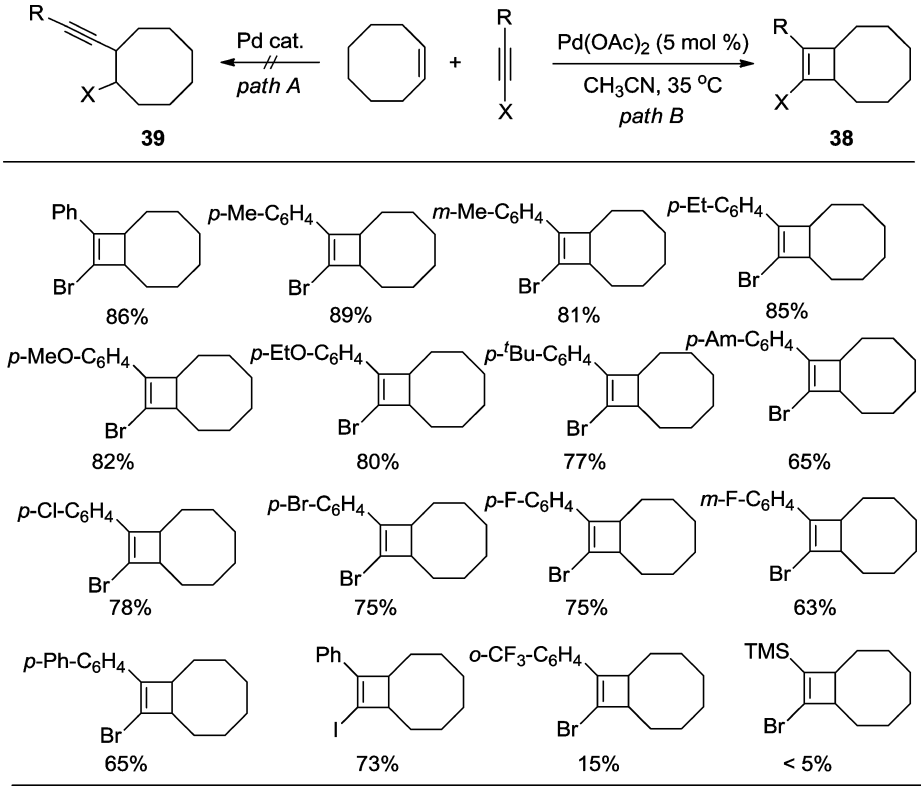
Table 7. Cycloaddition of Haloalkynes and Cyclooctene

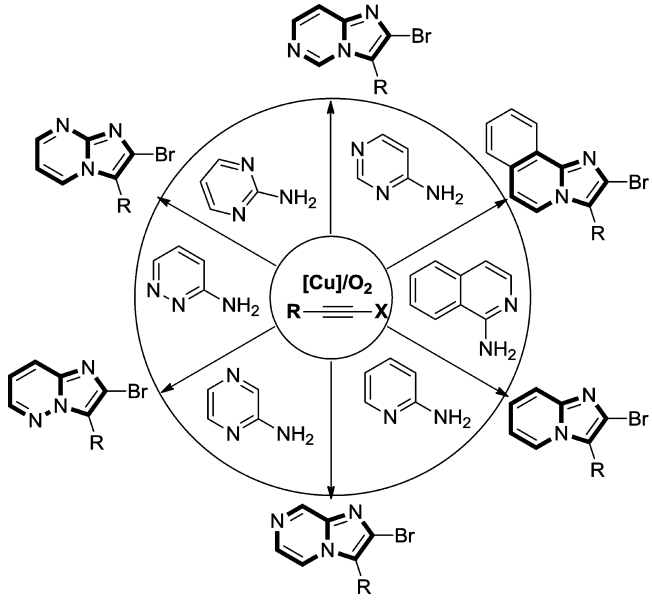


formation process and provided the desired products in good to excellent yields (Scheme 26).[49] To the best of our knowledge, this catalytic version has not yet been reported.

According to the mechanistic studies, a possible catalytic cycle for this cascade process is outlined in Scheme 26. Initial nucleophilic addition of *o*-aminophenols to bromoalkynes gave **32**, which underwent oxidative addition to Pd^0 species to form vinylpalladium species **33**. Subsequent migratory insertion of isocyanide and extrusion of HBr under basic conditions generated the eight-membered azapalladacyclic intermediate **34**. Finally, reductive elimination and isomerization afforded the benzoxazepine product, while regenerating the active Pd^0 catalyst.

Polysubstituted iminopyrrolinone derivatives are also the core structures of numerous natural products, pharmaceuticals, and organic materials.[50] Recently, we reported the first Pd-catalyzed annulation reaction of bromoalkynes and isocyanides, which provided a straightforward and practical approach to a range of 5-iminopyrrolones **35** in a regioselective manner (Scheme 27, eq 1).[51] This chemistry proceeded smoothly under mild reaction conditions and various functional groups could be tolerated with excellent selectivity. Intriguingly, during the course of this work, we noticed the formation of 2,5-diimino-furan product **36**, an isomer with the same molecular weight as 5-iminopyrrolone, though the yield was low (Scheme 27, eq 2). This observation inspired us to further investigate the process.[52] Condition screening indicated that base and reaction time were critical for the reaction pathway. Moreover, the resultant furans could readily undergo hydrolysis to afford the maleamide skeletons **37**, which might have further applications in organic synthesis and medicinal chemistry. It was supposed that the different coordination with Pd catalyst might account for the one-pot

Scheme 29. Cu-Catalyzed Synthesis of Imidazopyridine Structures



reaction giving the N-containing heterocycles, whereas the two-step procedure afforded the O-containing cyclization products.

3.4. Cycloadditions

Transition metal-catalyzed cycloadditions have demonstrated their value in the construction of ring systems and complex skeletons. Haloalkynes are worth exploring since their electron-withdrawing ability could potentially increase the reaction rate of cycloaddition. Additionally, the halide moiety could be used for further decoration, offering an alternative protocol for those

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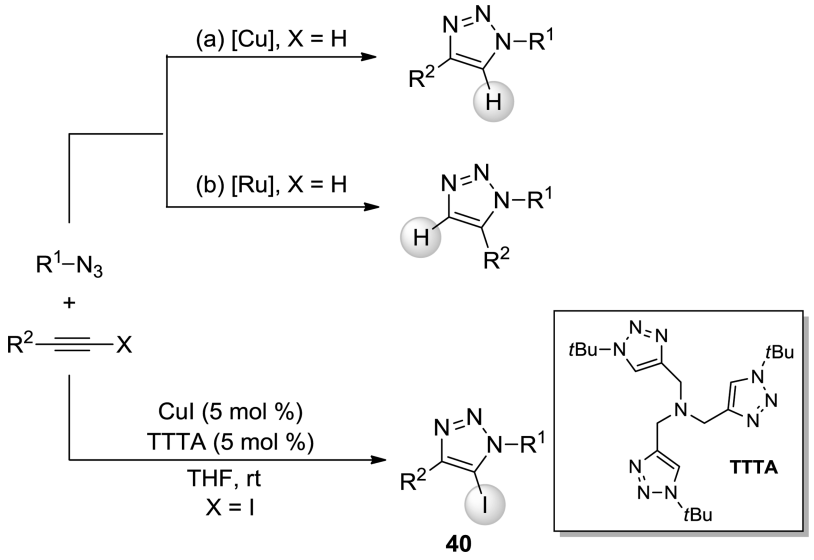
Table 8. Synthetic Routes to Substituted 1,2,3-Triazoles



cyclic structures difficult to achieve via a direct cycloaddition process.

3.4.1. [2 + 2] Cycloaddition. [2 + 2] Cycloadditions between alkenes and alkynes are known to be an efficient method for the synthesis of cyclobutene rings. In 2004, Tam's group reported the first example of Ru-catalyzed [2 + 2] cycloaddition of bicyclic alkenes with haloalkynes (Scheme 28).[53] The presence of the halide moiety was compatible in this catalytic system and greatly enhanced the reactivity of the alkyne component in the cycloaddition.

Interestingly, we discovered that the reaction between haloalkyne and cyclooctene, a flexible alkene, rather than the strained norbornene, led to a four-membered ring system **38** via a [2 + 2] cycloaddition process under mild conditions (Table 7, path B) instead of the 3-propynyl halide derivatives **39** (Table 7, path A).[28] This approach is another utilization of haloalkynes for carbocycle formation under Pd catalysis. Aromatic alkynyl bromides with either electron-donating or electron-withdrawing groups attached to the benzene rings were able to undergo the [2 + 2] cycloaddition smoothly and generated the corresponding products in moderate to good yields. It was found that the ring size of the cyclic alkene played a critical role in the formation of desired cycloadducts.

3.4.2. [3 + 2] Cycloaddition. The Cu-catalyzed azide–alkyne [3 + 2] cycloaddition reaction has been widely applied in the field of synthetic and medicinal chemistry, materials science, and polymer chemistry.[54] The efficiency and selectivity of this transformation are a direct consequence of the reactivity of *in situ* generated Cu^{I} acetylides and therefore the reaction partners are usually limited to terminal acetylenes, which produce only 1,4-disubstituted triazoles. A general method for the regio-controlled synthesis of different substituted triazoles would be a valuable addition to the "click chemistry". One prominent example is the rapid and practical method disclosed by Hein, Fokin, and co-workers for the chemo- and regioselective synthesis of iodotriazoles **40** from organic azides and iodoalkynes (Table 8).[55] The employment of the haloalkyne reagent was the key to the success of this transformation and their reactivity appeared to surpass that of terminal alkynes. As an additional benefit, the 5-iodo-1,2,3-triazole products are versatile synthetic intermediates that are amenable to further functionalizations.

Imidazo-containing skeletons are also versatile building blocks for natural products and bioactive compounds that have great

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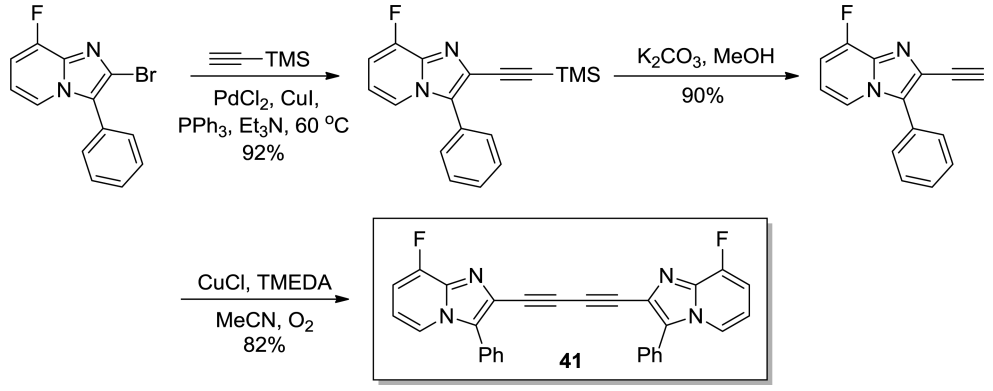
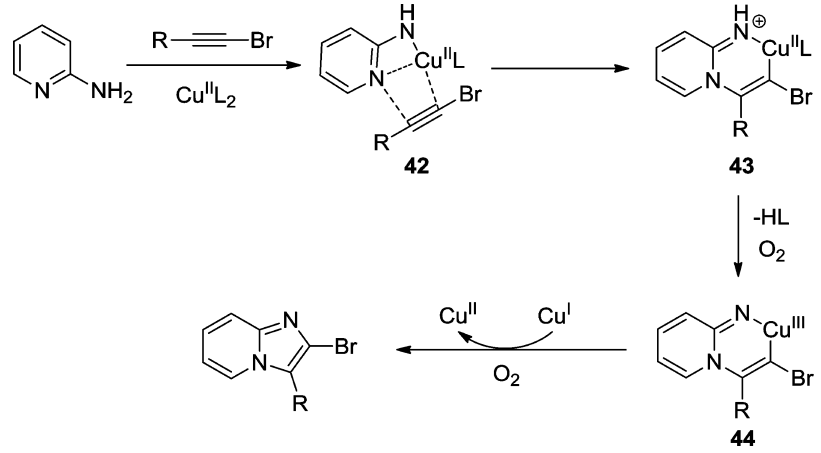
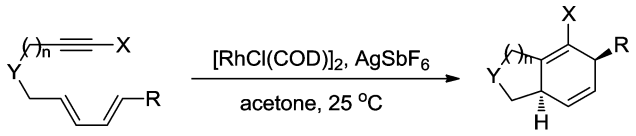
Scheme 30. Synthetic Applications of Imidazopyridine Products



Scheme 31. Proposed Mechanism



Scheme 32. Rh-Catalyzed [4 + 2] Cycloaddition of Diene-Tethered Alkynyl Halides



X = Cl, Br, I
Y = O, NTs, $C(CO_2Et)_2$
R = H, Me

70-87% yields

importance in the area of pharmaceuticals.[56] In 2012, we revealed a new and convenient protocol to construct 2-halo-substituted imidazo[1,2-*a*]pyridines via a Cu-catalyzed oxidative cyclization reaction of *o*-aminopyridines and haloalkynes. A variety of 2-halo-substituted imidazopyridine, imidazopyrazine, and imidazopyrimidine products were obtained with high regioselectivity under mild reaction conditions (Scheme 29).[57] Furthermore, the resultant 2-halo-substituted products could be easily functionalized via elegant cross-coupling reactions. A highly conjugated structure **41** was successfully achieved after three-step modifications (Scheme 30). The practicality of this Cu-catalyzed oxidative cyclization reaction should find its potential utilities in optoelectronic materials.

According to the mechanistic studies, this reaction was likely to be initiated by the coordination of 2-aminopyridine to Cu catalyst, and complex **42** was formed (Scheme 31). Then, migratory insertion of haloalkyne occurred to give **43**, with the formation of a new $C(sp^2)$−N bond. The organocopper species **43** subsequently underwent ligand exchange with the remaining nitrogen and was further oxidized to a reactive Cu^{III} intermediate **44**. Finally, the reductive elimination of **44** afforded the cyclization product. Although another mechanistic scenario involving single electron transfer (SET) might also be possible, the radical-trapping experiments indicated that the radical scavengers, such as TEMPO and 1,1-diphenylethylene did not inhibit the present reaction. Thus, the organocopper pathway was preferred for this transformation.

3.4.3. [4 + 2] and [2 + 2 + 2]Cycloadditions. Transition metal-catalyzed [4 + 2] cycloaddition is a highly convergent and convenient method for the construction of six-membered rings. Tam's group[58] reported the first example of cationic Rh-catalyzed intramolecular [4 + 2] cycloaddition of diene-tethered alkynyl halides (Scheme 32). The halide moiety was found to be compatible with this catalytic system. Importantly, the halogen-containing cycloadducts could be transformed into various products of synthetic usefulness.

[2 + 2 + 2] Cycloaddition is another important method for the synthesis of six-membered rings. In 2009, Nicolaou et al.[59] reported the first total synthesis of sporolides B, an unusual natural product isolated from the marine actinomycete *Salinospora tropica*. They successfully forged the chlorobenzenoid indane structural motif using a regio- and stereoselective Ru-catalyzed intermolecular [2 + 2 + 2] cycloaddition reaction between two acetylenic units, one of which bears the chlorine residue (Scheme 33). This excellent work showed the prominent potential of haloalkyne derivatives in natural product synthesis.

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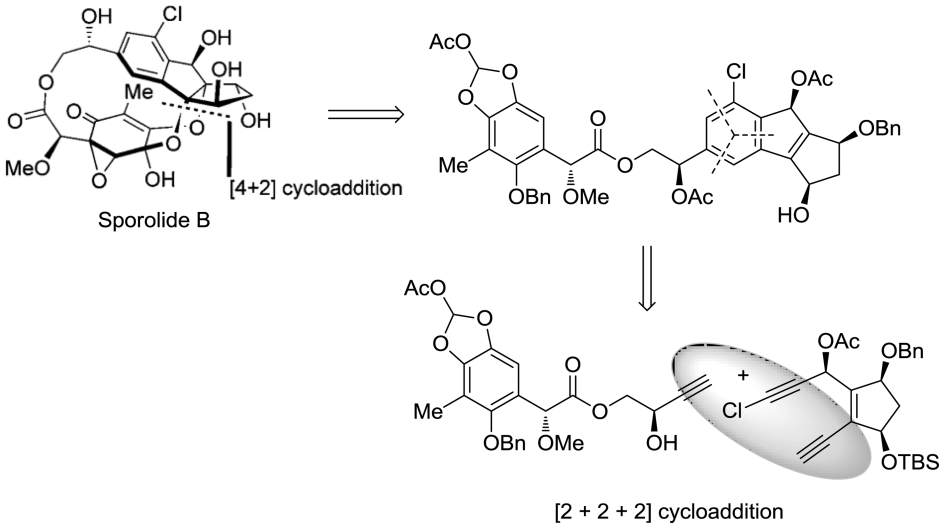
Scheme 33. [2 + 2 + 2] Cycloaddition of Haloalkyne in Natural Product Synthesis



4. CONCLUSIONS AND OUTLOOK

This Account has highlighted our recent advances in the development of novel and efficient methods involving haloalkyne reagents. The transformations presented are significant due to their rapid assembly of structural complexity. The unique reactivity of haloalkynes allow these reactions to deliver a diverse array of novel acyclic and cyclic structures representing prevalent and important scaffolds, as well as being useful platforms for further transformations. In addition, we have also made efforts in elucidating the mechanistic pathways for these chemical processes, which provide us valuable insight to develop more green and atom-economical methodologies with the utilization of haloalkynes. We hope this Account will help promote continued interest in the field of haloalkyne chemistry.

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Notes

The authors declare no competing financial interest.

Biographies

Wanqing Wu received her Ph.D. from Peking University with Prof. Zhen Yang and Chi-Sing Lee in 2010. And then she became a postdoctoral fellow at South China University of Technology (SCUT) with Prof. Huanfeng Jiang and was promoted to Associate Professor in 2012. Her research interests include the development and applications of new synthetic methods.

Huanfeng Jiang received his Ph.D. from Shanghai Institute of Organic Chemistry, CAS, in 1993 with Prof. Xiyan Lu and then became a research fellow at Guangzhou Institute of Chemistry, CAS. In 2003, he joined the faculty at South China University of Technology (SCUT) as the Leading Professor of Chemistry. He received Chinese Chemical Society-BASF Young Investigator's Award in 2002 and National Natural Science Funds for Distinguished Young Scholar in 2006. His current research efforts are focused on synthetic methodology and green and sustainable chemistry.

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