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Preface

Green method, atom economy, and concise synthesis are terms frequently mentioned in chemistry-related publications and presentations nowadays. Inspired by the requirements of green and sustainable chemistry, considerable efforts have been devoted to developing general and practical methods to construct complex molecules by taking advantages of chemical reagents with diverse and tunable reactivity. Haloalkynes, such as bromoalkynes, chloroalkynes, and iodoalkynes, are a significant class of molecules that have these futures and been widely utilized in organic synthesis.

This book summarizes the general methods to prepare haloalkyne reagents and also presents the selected examples to highlight the progress on the development and applications of convenient and concise synthetic approaches involving haloalkynes. According to the reactive sites of haloalkynes involved in the transformations, we classify these reactions into three types: (i) the transformations of carbon–halo bond motif; (ii) the diverse functionalization of carbon–carbon triple bond unit; and (iii) the reactions involving both carbon–halo bond motif and carbon–carbon triple bond unit. The emphasis is put on the reaction mechanism aspects and the synthetic utilities of the obtained products.

The primary purpose of this book is to illustrate the diverse reactivities and applications of haloalkyne reagents, to describe the experimental techniques of these valuable transformations in detail, as well as to enlighten the researchers to answer the unsolved problems in haloalkyne chemistry. This book should be useful to researchers in organic and organometallic chemistry as well as catalysis from both academia and industry. Significantly, doctorate students and postdoctoral researchers should be motivated by these innovations in chemistry.

I am especially grateful to the cooperative contributions made by all the authors. Without their efforts and expertise, this book would not have been possible. I would also like to thank the organizational support from Springer to overcome the troubles encountered in the production of this book.

Guangzhou, China Huanfeng Jiang
September 2015

Contents

Abbreviations

Ac	Acetyl
Ad	Adamantyl
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphtyl
Bn	Benzyl
BQ	Benzoquinone
Bu	Butyl
COD	Cyclooctadiene
Cp	Cyclopentadienyl
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
dba	Dibenzylideneacetone
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMEDA	*N*,*N*′-Dimethyl-1,2-ethanediamine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
Equiv	Equivalent(s)
Et	Ethyl
h	Hour(s)
HMPT	Hexamethyl phosphoryl triamide
ILs	Ionic liquids
*i*Pr	Isopropyl
NBS	*N*-Bromosuccinimide
NHC	*N*-Heterocyclic carbene
NIS	*N*-Iodosuccinimide
Nu	Nucleophile
OTf	Trifluoromethanesulfonic
PE	Petroleum ether
Ph	Phenyl
Py	Pyridyl

1,10-phen	1,10-Phenanthroline
rt	Room temperature
$scCO_2$	Supercritical carbon dioxide
Sia	(Secondary)isoamyl
TBAB	Tetrabutylammonium bromide
TBAF	Tetrabutylammonium fluoride
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-Butyldimethylsilyl
TEA	Triethyl amine
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin-layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Tol	4-Methylphenyl

Chapter 1
Introduction

Abstract Inspired by the demand of green and sustainable chemistry, modern synthetic chemists have devoted to develop general and practical methods to construct complex molecules. Due to the *sp* hybridization of the triple bond and the connected halogen atom, haloalkynes, such as bromoalkynes, chloroalkynes and iodoalkynes, have shown both controllable electrophilic and nucleophilic properties, rendering them highly versatile and robust synthons. As the immense usefulness of haloalkynes, impressive efforts have been devoted to this area in the past decades and many novel chemical reactions have been developed. In this chapter, we will introduce the physical property of haloalkynes, classify the reaction intermediate types derived from haloalkynes, and also hope to give the readers a comprehensive understanding of haloalkyne chemistry.

Keywords Green and sustainable chemistry · General and practical methods · Haloalkyne chemistry · Controllable electrophilic and nucleophilic properties · Versatile and robust synthons

The development of efficient and practical synthetic methods upon readily available reagents to construct molecular complexity has greatly accelerated the advancement of synthetic chemistry and related subjects. Inspired by the demand of green and sustainable chemistry, modern synthetic chemists have devoted to develop general and practical methods to construct complex molecules, as well as maximizing atom economy and minimizing synthetic steps [1]. During the past few decades, considerable progress has been achieved to fulfil these goals by taking advantages of chemical reagents with diverse and tunable reactive properties. Among them, haloalkynes, such as bromoalkynes, chloroalkynes and iodoalkynes, are a significant class of molecules that have been widely utilized in organic synthesis [2].

Generally, haloalkynes, especially iodoalkynes, are good Lewis acids. In 1981, Laurence and co-workers have demonstrated that the Lewis acidity of haloalkynes could affect the vibrational spectra of these compounds [3]. In 2000, Goroff and co-workers reported an unusual solvent effect, in which the solvent could significantly change the ^{13}C NMR chemical shift of iodoalkynes **1** and **2** (Table 1.1) [4].

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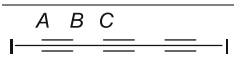
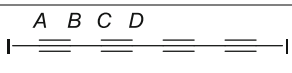
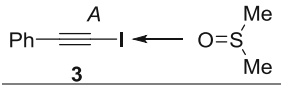
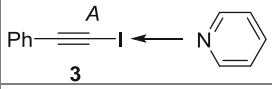
Table 1.1 ^{13}C NMR chemical shifts of **1** and **2** (in ppm)

 **1**		 **2**	
Compound **1** in	δ(*A*)	δ(*B*)	δ(*C*)
$CDCl_3$	0.9	78.5	59.7
DMSO-d_6	14.6	76.3	58.8
Compound **2** in	δ(*A*)	δ(*B*)	δ(*C*, *D*)
$CDCl_3$	1.9	78.8	58.8, 62.0
DMSO-d_6	17.9	77.4	58.3, 62.7

Later, they confirmed that it was a general phenomenon. The chemical shift of C-1 in 1-iodo-2-phenylethyne (**3**) is 6.2 ppm in $CDCl_3$, but moves to 17.7 ppm in DMSO-d_6 and 19.4 ppm in pyridine-d_5 (Table 1.2) [5]. Computational evidences indicated that this solvent effect came directly from polarization of iodoalkyne triple bond in a Lewis acid-base complex with the solvent. It could predict that an increase in the electron density at C-1 would lead to a decrease in chemical shift.

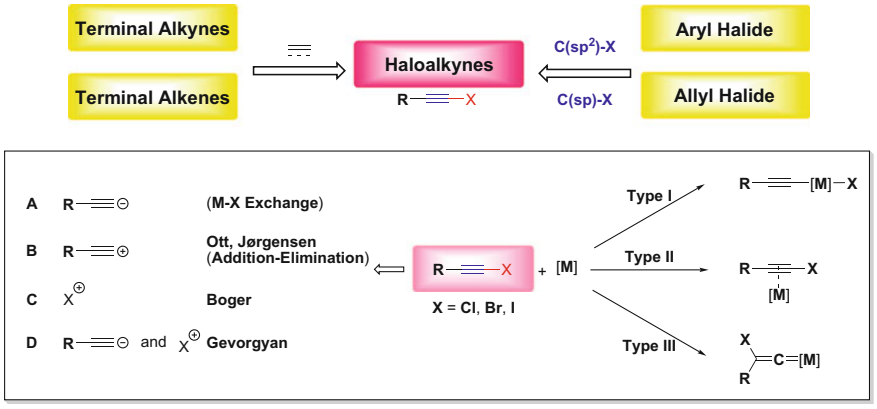
Due to the *sp* hybridization of the triple bond and the connected halogen atom, haloalkynes show both controllable electrophilic and nucleophilic properties, rendering them highly versatile and robust synthons. Traditionally, haloalkyne reagents are served as a source of acetylides through metal-halogen exchange (Scheme 1.1, A). Until 1943, Ott [6] disclosed that haloalkyne derivatives could also be employed as equivalents of electrophilic acetylenic moiety, which would go through an addition-elimination procedure upon the reaction with nucleophiles. Importantly, the first enantioselective version was realized by Jørgensen [7] with the treatment of a chiral phase-transfer catalyst in 2006 (Scheme 1.1, B). Additionally, Boger [8] and Gevorgyan [9] reported respectively that haloalkynes could serve as effective sources of the corresponding X^+ ion or both X^+ and acetylide ions in the presence of organolithium species (Scheme 1.1, C and D). Noteworthy, as the continuous efforts of Jiang's group, the potential reactive abilities of haloalkyne reagents became fully apparent along with the development

Table 1.2 ^{13}C NMR chemical shifts of **3** formed Lewis acid-base complexes (in ppm)

 **3**	 **3**
Compound **3** in	δ(*A*)
$CDCl_3$	6.2
DMSO-d_6	17.7
pyridine-d_5	19.4

of transition metal catalysis [2]. Generally, under the treatment of transition metal catalysts, haloalkynes can be deemed as a dual functionalized molecule. Depending on reaction conditions, several reaction intermediates, such as σ-acetylene-metal complex (Scheme 1.1, Type I), π-acetylene complex (Scheme 1.1, Type II) and halovinylidene-metal complex (Scheme 1.1, Type III) can be formed and undergo further transformations to construct various of useful compounds. Additionally, the reactive halogen substituents can be further functionalization, which permits the rapid assembly of structural complexity. As the immense usefulness of haloalkynes, impressive efforts have been devoted in this area in the past decades and many novel chemical reactions have been developed [10].

In this book, we will classify the general methods to prepare haloalkyne reagents and also present selected examples to highlight the progress on the development and applications of convenient and concise synthetic approaches involving haloalkyne reagents. The designed methods, as well as serendipitous observations will be discussed with special emphasis on the mechanistic aspects and the synthetic utilities of the obtained products, aiming to illustrate the potential applications of haloalkyne chemistry in a wide spectrum of fields, including natural-product synthesis, materials science, and bioorganic chemistry. Importantly, the general procedure for each transformation of haloalkynes is described in detail. This book should be useful to researchers in organic and organometallic chemistry as well as catalysis both from academia and industry. Significantly, doctorate students, post-doctoral researchers and young researchers should be motivated by these innovations in chemistry. We hope this book could not only draw the blueprint of haloalkyne chemistry, and help the readers to comprehensively know and understand the diverse reactivities and applications of haloalkyne reagents, but also could be used as a handbook for researchers to develop novel catalytic systems to answer the unsolved challenges in haloalkyne chemistry and exploit new research areas.



Scheme 1.1 Potential reaction pathways of haloalkynes in transition metal catalysis

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Chapter 2
Preparation of Haloalkynes

Abstract Traditionally, haloalkynes were accessible through the deprotonation of the corresponding terminal alkynes with a strong base, followed by trapping with a halogenating reagent. During the past decades, several mild and convenient methods have been developed, thus increasing the attractiveness of this class of compounds in organic synthesis. Among which, the electrophilic bromination of terminal alkynes with *N*-bromosuccinimide (NBS) and Ag catalyst is one of the most commonly used methods for the preparation of bromoalkynes due to the mild reaction conditions, high efficiency and simple manipulation. In this chapter, we will detailedly describle the general and practical methods to prepare bromoalkynes, chloroalkynes, and iodoalkynes.

Keywords Terminal alkynes · Ag catalyst · Bromoalkyne synthesis · Chloroalkyne synthesis · Iodoalkyne synthesis

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 2.1), [1] thus increasing the attractiveness of this class of compounds in organic synthesis. Among which, the electrophilic bromination of terminal alkynes with *N*-bromosuccinimide (NBS) and Ag catalyst [2] is one of the most commonly used methods for the preparation of bromoalkynes due to the mild reaction conditions, high efficiency and simple manipulation (Scheme 2.2) [3].

General Procedure for the Synthesis of Bromoalkynes: To a solution of alkyne (1 equiv) in acetone (0.2 mmol/mL) was added NBS (1.1 equiv) and $AgNO_3$ (10 mol%) at room temperature with magnetic stirring. After 2–3 h, the reaction mixture was diluted with hexanes (100 mL) and filtered off the crystals formed. The filtrate was concentrated under reduced pressure and passed through a pad of silica gel using hexanes as an eluent. The filtrate was collected and evaporated under reduced pressure to afford a pure colorless oil of bromoalkyne.

General Procedure for the Synthesis of Chloroalkynes: To a solution of alkyne (1 equiv) in CCl_4 (2 mmol/mL) was added Cs_2CO_3 (1.1 equiv) and Bu_4NCl (5 mol %) at 70 °C with magnetic stirring. After 6–7 h, the reaction mixture was diluted

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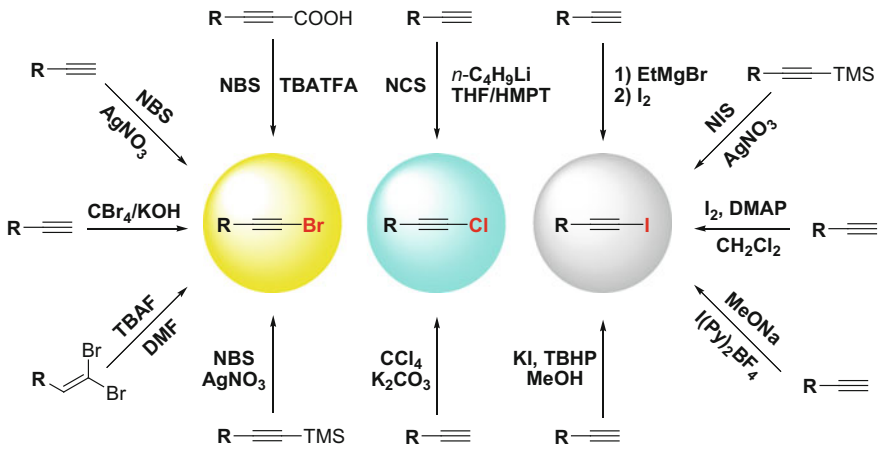
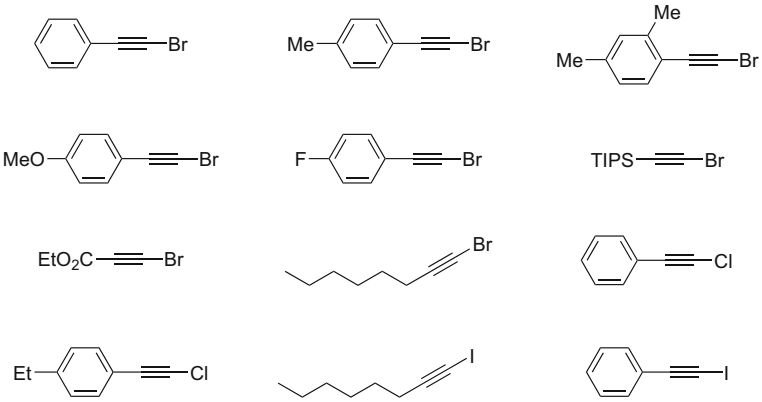


Scheme 2.1 Preparation methods for haloalkynes



Scheme 2.2 Representative haloalkynes

with hexanes (100 mL) and filtered off the crystals formed. The filtrate was concentrated under reduced pressure and passed through a pad of silica gel using hexanes as an eluent. The filtrate was collected and evaporated under reduced pressure to afford a pure colorless oil of chloroalkyne.

General Procedure for the Synthesis of Iodoalkynes: To a solution of alkyne (1 equiv) in acetone (0.2 mmol/mL) was added NIS (1.1 equiv) and $AgNO_3$ (10 mol %) at room temperature with magnetic stirring. After 2–3 h, the reaction mixture was diluted with hexanes (100 mL) and filtered off the crystals formed. The filtrate was concentrated under reduced pressure and passed through a pad of silica gel using hexanes as an eluent. The filtrate was collected and evaporated under reduced pressure to afford a pure colorless oil of iodoalkyne.

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Chapter 3
Reactions of Haloalkynes

Abstract Haloalkynes are a significant class of molecules that have been widely utilized in organic synthesis. In this chapter, we will describe representative examples of haloalkynes, with particular attention paid to the reaction design and mechanistic investigation as well as the general experimental procedures. According to the reactive sites of haloalkynes involved in the transformations, the reactions are classified to three types: (i) the transformations of carbon-halo bond motif; (ii) the diverse functionalization of carbon-carbon triple bond unit; (iii) the reactions involved both carbon-halo bond motif and carbon-carbon triple bond unit. These transformations present a powerful tool for haloalkynes to construct molecular complexity efficiently.

Keywords Haloakyne reagents · Diverse transformations · Reactive sites · Reaction design · Mechanism investigation

In this chapter, the emphasis will be put on the reaction development of haloalkynes. According to the reactive sites of haloalkynes involved in the transformations, the reactions are classified to three types: (i) the transformations of carbon-halo bond motif (Scheme 3.1, path A); (ii) the diverse functionalization of carbon-carbon triple bond unit (Scheme 3.1, path B); (iii) the reactions involved both carbon-halo bond motif and carbon-carbon triple bond unit (Scheme 3.1, path C). These transformations present a powerful tool to construct molecular complexity efficiently. Representative examples are described, with particular attention paid to the reaction design and mechanistic investigation.

3.1 Transformations of Carbon-Halo Bond Motif

Alkyne motif is one of the most important and useful building blocks in natural products, pharmaceuticals, as well as functional materials. Subsequently, the construction of alkyne motif contained molecules has attracted considerable attention during the past decades. Transformations of haloalkyne reagents based on the

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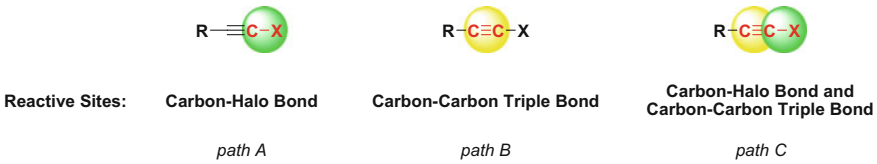


Scheme 3.1 Reactive sites of haloalkynes

highly reactive carbon-halo bond, could realize the facile synthesis of skeletons that previously were unable or difficult to prepare.

3.1.1 Construction of Carbon-Carbon Bond

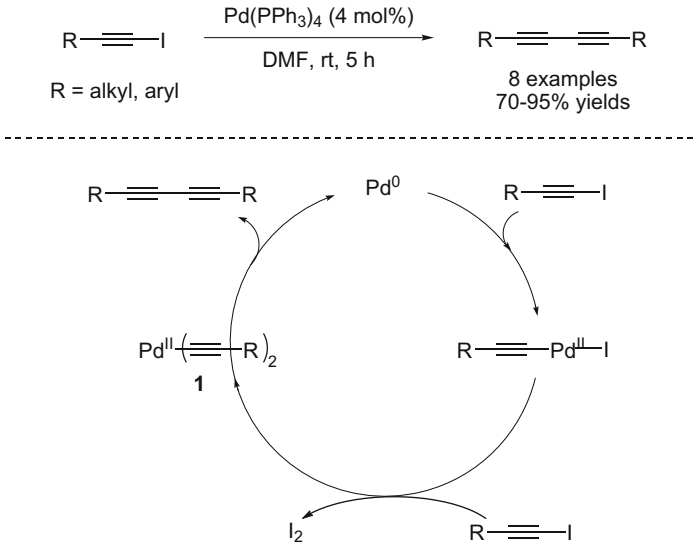
3.1.1.1 Construction of C(sp)–C(sp) Bond

Conjugated diynes, especially 1,3-diyne compounds, are of vital significance as versatile building blocks in the synthesis of natural products, bioactive compounds, as well as functional materials [1, 2]. Consequently, the construction of conjugated diynes has attracted great attention for a long time.

C(sp)–C(sp) Homo-Coupling

Due to the importance of symmetrical 1,3-diyne compounds, they are usually synthesized either by Cu-catalyzed homo-coupling reactions including Glaser coupling [3], Eglinton coupling [4], Hay coupling [5, 6], and Pd-mediated homo-coupling reactions [7] or other related modified methods [8]. In this context, the homo-coupling of haloalkynes would provide an alternative route to access 1,3-diyne compounds. In 2003, Lee's group [9] documented a highly efficient Pd^0-catalyzed homo-coupling reaction of 1-iodoalkynes to construct symmetrical 1,3-diynes under mild and simple reaction conditions. This reaction did not use copper salts or other metal reagents and a base, and was conducted under an inert atmosphere, thus preventing side reactions associated with the Glaser coupling reaction in which O_2 is usually used as the oxidant. Although the exact mechanism of this homo-coupling reaction of 1-iodoalkynes was not clear yet, the author proposed that the formation of dialkynylpalladium intermediate (**1**) through the oxidative addition product of Pd^0 to 1-iodoalkyne reacted with another 1-iodoalkyne, which then converted to the 1,3-diyne and iodine (Scheme 3.2).

General Procedure for Pd-Catalyzed Homo-Coupling Reactions of Iodoalkynes: To $Pd(PPh_3)_4$ (4 mol%) was added a solution of 1-iodoalkyne (1 mmol) in dry *N*,*N*-dimethylformamide (DMF) (2 mL) under a nitrogen atmosphere. After 2–5 h, the mixture was poured into an aqueous saturated $NaHCO_3$ solution (15 mL) and then extracted with diethyl ether (15 mL × 3). The combined organics were washed with

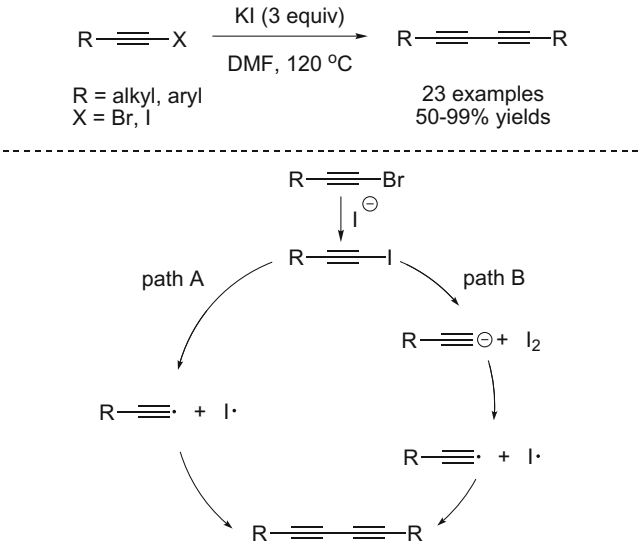


Scheme 3.2 Pd-catalyzed homo-coupling reactions of iodoalkynes

brine (15 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the corresponding 1,3-diyne.

Given the environmental and economical factors, the development of transition metal-free reaction systems for the construction of 1,3-diynes is highly demanded. In 2010, Jiang's group [10] successfully developed an efficient synthetic method to 1,3-diynes from haloalkynes under the treatment of KI in DMF solvent. This approach also featured both oxidant and base free (Scheme 3.3). Generally, better yields of symmetrical 1,3-diynes were obtained from iodoalkynes than the corresponding bromoalkynes. Both aromatic and aliphatic alkynyl halides could perform this homo-coupling reaction smoothly under the standard reaction conditions. And diverse functional groups on haloalkyne substrates, such as fluoro, chloro, hydroxyl, nitrile group could be tolerated. To the reaction mechanism, the author proposed the involvement of iodoalkyne intermediate generated from the substitution of bromoalkyne with KI, which might undergo two pathways for the obtained 1,3-diyne product. The iodoalkyne would be transformed to iodine- and alkyne-radicals, which were then homo-coupled to deliver the symmetrical 1,3-diyne and iodine (Scheme 3.3, path A). Alternatively, the iodoalkyne intermediate was decomposed to iodine and alkyne anion, followed by a redox process to give the alkyne radical, which would undergo further transformation to afford the final product (Scheme 3.3, path B).

General Procedure for KI-Mediated Homo-Coupling Reactions of Haloalkynes: Haloalkyne (1 mmol) and KI (3 mmol) in DMF (2 mL) were stirred at 120 °C for 12 h in a Schlenk tube (25 mL). Water (8 mL) was added after the completion of the



Scheme 3.3 KI-mediated homo-coupling reactions of haloalkynes

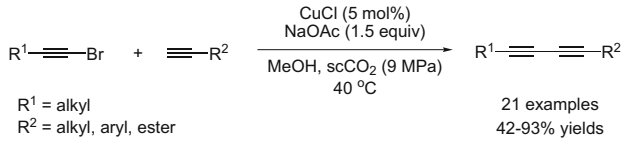
reaction, the aqueous solution was extracted with diethyl ether (15 mL × 3), and the combined extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the corresponding 1,3-diyne.

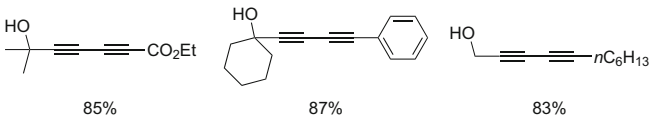
C(sp)–C(sp) Cross-Coupling

Compared to symmetrical 1,3-diyne compounds, the synthesis of unsymmetrical 1,3-diynes is rather difficult, due to the competition of homo-coupling reaction. Among the methods for the synthesis of unsymmetrical 1,3-diynes, Cadiot-Chodkiewicz cross-coupling reaction is one of the most representative examples [11]. In 2007, Jiang's group documented a mild and environmentally friendly method for the Cu-catalyzed Cadiot-Chodkiewicz coupling of bromoalkynols with terminal acetylenes in $scCO_2$ utilizing NaOAc as base (Table 3.1) [12]. Methanol, as a co-solvent, could improve the dissolution of inorganic salts in $scCO_2$ and facilitate the reaction rate. This new cross-coupling reaction system not only tolerated a wide range of functional groups to deliver diverse unsymmetrically substituted 1,3-diynes, but also avoided the employment of amine. However, experiment results revealed that this transformation was sensitive to the pressure of $scCO_2$ and high reaction temperature.

General Procedure for Cu-Catalyzed Cross-Coupling Reactions of Bromoalkynols: CuCl (5 mol%), AcONa (1.5 mmol), MeOH (1 mL), bromoalkyne (1 mmol) and alkyne (1.2 mmol) were added to an autoclave vessel (15 mL) in

Table 3.1 Cu-catalyzed cross-coupling reactions of bromoalkynols





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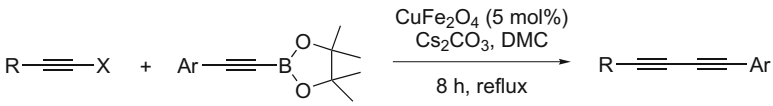
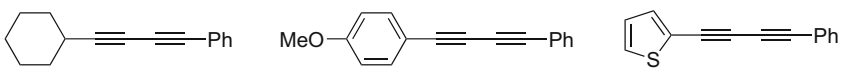




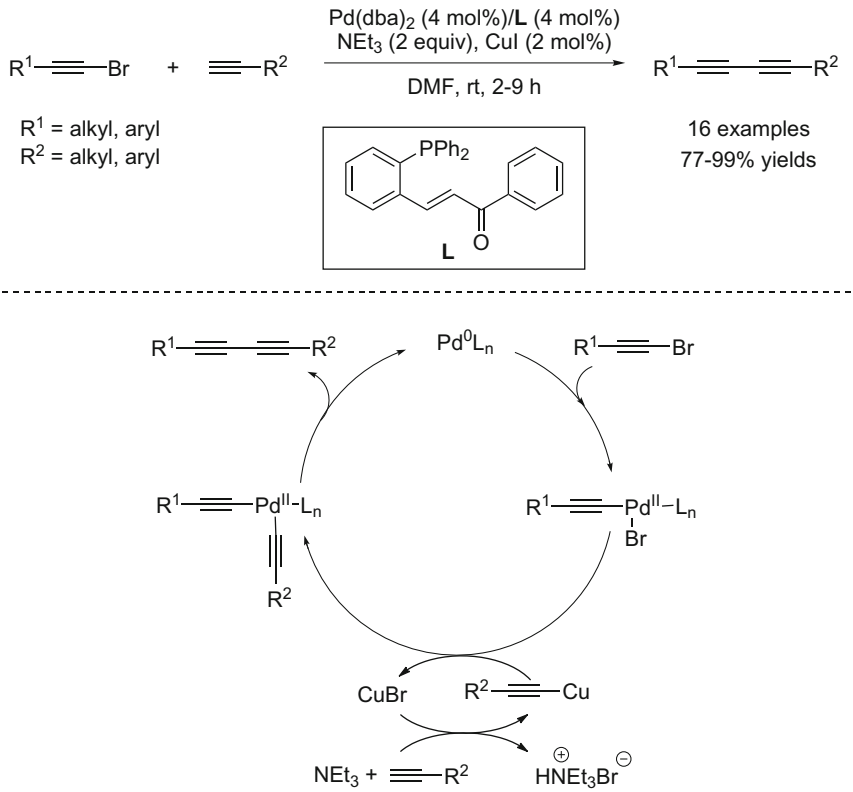
82% 82% 84%

Scheme 3.4 $CuFe_2O_4$ nanoparticle catalyzed cross-coupling reactions of haloalkynes

sequence. Liquid CO_2 was pumped into the autoclave by a cooling pump until the desired pressure was reached then the autoclave was heated in an oil bath under magnetic stirring for the desired reaction time. After the reaction was completed, the autoclave was allowed to cool to 0 °C and CO_2 was vented. The residue was extracted with Et_2O (20 mL). The extract was filtered and concentrated under reduced pressure to give a residue that was purified by chromatography on a silica gel column using light PE-EtOAc as eluent.

Later in 2014, Ranu and co-workers developed a novel protocol for C(sp)–C(sp) cross-coupling of haloalkynes with pinacol ester of alkynyl boronic acid in dimethyl carbonate (DMC) using a commercially available and magnetically separable $CuFe_2O_4$ nanoparticle catalyst. The reaction has a broad substrate scope and tolerates diverse functional groups. Importantly, the $CuFe_2O_4$ nanoparticle catalyst was recycled more than 10 times with marginal loss of activity in subsequent runs (Scheme 3.4) [13].

General Procedure for $CuFe_2O_4$ Nanoparticle Catalyzed Cross-Coupling Reactions of Haloalkynes: A suspension of haloalkyne (1 mmol), pinacol ester of



Scheme 3.5 Ligand accelerated Pd-catalyzed cross-coupling reactions of bromoalkynes

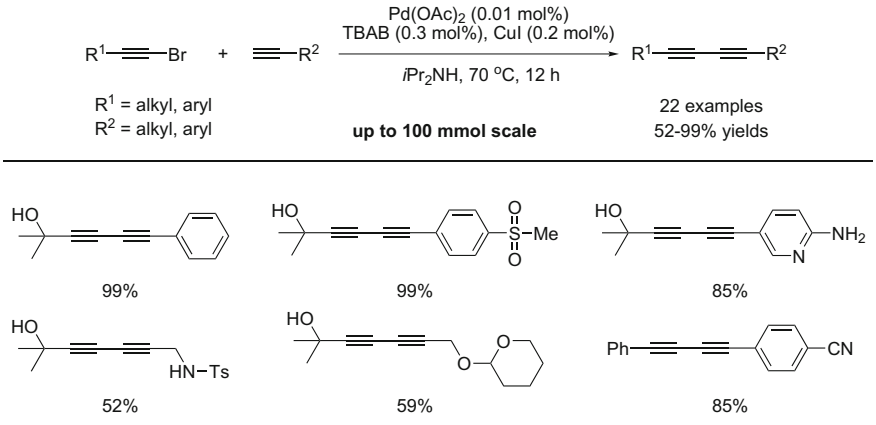
alkynelboronic acid (1.5 mmol), Cs_2CO_3 (2 mmol), and $CuFe_2O_4$ (5 mol%) in DMC (5 mL) was stirred at 100 °C (oil bath temperature) for 8 h under argon. The reaction mixture was allowed to cool and extracted with ethyl acetate (20 mL × 3). The organic extracts were washed with brine, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was obtained by flash column chromatography.

Except for Cu catalysis, Pd complexes also serve as a powerful catalysts to construct several conjugated diynes [14]. However, the competitive homo-coupling process is still the major challenge in Pd-catalyzed C(sp)–C(sp) cross-coupling reactions. In 2008, Lei's group [15] reported an efficient method to synthesize unsymmetrical 1,3-diynes which was promoted by $Pd(dba)_2$ with a phosphine-olefin ligand **L** (Scheme 3.5). This protocol realized the cross-coupling reaction of a wide spectrum of terminal alkynes and haloalkynes, affording the corresponding conjugated diynes in good to excellent yields with high selectivity. Notably, one-pot synthesis of symmetrical and unsymmetrical triynes was also achieved. Mechanistic investigations indicated that the phosphine-olefin ligand could accelerate the reductive elimination process in the catalytic cycle, thereby enhancing the selectivity.

General Procedure for Ligand Accelerated Pd-Catalyzed Cross-Coupling Reactions of Bromoalkynes: To an oven-dried Schlenk tube with a magnetic stir bar were added $Pd(dba)_2$ (4 mol%), **L** ligand (4 mol%), and CuI (2 mol%). DMF (1 mL) was added via a syringe. The system was vacuumed with an oil pump at 0 °C and filled with nitrogen, and this procedure was repeated five times. After the mixture was stirred under nitrogen for about 10 min, alkyne (0.6 mmol) was added via a microliter and stirred for another 5 min. 1-Bromoalkyne (0.5 mmol) was added last via a microliter syringe. The system was stirred at room temperature for 10 h. Upon completion, brine (4 mL) was added, and the mixture was extracted by ethyl acetate (3 mL × 3), and the combined extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The product was obtained by flash column chromatography.

Later in 2012, Lei and co-workers developed a more efficient Pd^0-catalyzed C(sp)–C(sp) cross-coupling reaction of terminal alkynes with bromoalkynes. Interestingly, the reaction could run at 100 mmol scale, and more than 99 % of the cross-coupling product was obtained without any bromoalkyne homo-coupled by-product. The key to the success of this transformation was the utilization of TBAB (tetrabutylammonium bromide) as a stabilizer, which could prevent the aggregation and precipitation of palladium catalyst. Even when the catalyst loading was reduced to 0.01 mol%, the reaction could still proceed efficiently, and the catalyst was kept active. Kinetic studies indicated that the reaction rate was not first order to Pd catalyst via in situ IR spectroscopy, and only part of the Pd species was employed to catalyze this C(sp)–C(sp) cross-coupling reaction. Importantly, palladium nanoparticles were observed in this reaction (Scheme 3.6) [16].

General Procedure for TBAB Stabilized Pd-Catalyzed Cross-Coupling Reactions of Bromoalkynes: A mixture of haloalkyne (1 mmol), terminal alkyne (1.5 mmol), TBAB (0.3 mol%), and CuI (0.2 mol%) in iPr_2NH (5 mL) was stirred under N_2 at 70 °C for 5 min. Then $Pd(OAc)_2$ (0.01 mol%) was added in one



Scheme 3.6 TBAB stabilized Pd-catalyzed cross-coupling reactions of bromoalkynes

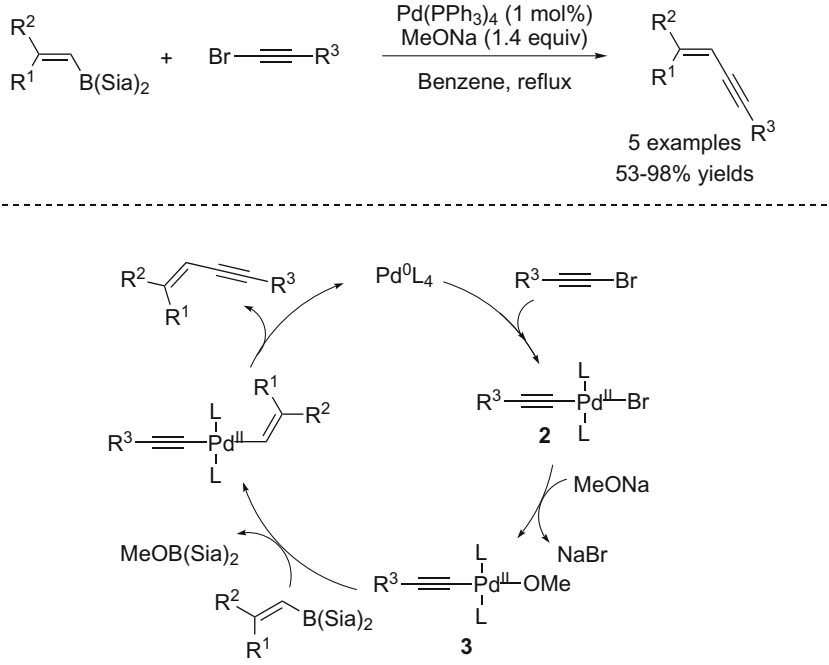
portion. After reaction completion, as indicated by TLC and GC, the mixture was quenched with diluted hydrochloric acid (4 mL, 2 M), and the solution was extracted with ethyl acetate (15 mL × 3). The organic layers were combined and dried over sodium sulfate. The pure product was obtained by flash column chromatography on silica gel.

3.1.1.2 Construction of C(sp)–C(sp^2) Bond

Functionalized cyclic and acyclic enynes are all-pervading subunits in a wide range of natural products, functional materials and bioactive compounds [17]. To this regard, the development of efficient and practical methods for the construction of conjugated enyne molecules has become the subject of intensive investigation in the area of synthetic and medicinal chemistry.

C(sp)–C(sp^2) Cross-Coupling

In 1985, Suzuki and co-workers reported the synthesis of alkyenynes via palladium-catalyzed cross-coupling reaction of 1-alkenylboranes with bromoalkynes (Scheme 3.7) [18]. This reaction was stereo- and regiospecifically, and the

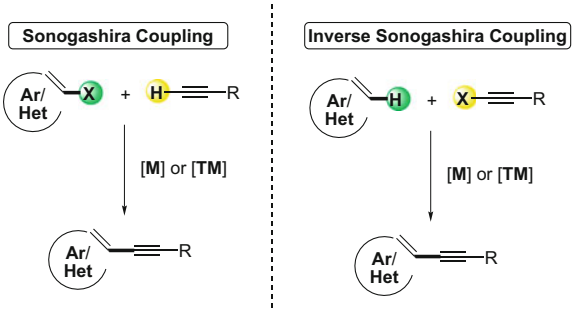


Scheme 3.7 Cross-coupling reaction of 1-alkenylboranes with bromoalkynes

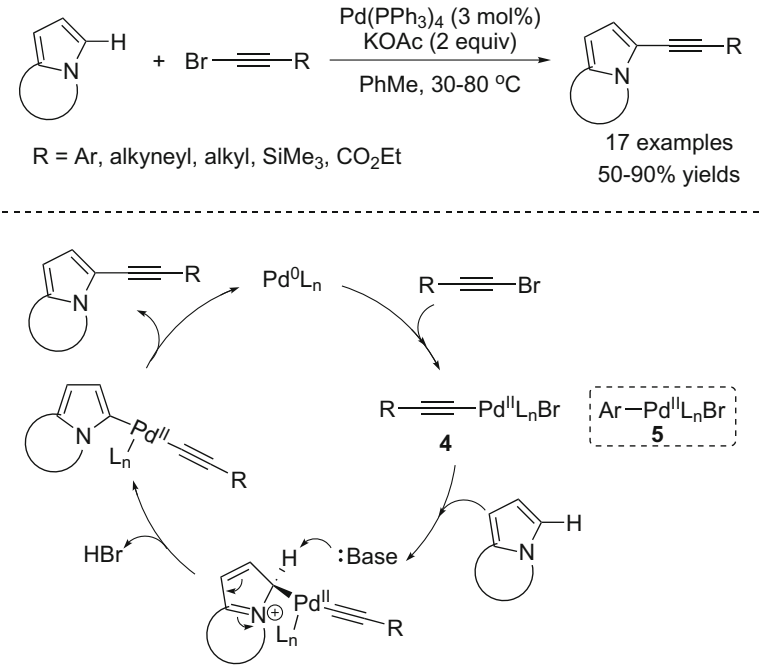
configurations of both the starting alkynylboranes and bromoalkynes were retained. Mechanistic studies indicated that the transmetalation between an alkynylborane and an alkoxypalladium(II) complex **3** generated through the metathetical displacement of a halogen atom from the intermediate **2** with the base. Later, the cross-coupling reactions of haloalkynes with activated alkenes have been broadly investigated, such as alkenylboronic acid [19–21]. oragnozinc reagents [22, 23], vinylstannanes [24–26]. Grignard reagents [27], vinylzirconocene [28, 29], and vinylsiloxanes [30].

General Procedure for Palladium Catalyzed Cross-Coupling Reaction of 1-Alkenylboranes with Bromoalkynes: A flask (50 mL) was charged with $Pd(PPh_3)_4$ (1 mol%), dry benzene (12 mL), and bromoalkyne (5 mmol) under a nitrogen atmosphere. The reaction mixture was stirred for 30 min at room temperature, and to the solution were added alkenylborane (6 mmol) and MeONa (7 mmol, 1 M in MeOH). The reaction mixture was heated under reflux for 2 h and then treated with aqueous NaOH (1.8 mL, 3 M solution) and H_2O_2 (1.8 mL of a 30 % solution) for 1.5 h at room temperature to remove the unreacted alkenylborane. The product was extracted with hexane and dried over $MgSO_4$. After the removal of the solvent, the enyne product was purified by distillation.

Alternatively, the Sonogashira coupling, the cross-coupling reaction between vinyl halides and terminal alkynes also represents one of the most widely used strategies achieving the synthesis of functionalized enynes [31]. In this context, the development of "Inverse Sonogashira Coupling", the term which was first introduced by Trofimov [32], has attracted more and more attention (Scheme 3.8) [33]. It stands as a complementary strategy for the synthesis of aryl/heteroaryl alkynes through the direct alkynylation of unreactive $C(sp^2)$–H bonds with readily available haloalkynes. In 1992, Kalinin and coworkers firstly reported this type of alkynylation reaction with a stoichiometric amount of Cu^I salt [34]. Later, Trofimov and co-workers devoted great efforts in this area [35–42]. However, the major breakthrough was achieved until 2007, as the first example of a transition metal-catalyzed direct alkynylation of electron-rich *N*-fused heterocycles was promulgated by Gevorgyan's group (Scheme 3.9) [43]. A wide spectrum of indolizine, pyrroloisoquinoline, pyrroloquinoline, and pyrrolooxazole derivatives could be regioselectively alkynylated with different substituted bromoalkynes in the presence



Scheme 3.8 Development of "Inverse Sonogashira Coupling"

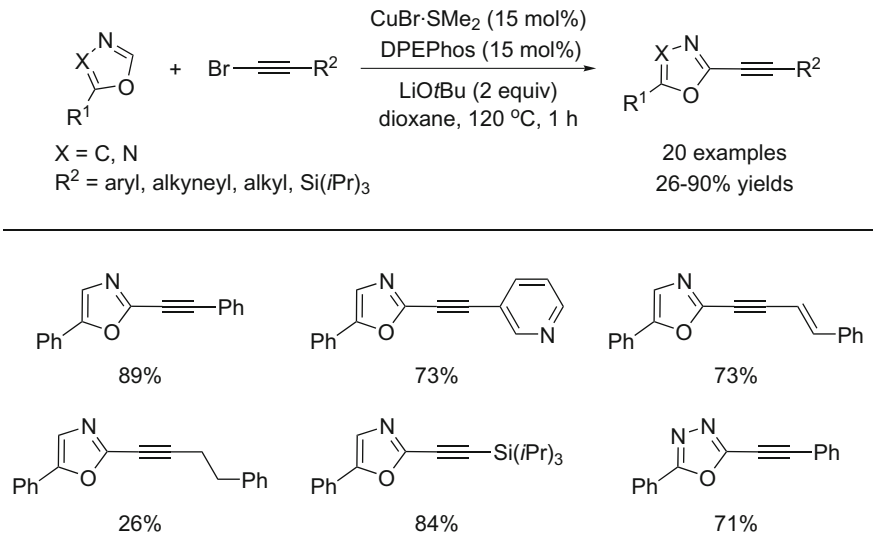


Scheme 3.9 Pd-catalyzed alkynylation of *N*-fused heterocycles

of Pd catalyst. The alkynylpalladium intermediate **4**, which is essential for conceptual advance, generated through Pd^0 catalyst oxidative addition into the C–Br bond of bromoalkyne, exhibited the similar reactivity to that of arylpalladium species **5**, which is well known to undergo an electrophilic pathway in the process of indolizine arylation. Subsequently, Gu [44], Chang [45], Jiang [46, 47], and Loh [48] documented different cross-coupling partners with haloalkynes under palladium catalysis.

General Procedure for Pd-Catalyzed Alkynylation of N-Fused Heterocycles: In a glovebox under nitrogen atmosphere, to a Wheaton microreactor (5 mL) equipped with a spin vane and screw cap with a polytetrafluoroethylene (PTFE) faced silicone septum under nitrogen atmosphere were added heterocyclic substrate (1 equiv), $Pd(PPh_3)_2Cl_2$ (3–5 mol%) and KOAc (2 equiv). The microreactor was removed from the glovebox, bromoalkyne (1.3–1.8 equiv) and anhydrous toluene (0.001–0.010 M) were successively added and the mixture was stirred until completion (as monitored by TLC and/or GC/MS). The solvent was removed under reduced pressure and the residue was purified using flash-column chromatography using hexane or hexanes/ethylacetate combination as eluent to afford pure alkynyl-heterocycles.

Despite palladium catalysis, Piguel [49] reported a more efficient general procedure for the direct alkynylation of various heterocycles with copper-catalysis. The author found out that the success of the copper bromide/dimethyl sulfide complex

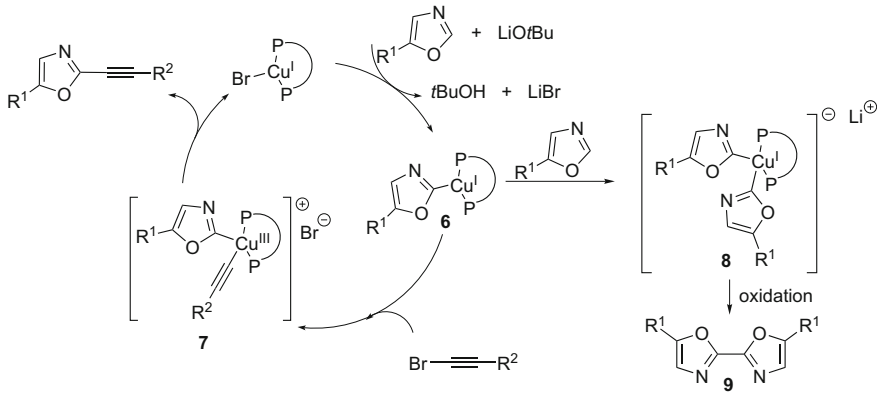


Scheme 3.10 Copper-catalyzed alkynylation of azoles

lied in the better solubility compared that with the uncomplexed copper bromide, which allowed it to coordinate immediately in the reaction medium. This method did not need high dilution reaction condition. Especially, the minimal cost and toxicity of copper catalyst could tolerate various oxazoles with different electron property and structural diversity, and gave the coupling product in good yields (Scheme 3.10). Notably, the azoles are with high pK_a values (>30), while the carbon-halo bond of the substrate could survive under the standard reaction conditions. Additionally, the structure of the product was unambiguously confirmed by single-crystal X-ray diffraction analysis.

General Procedure for Copper-Catalyzed Alkynylation of Azoles: A flame dried tube under argon was charged with azole (0.69 mmol), $CuBr{\cdot}SMe_2$ (15 mol%), DPE-Phos (15 mol%), *t*BuLi (1.38 mmol). Then bromoalkyne (1.38 mmol) was diluted into dioxane (2 mL) and the solution was added to the medium. The tube was sealed with Teflon cap and put in a pre-heated oil bath at 120 °C for 1 h. The reaction mixture was diluted with ethyl acetate and water was added. This mixture was extracted with ethyl acetate and the combined organic layers were put together and dried over $MgSO_4$. Solvents were removed under reduced pressure and the crude was purified by flash chromatography on silica gel to afford the desired product.

Based on the experimental results and previous literatures [50, 51], the authors proposed the possible reaction mechanism as illustrated in Scheme 3.11. Firstly, the deprotonation of oxazole lithium base, followed by lithium-copper transmetallation to generate Cu^{I} intermediate **6**. Subsequently, the oxidative addition of **6** to bromoalkyne gave the four-coordinated Cu^{III} complex **7**. Finally, the reductive elimination led to the desired alkynylated product, and regenerated the catalytic Cu^{I}



Scheme 3.11 Proposed reaction mechanism

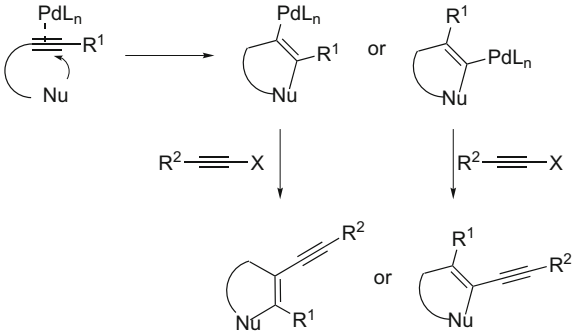
species. Undoubtedly, the formation of Cu^{III} complex **7** would compete with activation of another oxaole, which would deliver the bis(oxazolte) Cu^{I} species **8**, and afforded the undersired bis(oxazole) dimer **9**. Importantly, the steric hindrance of the copper center favored the less sterically demanding haloalkyne, thus **7** was formed preferentially. Finally, due to the solubility of dimethylsulfide complex and the bulky steric hindrance effect of the ligand, the catalytic cycle was driven towards the formation of the alkynylated product.

Later, Miura [52] and Das [53] independently realized the copper-catalyzed alkynylation of 1,3,4-oxadiazoles. In the mean time, other transition metals, such as nickel, were found to be suitable catalysts for the inverse Sonogashira coupling reactions of haloalkynes [54]. These achievements in the area of direct alkynylation reactions involving haloalkyne reagents open up new exciting opportunities for the functionalization of diverse $C(sp^2)$–H bonds.

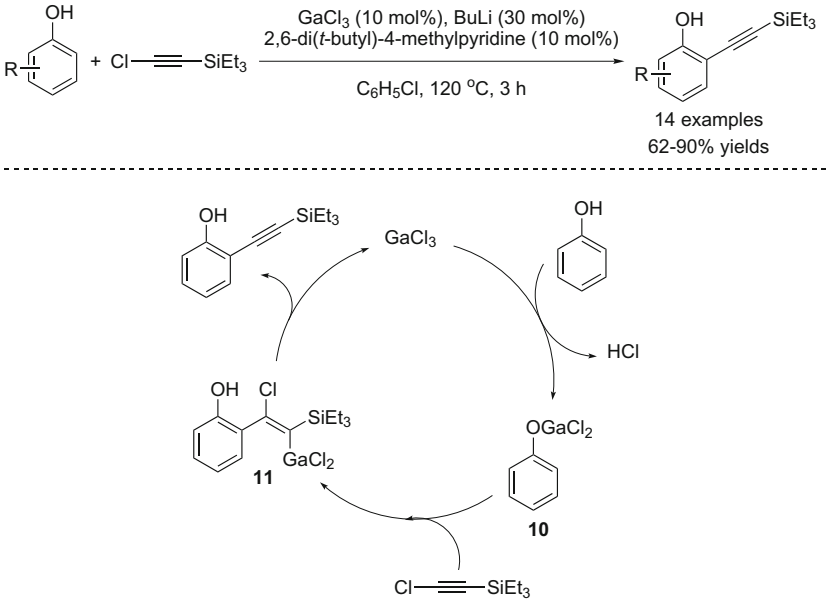
The cyclization of alkynes bearing proximate nucleophilic centers promoted by organopalladium complexes is an effective strategy for heterocyclic ring synthesis [55]. This chemistry provides a direct method to the construction of functionalized cycles through the regio- and stereoselective addition of a nucleophile to the carbon-carbon triple bond with the generation of a vinylpalladium complex, which could proceed diverse transformations (Scheme 3.12). Taking the advantages of this strategy, Larock [56], Cacchi [57], and Yorimitsu [58] independently demonstrated that nucleophilic addition triggered cross-coupling reaction of haloalkynes to synthesize 3,4-disubstituted isoquinolines, 3-alkynylindoles and 1,2-disubstituted cyclopentenes, respectively.

Alkynylation Reactions

Compared to cross coupling reactions, electrophilic ethynylation of carbon nucleophiles is another attractive methodology to construct C(sp)–$C(sp^2)$ bonds. In 2002,



Scheme 3.12 Pd-catalyzed nucleophilic addition triggered cross-coupling reaction



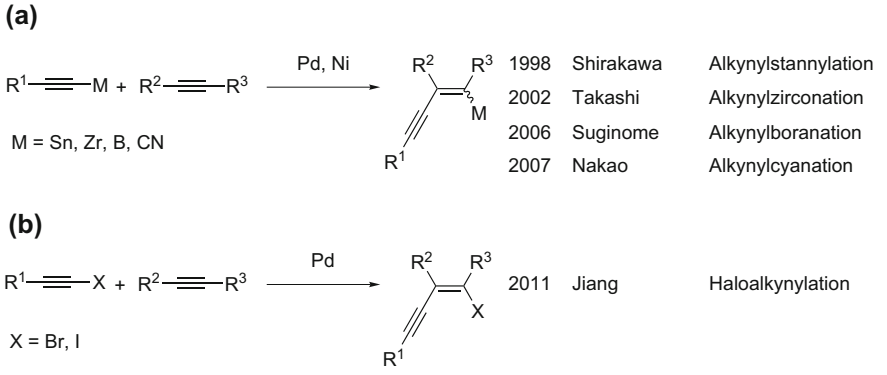
Scheme 3.13 $GaCl_3$-catalyzed *ortho*-ethynylation of phenols

Yamaguchi and co-workers reported $GaCl_3$-catalyzed ortho-ethynylation of phenols. Various substituted phenols were applicable to this method, and the turnover number based on the catalyst ($GaCl_3$) was between 8 and 10. The mechanism studies indicated this catalytic ethynylation involved carbogallation of haloalkyne and the formation of intermediate **10** under the effect of lithium salts. Interestingly, the protonated product of intermediate **11** was not detected in the reaction mixture. It seemed that β-elimination of **11** happened to be more rapid (Scheme 3.13) [59]. The author also applied this method to the *ortho*-ethynylation of silyl enol ethers

[60] and anilines [61]. Later, Chatani [62, 63], and Chen [64] independently reported palladium-catalyzed *ortho*-alkynylation of C(sp^2)–H bond in benzenes with different directing groups.

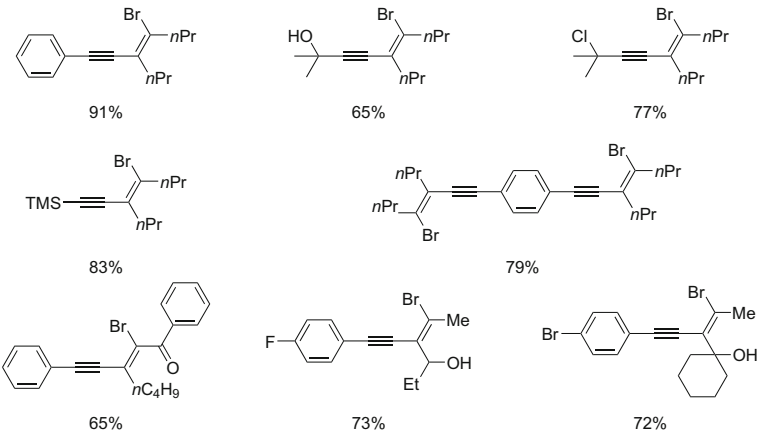
General Procedure for $GaCl_3$-Catalyzed ortho-Ethynylation of Phenols: Under an argon atmosphere, to a solution of phenol (10 mmol) in chlorobenzene (50 mL) were added butyllithium (3 mmol, 1.6 M in hexane) and $GaCl_3$ (1 mmol, 1 M in methylcyclohexane) at 0 °C successively. The mixture was stirred for 10 min at room temperature, and then 2,6-di(*tert*-butyl)-4-methylpyridine (1 mmol) and chlorotriethylsilylethyne (10 mmol) were added. The mixture was heated at 120 °C for 3 h. Water (25 mL) and THF (25 mL) were added, and the organic materials were extracted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography over silica gel to provide the pure product.

On the other hand, the development of practical and efficient alkynylation methods for functionalized acyclic enyne compounds is also highly demanded. Undoubtedly, one of the most straightforward strategies to achieve this goal is the direct addition of an "activated" alkyne to another alkyne. In this context, several catalytic systems for alkynylstannylation [65], alkynylzirconation [66, 67], alkynylboranation [68], and alkynylcyanation [69] have been developed (Scheme 3.14a). In 2010, Jiang and coworkers revealed a Pd-catalyzed selective intermolecular cross-coupling reaction between haloalkynes and internal alkynes, delivering various halogenated enyne products through a new type of direct bromoalkynylation process (Scheme 3.14b) [70]. Condition optimization indicated that Pd^{II} was crucial to the product formation, while Pd^0 just impeded the reaction. Reductive additives and inorganic bases would also retard the transformation. However, air or organic oxidant did not interrupt the reaction. This approach was found to have a broad substrate scope (Table 3.2). A wide range of haloalkynes, including aryl-, alkynyl-, and trimethylsilyl- alkynyl bromides, were able to proceed



Scheme 3.14 Strategies for the conjugated enyne synthesis. **a** Previous alkynylation strategies. **b** Jiang's strategy

Table 3.2 Pd-catalyzed bromoalkynylation of alkynes

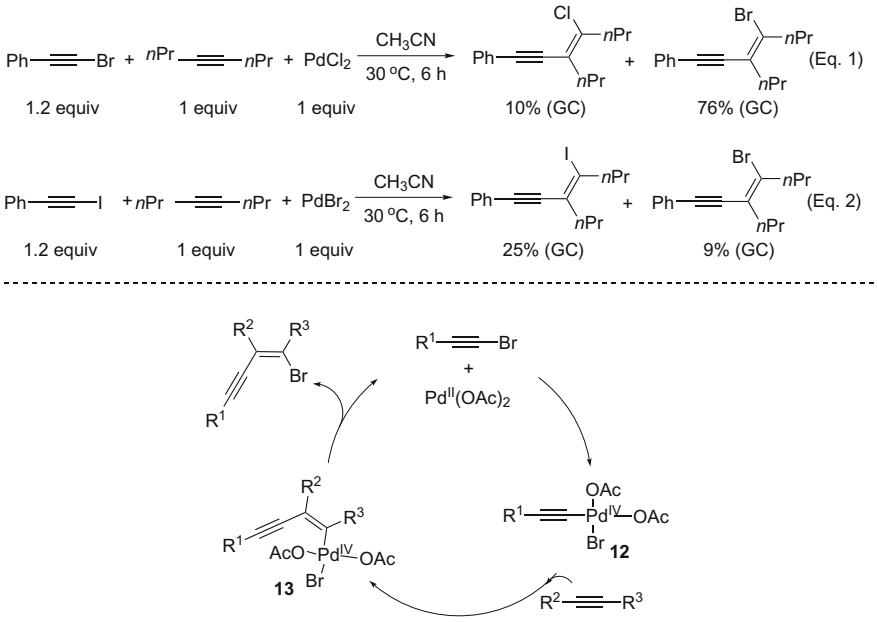


this bromoalkynylation reaction smoothly to afford the corresponding products in good to excellent yields. Additionally, reasonable yields were achieved when this reaction was extended to iodoalkynes instead of bromoalkynes. Importantly, exclusively *cis*-addition products were obtained for symmetrical internal alkynes. While the regioselectivity of the unsymmetrical disubstituted acetylenes was mainly influenced by the functional groups in the internal alkynes.

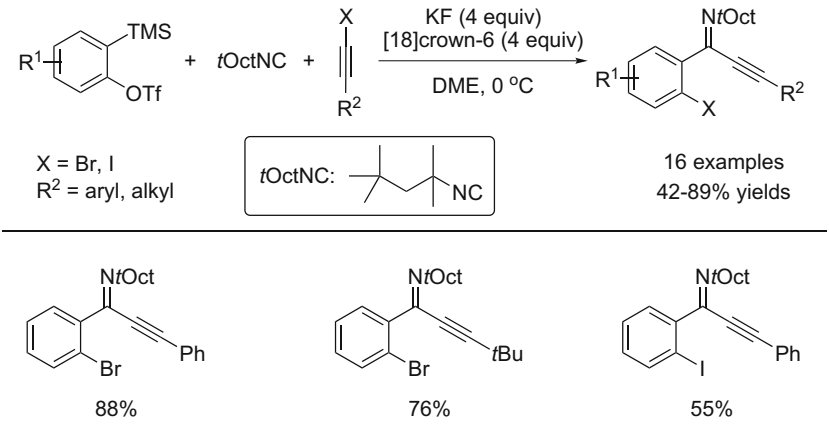
General Procedure for Pd-Catalyzed Bromoalkynylation of Alkynes: To a Schlenk tube (25 mL) was successively added $Pd(OAc)_2$ (5 mol%), CH_3CN (2 mL), 4-octyne (1 mmol) and haloalkyne (1.2 mmol). The resulting mixture was stirred at 30 °C for 8 h. Then, the mixture was filtered through a small amount of silica gel. The filtrate was concentrated under reduced pressure, and the residue was purified by silica gel preparative TLC (*n*-hexane) to give the desired product.

To gain some insight of the reaction mechanism, the authors performed some control experiments with stoichiometric Pd catalysts and the major halogenated products were identified to be originated from phenylethynyl halides [Scheme 3.15, Eqs. (1) and (2)]. These results provided evidence of a mechanism that Pd^{II} species underwent an unusual oxidative addition to phenylethynyl bromide, rather than a direct halopalladation reaction of alkynes. Accordingly, the mechanism of this transformation was initiated by the oxidative addition of Pd^{II} salt to bromoalkyne to form the Pd^{IV} complex **12**. Then, the *cis*-addition of **12** to internal alkyne afforded the *cis*-alkynyl vinylpalladium intermediate **13**, which underwent a reductive elimination to deliver the brominated enyne product and regenerate the active Pd^{II} catalyst (Scheme 3.15).

Yn-1-imines are an important class of compounds with novel π-system, which have wide applications in functional materials [71]. In 2011, an elegant three-component coupling reaction of arynes, isocyanides and bromoalkynes for the



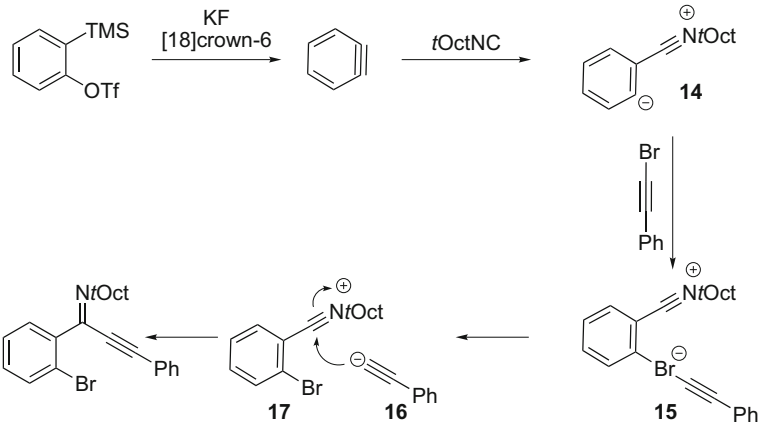
Scheme 3.15 Control experiments and proposed catalytic cycle



Scheme 3.16 Three-component coupling of arynes, isocyanide and haloalkynes

synthesis of yn-1-imine compounds has been reported by Yoshida and co-workers [72]. The benzyne was in situ generated from its precursor under the treatment of KF/[18] crown-6. Importantly, this reaction adapted to broad substrate scope and tolerated various functional groups (Scheme 3.16).

General Procedure for Three-Component Coupling of Arynes, Isocyanide and Haloalkynes: A Schlenk tube equipped with a magnetic stirring bar was charged with KF (0.6 mmol) and [18]crown-6 (0.6 mmol). The tube was evacuated at room



Scheme 3.17 Proposed mechanism

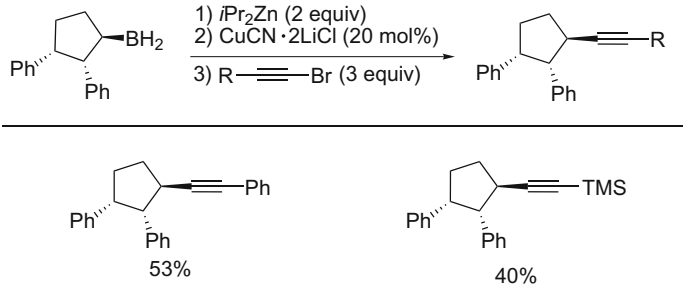
temperature for 1 h with stirring before addition of DME (1 mL) and a haloalkyne (0.15 mmol) under an argon atmosphere. Then an isocyanide (0.23 mol), and aryne precursor (0.3 mmol), and DME (1 mL) were added at 0 °C, and the resulting mixture was stirring at 0 °C. Upon completion, the reaction mixture was diluted with ethyl acetate and filtered through a Celite plug. The organic solution was washed with brine three times and dried over $MgSO_4$. Evaporation of the solvent and followed by recycling preparative HPLC gave the desired product.

As to the mechanism, the authors believed that this reaction could be triggered by the generation of zwitterion **14** (1,4-dipoles) from aryne and isocyanide. Subsequently, the zwitterion **14** underwent nucleophilic attack on the carbon-bromo bond of the bromoalkyne motif and provided the phenylacetylide **16** through the bromine ate complex **15**, followed by the carbon-carbon bond formation of **16** and the nitrilium cation **17** to furnish the final yn-1-imine product (Scheme 3.17).

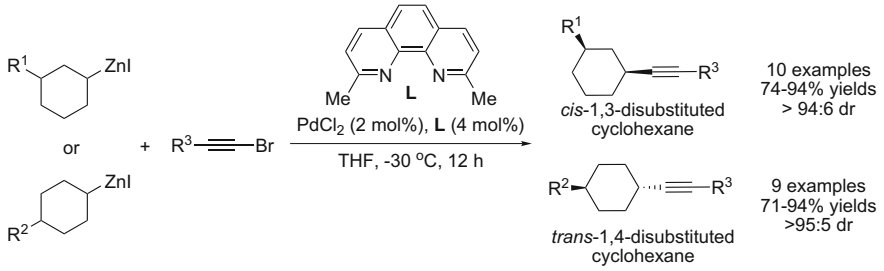
3.1.1.3 Construction of C(sp)–C(sp^3) Bond

As the importance and diverse applications of alkyne units contained complex molecules, the development of efficient and sustainable methods for the construction of C(sp)–C(sp^3) bonds continues to be a challenging research topic in modern organic chemistry. In this context, the development of practical methods to construct C(sp)–C(sp^3) bonds with haloalkynes attracted considerable attention [73–79]. In this part, representative examples will be detailed discussed.

The coupling reaction of zinc-copper reagents with haloalkynes was one of most efficient strategy to construct C(sp)–C(sp^3) bonds. In 1998, Knochel's group reported that alkylborane could proceed transmetalation to the corresponding organozinc coumpound under the treatment of diisopropylzinc reagent, and subsequent transformation to the zinc-copper reagent with the addition of CuCN·2LiCl,



Scheme 3.18 Haloalkynes captured the zinc-copper reagent



Scheme 3.19 Pd-catalyzed cross-coupling of cyclohexylzinc reagents with bromoalkynes

which could be captured by haloalkynes (Scheme 3.18) [80]. With the same strategy, Knochel [81], Williams [82], and Burton [83] respectively documented different zinc-copper reagents coupled with haloalkynes to construct C(sp)–C(sp^3) bonds.

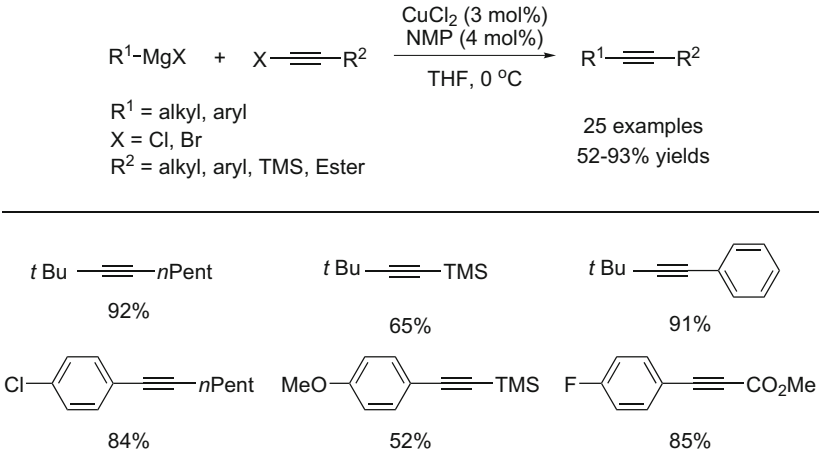
General Procedure for Haloalkynes Captured the Zinc-Copper Reagent: A BH_3·THF solution (3 mmol) was slowly added to 1,2-diphenylcyclopentene (2 mmol) in THF (10 mL) at 20 °C. After 10 min, the resulting solution was heated at 50 °C for 3 h. The solvent and excess borane were removed under vaccum, and the residue was treated with a solution of iPr$_2$Zn (4 mmol) in ether at 25 °C for 4 h. After removal of the solvent and excess of iPr$_2$Zn under vacuum, the residue was diluted with THF (10 mL). The black precipitate of zinc was removed by filtration, and the filtrate was slowly treated at −90 °C with a solution of CuCN·2LiCl (20 mol%) in THF and after 15 min with haloalkyne (6 mmol) in THF. The reaction was allowed to warm to 25 °C and was quenched after 1 h with aq HCl (10 mL, 3 M) and extracted with ether. The crude product obtained after evaporation of the solvent was purified by chromatography.

Until 2011, the first Pd-catalyzed diastereoselective cross-coupling reaction of cyclohexylzinc reagents with bromoalkynes was reported by Knochel and co-workers (Scheme 3.19) [84]. Interestingly, the 3-substituted cyclohexylzinc reagent preferred to form *cis*-1,3-disubstituted cylcohexane derivatives, while 4-substituted cyclohexylzinc reagent favored to give *trans*-1,4-disubsituted

cylcohexane derivatives. The high diastereoselectivity was assumed to be effected by a selective transmetalation step between the respective alkynyl(bromo)palladium complex and the cyclohexylzinc reagents, which led to the formation of the most thermodynamically stable palladium intermediates. Subsequently, reductive elimination proceeded with the retention of configuration and delivered the corresponding 1,3- and 1,4-disubstituted products. Later, they [85] and Baudoin [86] reported palladium-catalyzed cross-coupling reactions of haloalkynes with adamantylzinc reagents and α-zincated acyclic amines, respectively.

General Procedure for Pd-Catalyzed Cross-Coupling of Cyclohexylzinc Reagents with Bromoalkynes: A dry and N_2-flushed Schlenk tube (10 mL), equipped with a magnetic stirring bar and a septum, was charged with a solution of the respective alkynyl bromide (0.4 mmol), $PdCl_2$ (2 mol%) and neocuproine (4 mol%) in THF (1.5 mL) and cooled to −30 °C. A solution of the respective cyclohexylzinc iodide in THF (0.5 mmol) was slowly added at this temperature. The reaction mixture was stirred for 12 h. Then saturated aq. NH_4Cl solution (5 mL) was added. Phases were separated and the aqueous phase was extracted with Et_2O (20 mL × 3). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The solvents were evaporated and the alkynylated product was purified via column chromatography on silica gel.

Grignard reagents could also coupled with haloalkynes [87]. In 2010, Cahiez reported the first efficient and practical copper-catalyzed alkynylation reaction of aryl and alkyl Grignard reagents [88]. This reaction has broad substrate scope and tolerates diverse functional groups, even tertiary alkyl Grignard reagent could also be used successfully. Notably, this reaction was highly chemoselective, and the key to obtain satisfactory yields was the slow addition of the Grignard reagents to the reaction mixture. Importantly, no Br/Mg exchange was observed in the arylation of alkynyl bromides (Scheme 3.20).

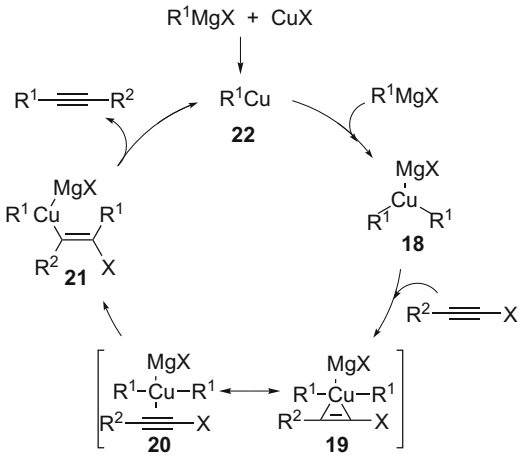


Scheme 3.20 Copper-catalyzed cross-coupling of Grignard reagents with haloalkynes

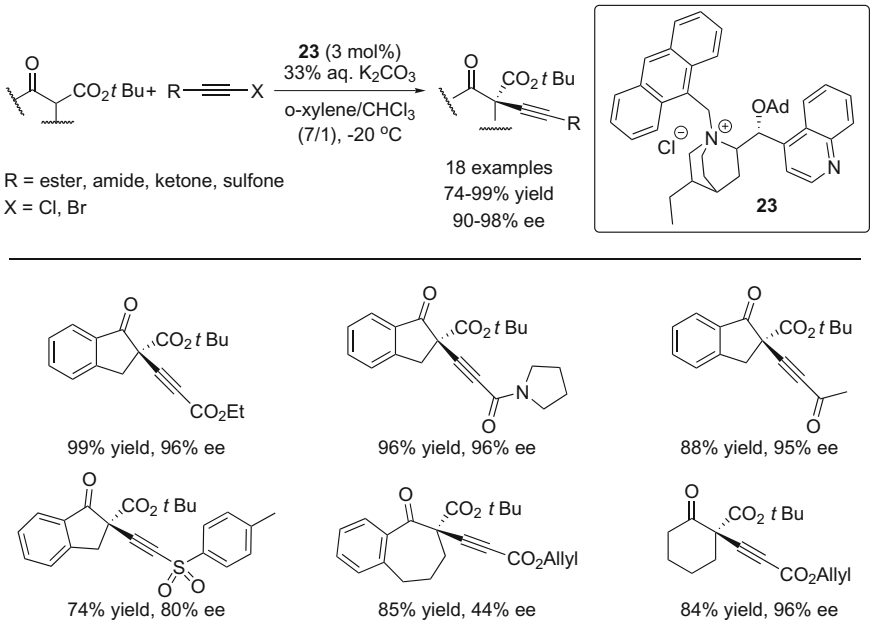
General Procedure for Copper-Catalyzed Cross-Coupling of Grignard Reagents with Haloalkynes: A dry and nitrogen flushed four-necked flask (100 mL) equipped with a mechanical stirrer, a thermometer, a nitrogen inlet, and a septum was charged with $CuCl_2$ (3 mol%), *N*-methylpyrrolidinone (4 mol%), haloalkyne (10 mmol), and THF (9 mL). After complete dissolution of the cuprous chloride (less than 30 min), the reaction mixture was cooled to 0 °C and a solution of Grignard reagent (12 mmol) was added with a syringe pump over a period of 45 min. At the end of the addition, stirring was continued for 30 min at 0 °C then the reaction was quenched with 1 N aqueous HCl solution (20 mL). The aqueous phase was extracted with diethyl ether (20 mL × 3). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel.

On the basis of the experimental results and related literatures [89, 90], the authors proposed a reasonable mechanism in Scheme 3.21. The catalytic cycle was initiated by the generation of cuprate **18** from the Grignard reagent. Subsequently, the haloalkyne reacted with **18** to afford the vinylcopper reagent **21** through the complex **19/20** (carbocupration). Generally, **21** was generated via the reductive elimination of metallacyclopropene **19**. Finally, the unstable vinyl copper **21** underwent a β-halogen elimination to give the desired product and the organocooper **22**, which then reacted with another Grignard reagent to regenerate the cuprate **18**.

Besides organozinc reagents, Grignard reagents and zirconacyles [91], the more environmental friendly strategy to construct C(sp)–C(sp^3) bonds from haloalkynes was the utilization of activated C(sp^3)–H bonds. In 2007, Jørgensen and co-workers reported the first asymmetric direct alkynylation of cyclic β-ketoesters with haloalkynes under chiral phase transfer catalyst **23**. A large number of alkynylating reagents with chloride and bromide as the leaving groups and substituents such as alkyl and allyl esters, amides, ketones, and sulfones were demonstrated to be suitable substrates. Various cyclic β-ketoesters with different ring-sizes and also



Scheme 3.21 Proposed reaction mechanism

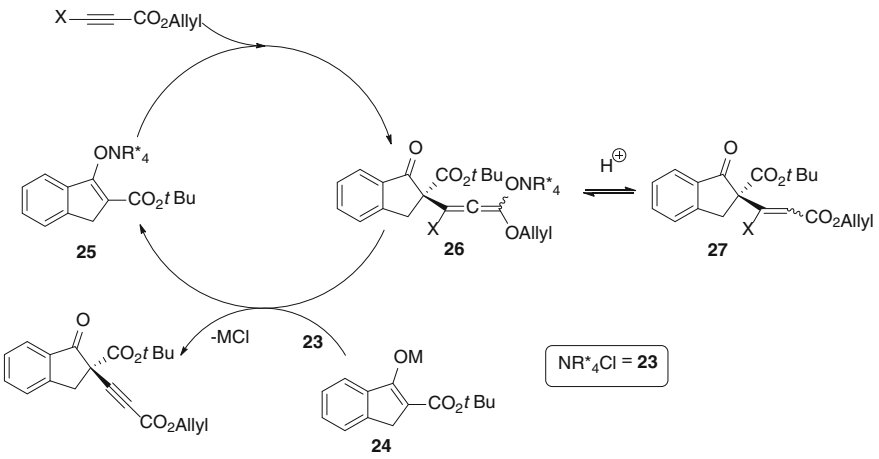


Scheme 3.22 Asymmetric alkynylation of cyclic β-ketoesters

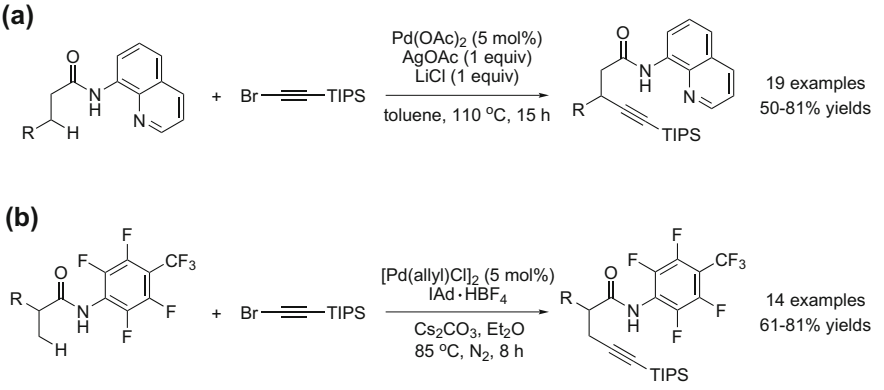
including oxindoles were applicable to the standard reaction conditions. The corresponding optically active products were obtained in high yields with excellent enantioselectivities (Scheme 3.22) [92].

General Procedure for Asymmetric Alkynylation of Cyclic β-Ketoesters: To a sample vial equipped with a magnetic stirring bar was added β-ketoester (0.2 mmol), *o*-xylene/$CHCl_3$ (7:1, 1.3 mL), haloalkyne (0.26 mmol), and the catalyst **26** (3 mol%). The mixture was stirred for s short time at ambient temperature and was then placed at −20 °C. When the mixture had cooled, a cold solution of 33% aq. K_2CO_3 (0.6 mL) was added and the biphasic mixture was vigorously stirred. Upon completion, the organic phase was collected, and the aqueous layer was extracted with toluene two times. The combined organic fractions were loaded onto a chromatography column and the alkynylated product was obtained.

Importantly, the authors isolated and characterized the counterion of the catalyst and *p*-nitrophenolate by X-ray analysis, and they proposed a model of the catalyst-substrate intermediate which might explain the observed enantioselectivity of this organocatalytic enantioselective alkynylation reaction (Scheme 3.23). Alkali-metal enolate **24**, generated from the corresponding β-ketoesters by deprotonation with the bulk aqueous base, first underwent cation exchange with the chiral phase transfer catalyst **23**, which led to the organic soluable ammonium enolate **25** as a tight ion-pair. Due to the chiral environment provided by the ammonium motif, the enolate **25** added to the haloalkyne in a highly enantioselective manner, and formed the ammonium allenolate **26**. The allenolate **26** would undergo elimination



Scheme 3.23 The possible reaction mechanism



Scheme 3.24 Pd-catalyzed alkynlation of unactivated C(sp^3)–H bonds. **a** Chatani's work: Pd(II)/Pd(IV). **b** Yu's work: Pd(0)/Pd(II)

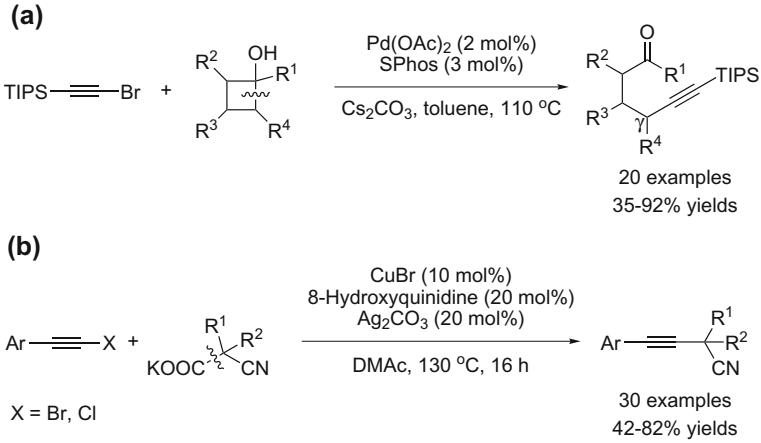
of X directly to deliver the desired alkynylated product or got protonated to afford trisubstituted vinylic ester **27**.

In 2011, taking advantages of C(sp^3)–H activation [93–95], Chatani [96] and co-workers documented the first alkynlation of unactivated C(sp^3)–H bonds via palladium(II/IV) process (Scheme 3.24a). Broad functional groups could be tolerated under the standard reaction conditions. Experiment results indicated that both the quinolone and the NH group were essential for the reaction. Two years later, Yu's group [97] reported a palladium(0)-catalyzed alkynlation of C(sp^3)–H bonds using Pd^0/NHC and Pd^0/PR_3 catalysts without the use of co-oxidants (Scheme 3.24b).

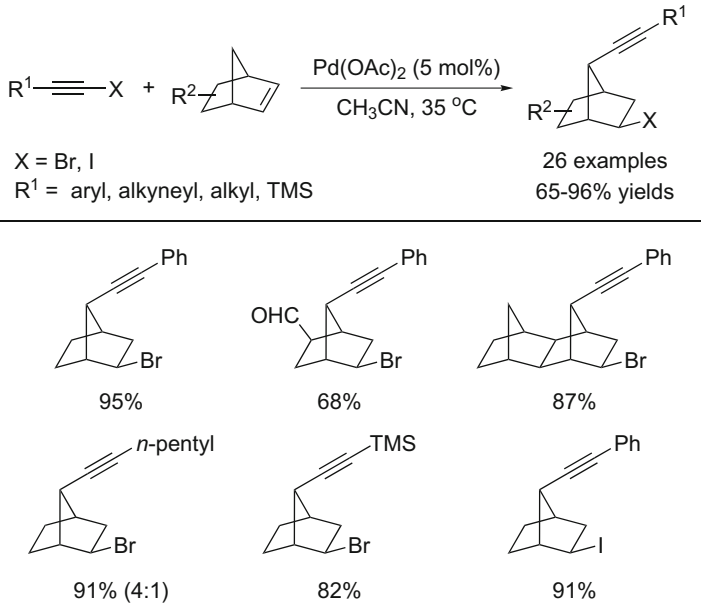
General Procedure for Pd-Catalyzed Alkynlation of Unactivated C(sp^3)–H Bonds (Chatani's Work): To an oven-dried screw-capped vial (5 mL), *N*-(8-quinolinyl)hexanamide (0.5 mmol), (bromoethynyl)triisopropylsilane (0.75 mmol), $Pd(OAc)_2$ (5 mol%), AgOAc (0.5 mmol), LiCl (0.5 mmol) and toluene (1 mL) were added under a gentle stream of nitrogen. The mixture was stirred for 15 h at 110 °C and followed by cooling. The mixture was filtered through a Celite pad and concentrated in vacuo. The residue was subjected to column chromatography on silica gel (eluent: hexanes/Et_2O = 5/1 to 3/1) to afford the desired alkynylated product.

General Procedure for Pd-Catalyzed Alkynlation of Unactivated C(sp^3)–H Bonds (Yu's Work): Substrate (0.1 mmol), $[Pd(allyl)Cl]_2$ (5 mol%), bis(adamantly) imidazolium tetrafluoroborate (0.02 mmol), and Cs_2CO_3 (0.2 mmol) were weighed in air and placed in Schlenk tube (50 mL) with a magnetic stir bar. The alkynyl bromide (0.2 mmol) and Et_2O (0.5 mL) were added, and the reaction vessel was evacuated and backfilled with nitrogen three times. The reaction mixture was first stirred at room temperature for 5 min and then heated to 85 °C for 8 h under vigorous stirring. Upon completion, the reaction mixture was cooled to room temperature. The solvents were removed under reduced pressure and the resulting mixture was purified by silica gel packed flash chromatography column using hexanes/EtOAc mixtures as the eluent.

Alternatively, the strategy of carbon-carbon bond cleavage could also be used to construct C(sp)–C(sp^3) bonds [98]. In 2013, Martin and co-workers reported the reaction of Pd-catalyzed C(sp^3)–C(sp^3) bond cleavage of *tert*-cyclobutanols reacted with bromoacetylenes, which gave γ-alkynylated ketones in good yields (Scheme 3.25a) [99]. Later, Xu's group demonstrated the decarboxylative alkynylation of quaternary α-cyano acetate salts under copper catalysis (Scheme 3.25b) [100].



Scheme 3.25 The cleavage of C(sp^3)–C(sp^3) bond to construct C(sp)–C(sp^3) bonds. **a** Martin's work: γ-alkynylation. **b** Xu's work: decarboxylation



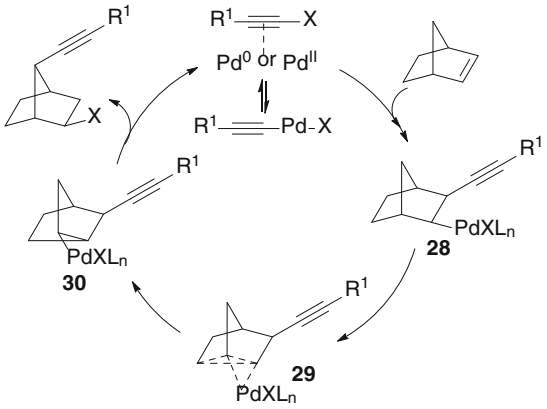
Scheme 3.26 Pd-catalyzed synthesis of 7-alkynyl norbornanes

However, all the previous reported method to construct C(sp)–C(sp^3) bonds with haloalkynes, the halide motif was removed to the waste salts. In 2011, Jiang and co-workers demonstrated the first example of highly selective Pd-catalyzed intermolecular alkynylation reaction of norbornene derivatives, delivering diverse 7-alkynyl norbornane adducts that could not be easily accessed via traditional methods (Scheme 3.26) [101]. Outwardly, this unique transformation proceeded through the direct cleavage of the alkynyl–halogen bond, and followed by the constructions of C(sp)–C(sp^3) and C(sp^3)–halogen bonds, featuring excellent atom economy. Their achievements in the synthesis of C7-functionalized norbornyl alkynes products proved the compatibility of nonclassical norbornonium cation with this catalytic system.

General Procedure for Pd-Catalyzed Synthesis of 7-Alkynyl Norbornanes: To a Schlenk tube (25 mL) was successively added $Pd(OAc)_2$ (5 mol%), CH_3CN (2 mL), norbornene (1.3 mmol) and haloalkyne (1 mmol). The resulting mixture was stirred at 30 °C for 10 h. Then, the mixture was filtered through a small amount of silica gel. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel preparative TLC (*n*-hexane) to give the desired product.

Base on their experimental results and previous reports [33, 102, 103], they tentatively proposed the reaction mechanism (Scheme 3.27). Initially, the oxidative addition of Pd^0 or Pd^{II} species to haloalkyne generated a high-valent alkynylpalladium complex, followed by *cis*-insertion to give intermediate **28**. Subsequently, the bridging Pd complex **29** was formed, and then the Pd catalyst was transferred to the bridged carbon on the same side as the incoming alkyne, which led to the highly

Scheme 3.27 Plausible reaction mechanism

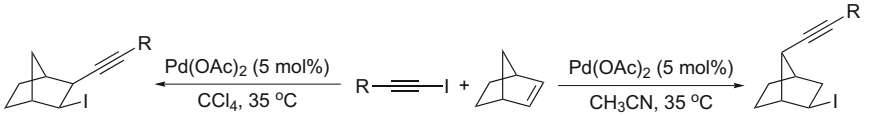


stereoselective formation of the alkylpalladium halide intermediate **30**. Finally, the reductive elimination afforded the brominated product and regenerated the active catalyst species.

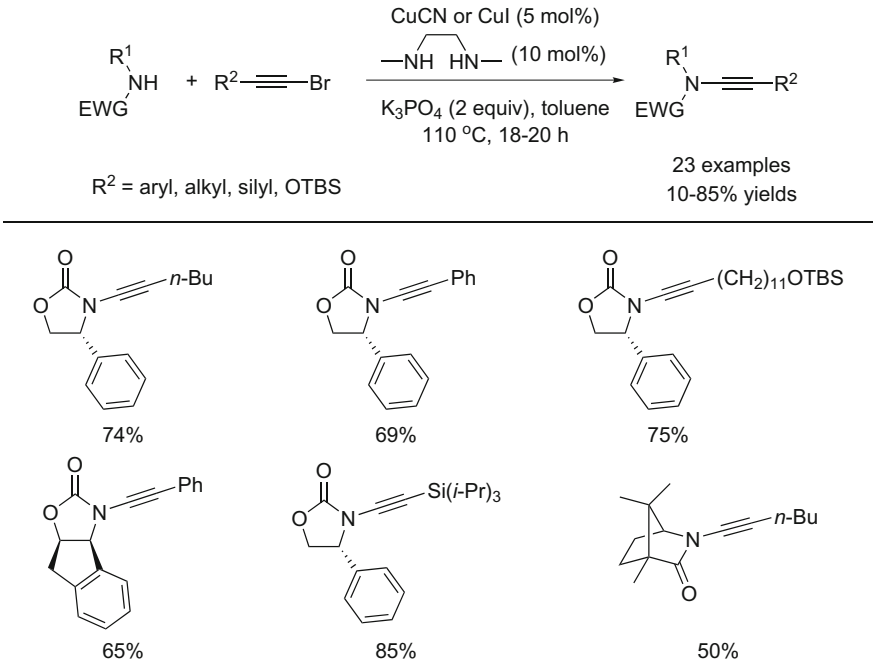
Interestingly, Tong's group [104] also reported a Pd-catalyzed iodoalkynation of norbornene with the employment of alkynyl iodides, which was found to be strongly solvent dependent (Scheme 3.28). Polar solvents favored the unexpected 1,7-iodoalkynation adducts, while nonpolar solvents tended to the formation of 1,2-iodoalkynation products. The authors proposed a Pd^0/Pd^{II} reaction mechanism, in which the formation of the product was relied on the solvent effects.

3.1.2 Construction of Carbon-Nitrogen Bond

Ynamines and ynamides are modern functional motifs with increasing significance that can easily and efficiently transfer to the nitrogen-containing compounds, providing access to privileged scaffolds widely existed in natural products, bioactive molecules and functional materials [105–107]. Taking advantages of the development of efficient methods for ynamide's preparation, the chemistry of ynamide has experienced rapid expansion during the past decade [108–111]. Particularly, the amidative cross-coupling of haloalkynes and amines has emerged as one of the most important strategies. Although the first example of ynamides were reported by



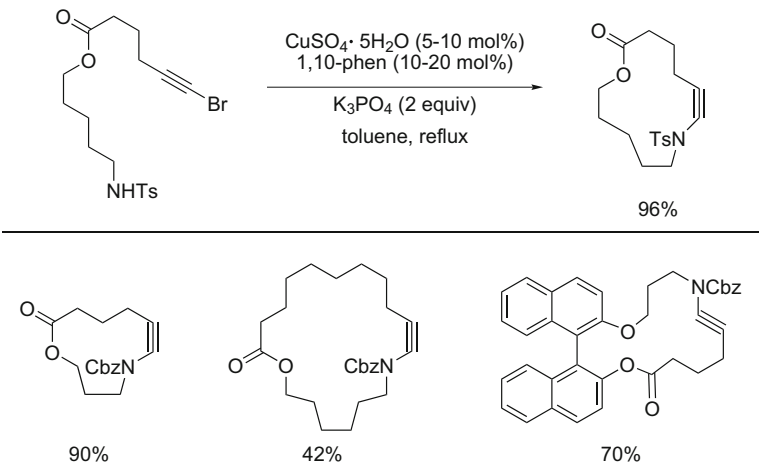
Scheme 3.28 Pd-catalyzed iodoalkynation of norbornenes



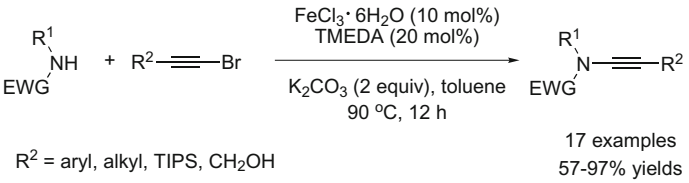
Scheme 3.29 Cu-catalyzed ynamide formation reactions

Viehe in 1972 [112], and the first synthesis of ynamides through metal-mediated reactions was documented in 1985 by Balsamo and Domiano [113]. However, limited progress [114] was achieved until 2003, Hsung et al. [115] disclosed the first Cu-catalyzed ynamide formation reaction, which provided a straightforward and atom-economical access to various ynamides (Scheme 3.29). Generally, CuCN led to more consistent results overall, although no significant different results appeared when CuI was used instead of CuCN. This coupling reaction tolerated various types of haloalkynes, and provided a direct entry to chiral ynamides in good yields. Later on, they developed a more efficient and practical catalytic system for ynamides synthesis, with the utilization of inexpensive $CuSO_4 \cdot 5H_2O$ as catalyst and 1,10-phenanthroline as the ligand [116, 117]. This protocol had a broad functional group tolerance and was also applicable for intramolecular amidation reactions, which could be applied to the construction of unique macrocyclic ynamides that contained up to 19-membered ring system (Scheme 3.30). Except for Cu salts [118–125], other transition metals also presented their high reactivity for the synthesis of ynamides. In 2009, Zhang's group disclosed the first Fe-catalyzed coupling of amides and alkynyl bromides [126]. It was announced that $FeCl_3 \cdot 6H_2O$, an environmentally friendly alternative to Cu salt, was also a practical and efficient catalyst for ynamide synthesis (Scheme 3.31).

General Procedure for the Cu-Catalyzed Ynamide Formation Reactions: To a reaction vial was added amide (1 mmol), K_3PO_4 (2 mmol), and CuCN (5 mol%).



Scheme 3.30 Construction of unique macrocyclic ynamides



Scheme 3.31 Fe-catalyzed coupling of amides and bromoalkynes

Bromoalkyne (1 mmol) was then added in a solution of anhydrous toluene (10 mL) followed by addition of *N*,*N*'-dimethylethylene diamine (0.1 mmol). The reaction vial was sealed and placed in an oil bath at 110 °C for 15–24 h. The reaction was followed with TLC, LCMS, and/or GCMS analysis. Upon completion, the reaction mixture was filtered through a small bed of silica gel and concentrated under vacuum. Purification of the residue by silica gel chromatography (gradient eluent: 0–50% EtOAc in hexane) afforded the corresponding ynamide products.

3.1.3 Construction of Carbon-Sulfur Bond

Acetylenic thioethers are an important class of compounds [127–129]. However, multi-step synthesis is usually involved for their preparation [130]. In 1962, Miller and co-workers developed a simple process to synthesize acetylenic thioethers from haloalkynes and sodium thiolates via nucleophilic subsitution at an acetylenic carbon (Scheme 3.32) [131]. The key factor for the success of this operation was the utilization of aprotic solvent DMF as the solvent. Interestingly, the nucleophilic displacement on these haloalkynes proved to be surprisingly facile even at −25 °C.

Scheme 3.32 Synthesis of acetylenic thioethers

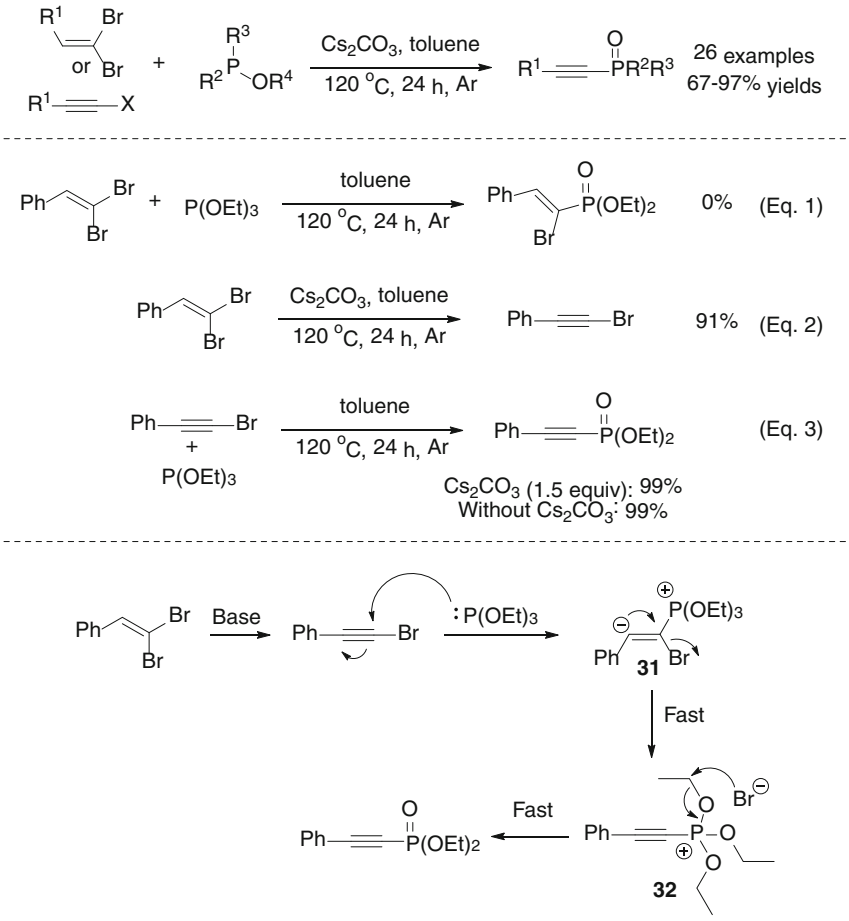
Importantly, it proved that the nucleophilic substitution at an acetlyenic carbon is possible.

General Procedure for the Synthesis of Acetylenic Thioethers: The solution of sodium thiolate (1.02 equiv) and haloalkyne (1.0 equiv) in DMF (0.12 mmol/mL) was mixed and stored at −30 °C in a stoppered flask which had been flushed with nitrogen. If the reaction was slow, the temperature of the solution was raised to 25 °C or higher if need be. Unnecessary heating appeared to reduce the yields of products. On completion of the reaction, the solution was treated with ice and water and extracted with ether to give the impure sulfides. Careful distillation gave the acetylenic thioether products.

3.1.4 Construction of Carbon-Phosphorus Bond

Alkynyl-phosphorus compounds are an important class of triple bond-containing, extremely versatile chemicals in modern synthetic chemistry, which are broadly available for the preparation of structurally sophisticated phosphorus-containing compounds [132]. In this context, the preparation of alkynyl-phophorus compounds has attracted considerable attention over the past decades [133]. In 2014, Gao and co-workers developed Cs_2CO_3-promoted one-pot synthesis of alkynylphophorus from bromoalkynes or 1,1-dibromo-1-alkenes via carbon-phosphorus bond formation. Without base, 1,1-dibromo-1-alkenes could not convert to the desired product under the standard reaction conditions [Scheme 3.33, Eq. (1)]. Mechanism investigation indicated that 1,1-dibromo-1-alkene could be transferred to the corresponding bromoalkyne under the treatment of base, and bromoalkyne was the reactive species [Scheme 3.33, Eqs. (2) and (3)]. Subsequently, the addition of triethyl phosphate led to the formation of quaternary phosphonium salt **31**, with the release of bromide group affording the phosphonium salt **32**, which then underwent Michaelis-Arbuzov type reaction to afford the alkynyl-phosphorus products (Scheme 3.33) [134].

General Procedure for the Synthesis of Alkynyl-Phosphorus Compounds: An oven-dried Schlenk tube with Cs_2CO_3 (0.75 mmol) was evacuated and purged with argon three times. A mixture of 1,1,-dibromo-1-alkene or bromoalkyne (0.5 mmol) and *P*-nucleophiles (0.55 mmol) in toluene (1.5 mL) was added to the tube and stirred at 120 °C for 24 h. The suspension was filtered and washed with EtOAc (5 mL × 3). The combined solvent was removed under reduce pressure. The residue was purified by silica gel chromatography using a mixture of petroleum ether and ethyl acetate as eluent.



Scheme 3.33 Synthesis of alkynyl-phosphorus compounds

3.2 Transformations of Carbon-Carbon Triple Bond Motif

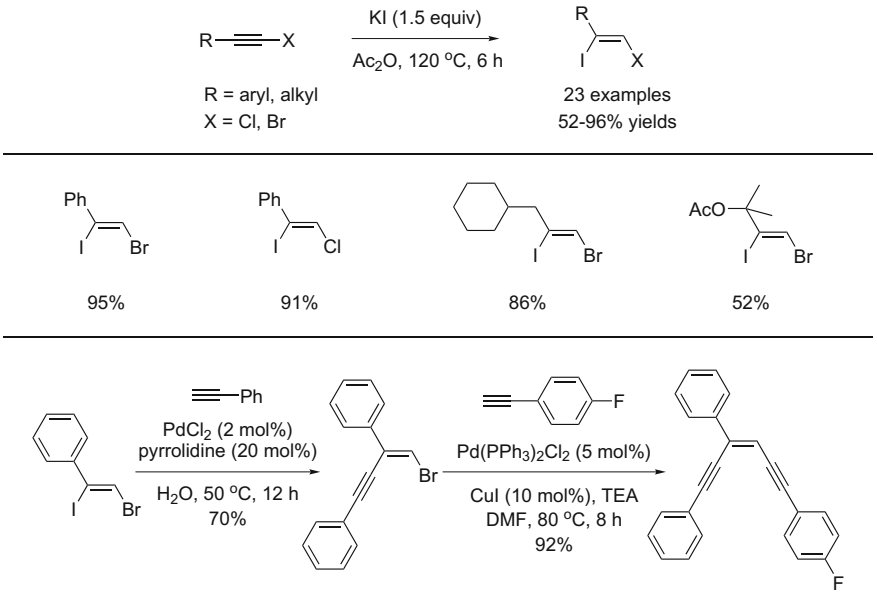
Alkyne motif is one of the most reactive and useful fundamental units in synthetic chemistry, which exhibits rich and tunable reactivity particularly under the treatment of transition metal catalysts. Consequently, the diverse transformations of alkyne motif contained molecules have attracted considerable attention during the past decades [135]. Accordingly, transformations of haloalkyne reagents based on the highly reactive carbon-carbon triple bond, could realize the facile synthesis of frameworks that previously were unable or difficult to obtain.

3.2.1 Nucleophilic Additions

Due to the central role of heteroatom-contained olefins in biological systems and pharmaceutical applications, the development of efficient and sustainable methods to synthesize this class of compounds is a long-term task in the area of synthetic and medicinal chemistry [136–139]. Among various protocols to achieve this goal, the nucleophilic addition of haloalkynes represents a series of reactions with important synthetic value to construct C(sp^2)–X bonds.

3.2.1.1 Halogen Nucleophiles

Dihaloalkenes have emerged as one of the most versatile intermediates in organic synthesis, especially in the transition metal-catalyzed cross-coupling reactions. However, the traditional methods for the preparation of dihaloalkenes usually suffer some limitations, such as poor selectivity and difficult purification [140–142]. In 2010, Jiang's group documented the first example of a facile two-step synthesis of (Z)-2-halo-1-iodoalkenes from simple terminal alkynes, delivering the desired products in moderate to excellent yields with high regio- and stereoselectivities (Scheme 3.34) [143]. This method was transition-metal free, and exhibited excellent functional group compatibility. Additionally, the useful halo-iodoalkene adducts could be easily transformed to the conjugated (Z)-haloenynes and



Scheme 3.34 Halogenation reaction of haloalkynes

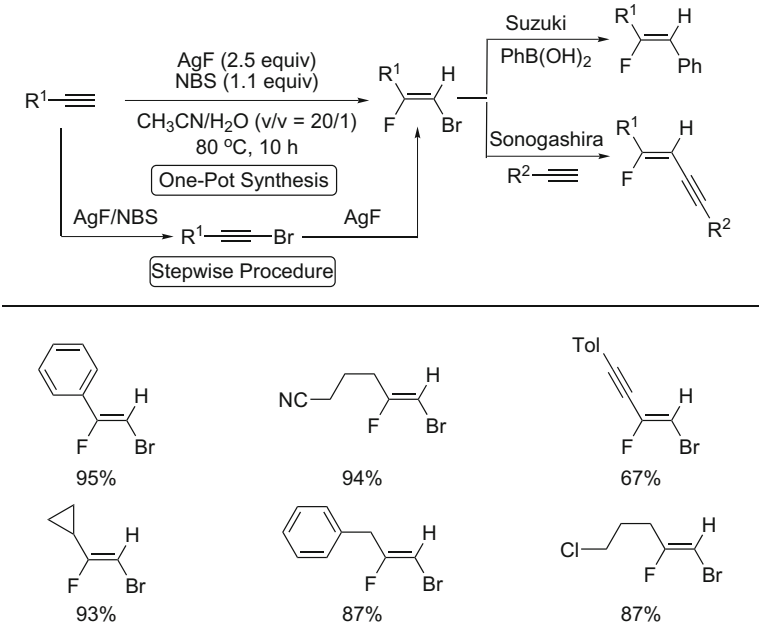
asymmetrical (Z)-enediynes in good yields through selective Sonogashira coupling pathway. Later in 2012, Zhu and co-workers realized the hydrohalogenation of alkynyl halides to construct (Z)-1,2-dihaloalkenes under palladium catalysis [144].

General Procedure for the Halogenation Reaction of Haloalkynes: The mixture of haloalkyne (1 mmol), KI (1.5 mmol) and acetic anhydride (1.5 mL) were heated at 120 °C for 6 h. Then, the mixture was allowed to cool to room temperature, and water was added. The resulting mixture was extracted with ethyl acetate (15 mL × 3), and the combined extract was dried with anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was separated by column chromatography to give the desired dihaloalkenes.

Due to the unique physical and biological properties of fluorinated molecules, the corresponding vinyl fluoride products were quite attractive for synthetic and medicinal chemists [145–149]. Although the halide nucleoaddition to haloalkynes have provided a diverse set of haloalkene derivatives, the incorporation of fluorine atom into the final olefin products through transition metal catalysis is still a challenging target. Rare effective methods are available for the transition metal-catalyzed direct synthesis of simple fluoroalkene derivatives without additional functional sites [150]. In 2012, Jiang and coworkers revealed a one-pot silver-assisted regio- and stereoselective bromofluorination reaction of terminal alkynes (Scheme 3.35) [151]. The corresponding bromofluoroalkenes could be obtained in high yields with excellent selectivity. It was found that the electron-rich internal carbon-carbon triple bond was tolerated under the standard reaction conditions. To gain further insight into the mechanism of the catalytic cycle, the authors conducted some control experiments, such as the direct fluorination reactions of haloalkynes. Gratifyingly, both bromoalkynes and chloroalkynes exclusively afforded the fluorinated products in good yields. However, the iodoalkynes transformed to the corresponding iodofluoroalkene and diiodofluoroalkene adducts in a ratio of 2:1, due to the higher reactivity of iodoalkynes than bromoalkynes and chloroalkynes. Notably, the stereoselective functionalization of bromide subunit was successfully realized via Sonogashira or Suzuki coupling reactions. Thus, the present synthetic protocol would be applicable to obtain the 1-fluoro-1,3-enyne molecules that widely exist in numerous organic materials and biologically active compounds.

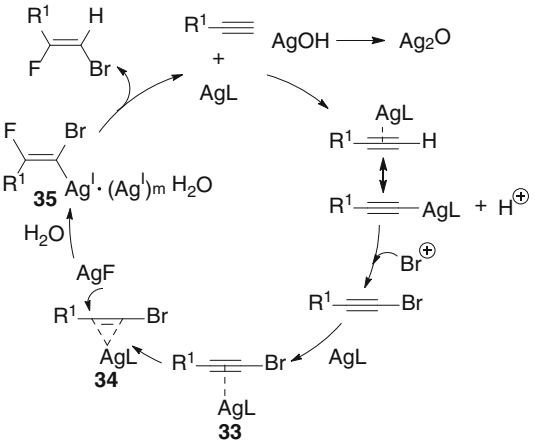
General Procedure for Ag-Assisted Bromofluorination Reaction of Terminal Alkynes: To a Schlenk tube was successively added NBS (1.1 mmol), AgF (2.5 mmol), CH_3CN (wet, 2 mL), and alkyne (1 mmol). The resulting mixture was stirred at 80 °C for 10 h. Then, the mixture was allowed to cool to room temperature, and filtered through a small amount of silica gel. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel preparative TLC (*n*-hexane) to give the desired product.

According to the previous literatures [152, 153] and the obtained experimental results, the authors tentatively proposed the possible reaction mechanism (Scheme 3.36). Initially, the bromoalkyne intermediate was formed through the Ag-promoted bromination of terminal alkynes. Subsequently, the Ag cation was attacked by the triple bond of bromoalkyne to give a π-complex **33**, which was then

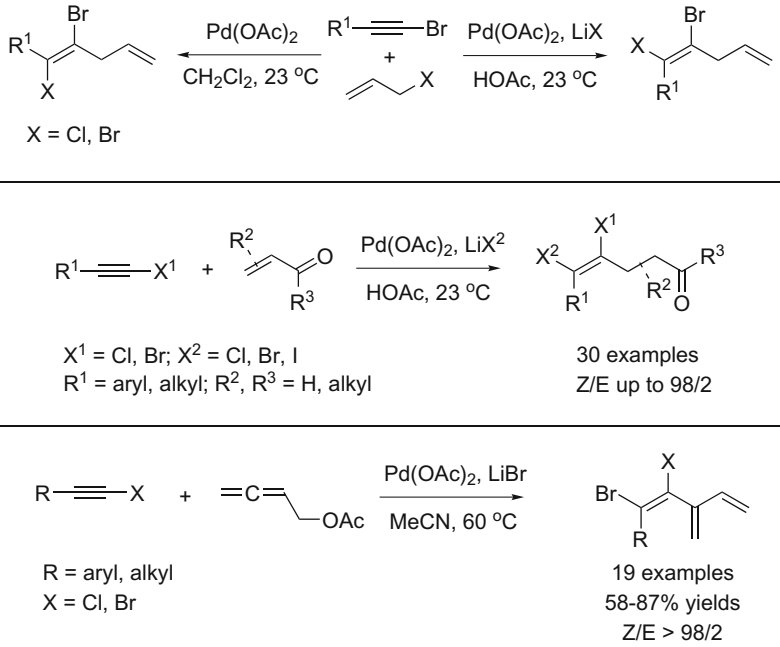


Scheme 3.35 Ag-assisted bromofluorination reaction of terminal alkynes

Scheme 3.36 Proposed mechanism



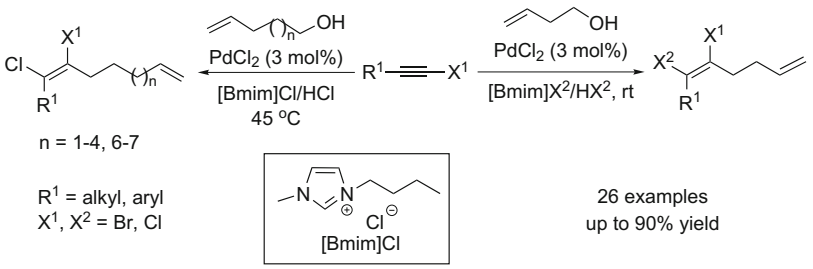
transferred to the corresponding vinylsilver intermediate **35** by *trans*-addition of AgF to bromoalkyne. Finally, protonation of **35** afforded the final product and silver oxide. The high regio- and stereoselectivities were proposed to be originated from the back-side attack of the fluoride anion (**34** to **35**) as well as the bromide atom was regarded as both an activating and regio-directing functional group. However, another mechanism involving the formation of vinylsilver intermediate **35** through the nucleophilic addition of fluoride to bromoalkyne could not be ruled out.

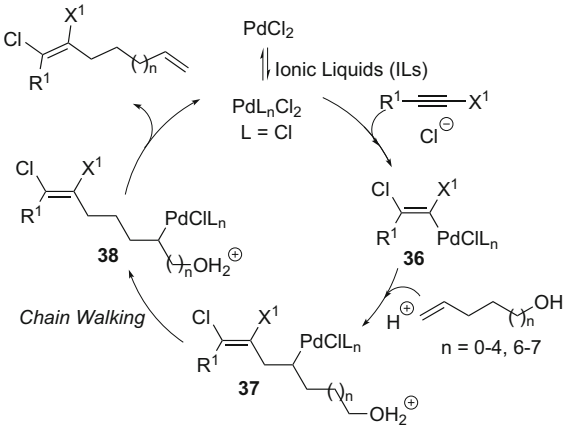


Scheme 3.37 Pd-catalyzed synthesis of haloalkenes

Halogenated 1,*n*-dienes, another significant kind of structural building blocks, are usually employed to construct biologically active and multifunctional compounds [154–157]. In 2011, Zhu's group documented an efficient and selective method for the synthesis of (1E)- or (1Z)-1,2-dihalo-1,4-dienes via Pd-catalyzed coupling of haloalkynes and allylic halides (Scheme 3.37) [158]. Interestingly, the E/Z selectivity of the diene product could be switched by the addition of stoichiometric lithium halides. With the same halopalladation strategy, they also reported a Pd-catalyzed coupling approach of alkynyl halides with α,β-unsaturated carbonyls [159] and 2,3-butadienyl acetates [160] for the synthesis of *cis*-1,2-dihaloalkene and (1Z)-1,2-dihalo-3-vinyl-1,3-diene derivatives.

In 2013, Jiang's research group reported Pd-catalyzed intermolecular cross-coupling reactions for the stereoselective synthesis of functionalized 1,*n*-dienes in ionic liquids (ILs) [161]. The ionic liquids not only acted as a solvent in the reaction, but also served as the excess halide ions source to control the Z/E selectivity. A chain-walking mechanism for this transformation is tentatively proposed in Scheme 3.38. Firstly, Pd complex was formed in situ in ILs and vinylpalladium intermediate **36** was generated by *trans*-halopalladation of the alkyne moiety in the presence of excess halide ions in a polar solvent system. Subsequently, **36** underwent alkene insertion to deliver the alkylpalladium species **37**, followed by rapid β-H elimination and reinsertion to change the position of the metal on the alkyl chain, affording the intermediate **38**. Finally, a β-heteroatom elimination gave the obtained dihalo-1,*n*-diene adduct.

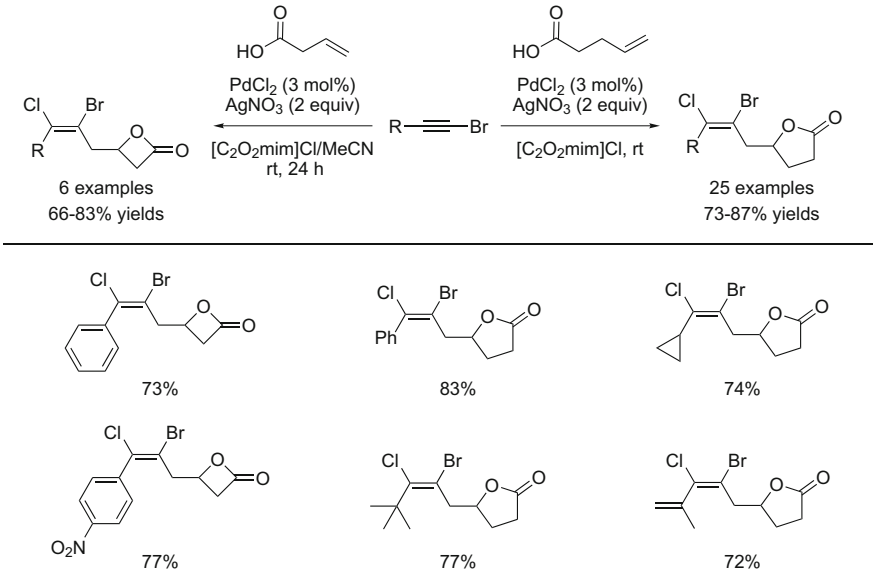




Scheme 3.38 Pd-catalyzed synthesis of functionalized dihalo-1,*n*-dienes

General Procedure for Pd-Catalyzed Synthesis of Functionalized Dihalo-1,n-dienes: To a test tube (10 mL) equipped with a magnetic stirring bar were successively added haloalkyne (0.5 mmol), alcohol (0.6 mmol), palladium chloride (3 mol %), ionic liquid (0.5 mL), HX (X = Cl, Br) (0.25 mL). The mixture was stirred under the atmosphere of air at room temperature. After the reaction was completed, the mixture was poured into ethyl acetate (30 mL). The organic layer was washed with brine to neutral, dried over anhydrous $MgSO_4$, concentrated in vacuum. Purification of the residue on a preparative TLC afforded the desired products.

Additionally, saturated lactones are found in a wide range of synthetically challenging and biologically significant natural products, which exhibit extraordinary pharmaceutical and biological properties [162–164]. Taking the advantages of halo-nucleopalladation, Jiang and coworkers realized the first example of palladium-catalyzed intermolecular cascade annulation for the construction of γ-lactones with regio- and stereoselectivity in ionic liquids (ILs) (Scheme 3.39) [165]. Besides the broad substrate scope, their cascade annulation reaction tolerated diverse functional groups. Significantly, all the obtained products were resulted from *trans* addition under the standard reaction conditions. Interestingly, they also applied

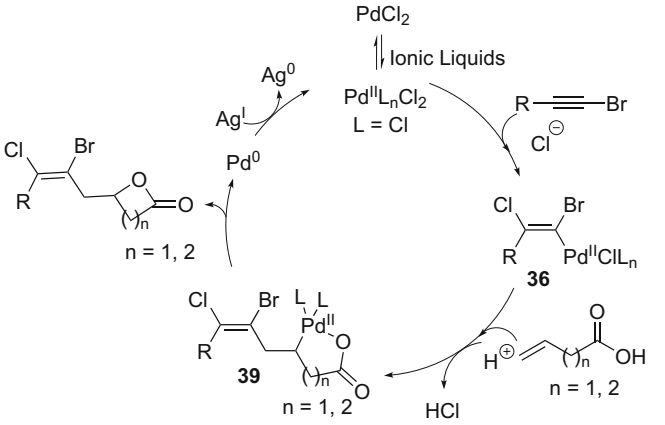


Scheme 3.39 Palladium-catalyzed synthesis of β- and γ-lactones

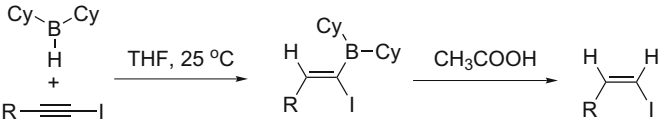
their method to the reaction with but-3-enoic acid, and various β-lactones could be successfully obtained under similar reaction conditions (Scheme 3.39) [165].

General Procedure for Palladium-Catalyzed Synthesis of β-, and γ-Lactones: To a test tube (10 mL) equipped with a magnetic stirring bar were successively added haloalkyne (0.25 mmol), the corresponding acid (0.3 mmol), palladium chloride (3 mol%), ionic liquid (0.5 mL). The mixture was stirred under the atmosphere of air at room temperature. After the reaction was completed, the mixture was poured into ethyl acetate (30 mL). The organic layer was washed with brine to neutral, dried over anhydrous $MgSO_4$, concentrated in vacuum. Purification of the residue on a preparative TLC afforded the lactone product.

Based on the current results and previous literatures [161, 166, 167], the authors proposed the possible reaction mechanism, which was illustrated in Scheme 3.40. Firstly, Pd complex was formed *in situ* in ILs and vinylpalladium intermediate **36** was generated by *trans*-halopalladation of the alkyne moiety in the presence of excess halide ions in a polar solvent system. Subsequently, **36** underwent alkene insertion. The vinylpalladium species coordinated to the oxygen atoms of the hydroxyl group to generate the palladium/alkyl intermediate **39**. Finally, a reductive elimination gave the obtained lactone adduct and Pd^0. Noteworthy, a silver mirror was observed after the completion of the reaction. Hence, the resulting Pd^0 was further oxidized to Pd^{II} which would be involved the next catalytic cycle.



Scheme 3.40 Possible mechanism for palladium-catalyzed synthesis of lactones



Scheme 3.41 Synthesis of *trans*-α-halovinylboranes

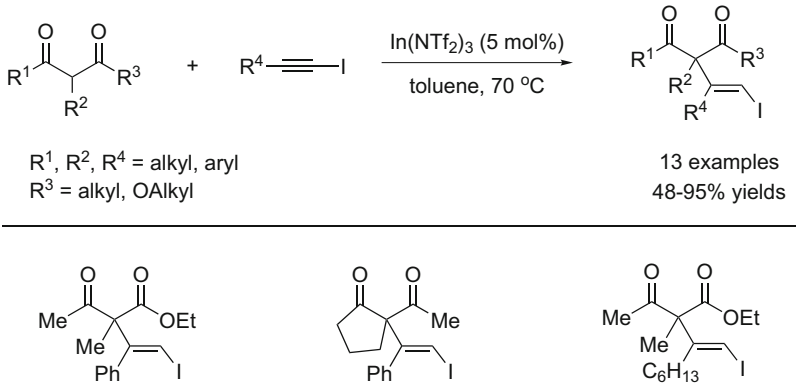
3.2.1.2 Boron Nucleophiles

As the diverse transformation abilities of organoborane compounds, the synthesis of α-halovinylboranes attracted the attention of scientists early in 1967 [168]. Addition of dicyclohexylborane to haloalkynes afforded the corresponding *trans*-α-halovinylboranes, which could directly convert to the corresponding ketones. Importantly, it was found out that *trans*-α-halovinylboranes were stable toward alkyl group migration in THF solvent as evidenced by their conversion into *cis*-vinyl halides upon hydrolysis with acetic acid (Scheme 3.41). With this protocol of α-halovinylboranes, Brown [169] and Walsh [170] applied them into diverse transformations.

General Procedure for the Synthesis of trans-α-Halovinylboranes: To a suspension of dicyclohexylborane (30 mmol) in THF (60 mL) at 0 °C was added haloalkyne (30 mmol). The reaction mixture was maintained for an additional 30 min at 20–30 °C, and then used directly for the next transformation.

3.2.1.3 Carbon Nucleophiles

The addition of carbon necleophiles to unsaturated bonds is a very important strategy to construct carbon-carbon bond. In 2008, Nakamura and co-worker



Scheme 3.42 Indium-catalyzed addition of 1,3-dicarbonyl compounds to 1-iodoalkynes

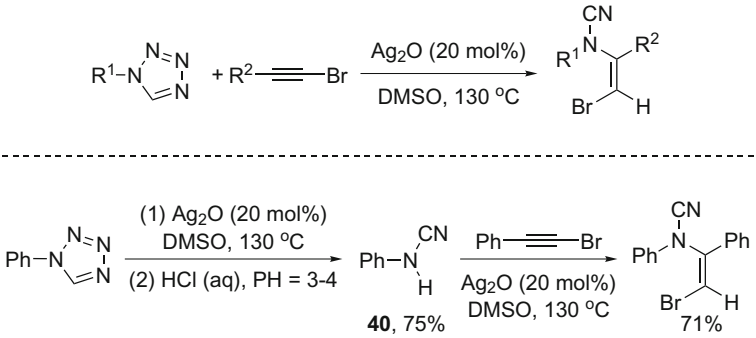
reported indium-catalyzed addition of 1,3-dicarbonyl compounds to 1-iodoalkynes [171]. This reaction proceeded exclusively in a *syn*-fashion to give E-alkenyl iodide in high yields. And the structure of the product was unambiguously determined by X-ray crystallographic analysis. Importantly, the iodine atom not only served as an activating group, but also as a direct group that controlled the regioselectivity of the addition (Scheme 3.42). Later, Jiang's group [172] documented the nucleophilic addition of isocyanides to bromoalkynes via palladium catalysis, and Vadola [173] realized the gold-catalyzed dearomative spirocyclization of aryl alkynoate esters.

General Procedure Indium-Catalyzed Addition of 1,3-Dicarbonyl Compounds to 1-Iodoalkynes: A mixture of 1,3-dicarbonyl compound (2 mmol), 1-iodoalkyne (3 mmol), and $In(NTf_2)_3$ (5 mol%) in toluene (2 mL) was heated in the dark at 70 °C for 4 h. The mixture was filtered through a pad of silica gel and concentrated. The crude product as purified by silica gel column chromatography to give the desired product.

3.2.1.4 Nitrogen Nucleophiles

β-Halo enamines are not only important building blocks in functional molecules, but also reactive intermediates for many chemical processes [174–176]. Undoubtedly, the addition of nitrogen to haloalkynes is a convenient route to facile access β-halo enamines. In 2013, Wang [177] and co-workers reported the silver-catalyzed addition reaction of tetrazoles with bromoalkynes, delivering the β-halo enamine products in good yields and excellent stereoselectivities. Control experiments indicated that *N*-phenylcyanamide (**40**) was the reactive intermediate (Scheme 3.43). Importantly, the β-halo enamine products could be further transformed to 2-arylindoles.

General Procedure for Ag-Catalyzed Synthesis of β-Halo Enamines: A reaction tube (10 mL) was charged with tetrazole (0.5 mmol), bromoalkyne (0.75 mmol), Ag_2O (20 mol%) and DMSO (2 mL). The reaction vessel was placed in an oil bath.



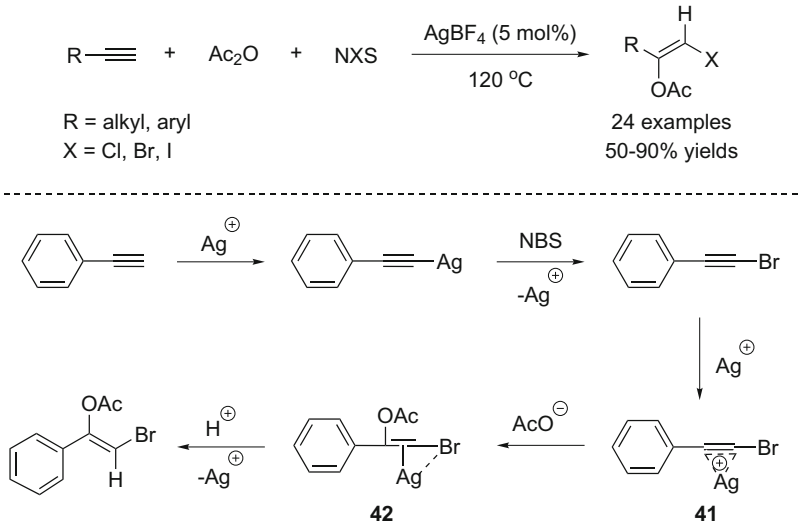
Scheme 3.43 Ag-catalyzed synthesis of β-halo enamines

After the reaction was carried out at 130 °C for 12 h, it was cooled to room temperature, extracted with EtOAc (5 mL × 3). The organic layers were combined, dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography on silica gel to give the β-halo enamine product.

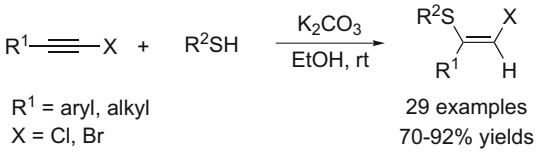
3.2.1.5 Oxygen Nucleophiles

The β-haloenol acetate subunits are of considerable significance in organic synthesis and pharmaceutical chemistry [178–180]. It is striking, however, very few catalytic methods have been developed to construct the OC=CX motif in one step from simple terminal alkynes [181, 182]. In 2010, Jiang's group reported the first example of Ag-catalyzed alkyne difunctionalization reaction to afford the (Z)-β-haloenol acetate derivatives with extremely high regio- and stereoselectivities (Scheme 3.44) [183]. They proposed that the haloalkyne intermediate was first generated and then the triple bond attacked the Ag cation to deliver a π-complex **41**, which was transferred to the corresponding σ-complex **42** through the nucleophilic attack of acetic anion. Finally, protonation of **42** gave the desired β-haloenol acetate product. Accordingly, the high regio- and stereoselectivities might be owing to the stabilization effect of halogen atom to the Ag catalyst. Later, plenty of methods have been developed for the nucleophilic addition of haloalkynes with diverse oxygen nucleophiles, and delivered the corresponding β-haloenol [184, 185] or α-haloketone [186, 187] derivatives in good yields.

General Procedure for Ag-Catalyzed Synthesis of (Z)-β-Haloenol Acetates: To a test tube (10 mL) equipped with a magnetic stirring bar were successively added terminal alkyne (1 mmol), NBS (1.2 mmol), acetic anhydride (2 mL), silver tetrafluoroborate (5 mol%). The mixture was stirred at 120 °C for 12 h. Then the solution was allowed to cool to room temperature, extracted with ethyl acetate (15 mL × 3). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuum. The residue was purified by column chromatography to give the haloenol acetate product.



Scheme 3.44 Ag-catalyzed synthesis of (Z)-β-haloenol acetates



Scheme 3.45 K_2CO_3-promoted hydrothiolation of haloalkynes

3.2.1.6 Sulfur Nucleophiles

The importance of β-halo alkenyl sulfides has made them attract the attention of many scientists [188]. One of the most effective methods to access these compounds is the hydrothiolation of haloalkynes. In 2014, Zhu's group documented a K_2CO_3-promoted hydrothiolation reaction of haloalkynes, producing β-halo alkenyl sulfides in high yields with excellent regio- and stereoselectivities. This operationally simple and efficient protocol tolerated diverse functional groups (Scheme 3.45) [189].

General Procedure for K_2CO_3-Promoted Hydrothiolation of Haloalkynes: To a mixture of 2-mercaptopyridine (0.6 mmol) and K_2CO_3 (0.65 mmol) in EtOH (2 mL) was added haloalkyne (0.5 mmol). After stirring at room temperature for 10 h, the reaction mixture was quenched with water, extracted with EtOAc, dried over Na_2SO_4 and concentrated. Column chromatography on silica gel gave the β-halo alkenyl sulfide products.

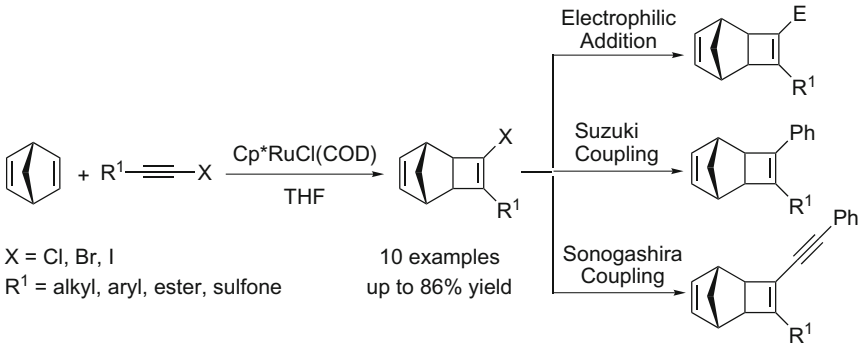
3.2.2 Cycloadditions

Transition metal-catalyzed cycloadditions have demonstrated their great value in the efficient construction of ring systems and complex skeletons [190, 191]. Due to their electron-withdrawing properties, haloalkynes could potentially accelerate the reaction rate of cycloaddition. In this context, transition metal-catalyzed cycloadditions of haloalkynes have attracted considerable attention. Additionally, the halide moiety could be utilized for further decoration, providing an alternative protocol for those cyclic structures difficult to access via direct cycloaddition procedure.

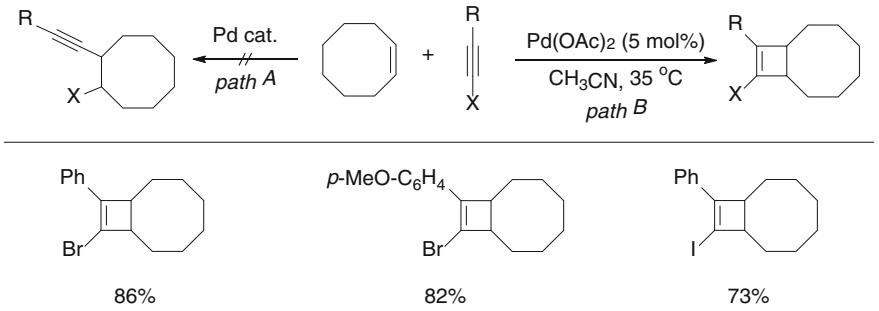
3.2.2.1 [2 + 2] Cycloaddition

The [2 + 2] cycloadditions between alkynes and alkenes are known to be an efficient method for the construction of cyclobutene rings [192, 193]. In 2004, Tam's group developed the [2 + 2] cycloaddition of bicyclic alkenes with haloalkynes under Ru catalysis (Scheme 3.46) [194]. Notably, the halide moiety greatly improved the reactivity of the alkyne component in the cycloaddition reaction. Importantly, the obtained cycloadducts could be transferred into various products via nucleophilic addition, Suzuki coupling, and Sonogashira coupling. Mechanism studies indicated that chloroalkynes reacted faster than bromoalkynes in this cycloaddition [195, 196]. Later, Koldobskii [197, 198] reported the [2 + 2] cycloaddition reaction of haloalkynes and vinyl ethers.

General Procedure for Ru-Catalyzed [2 + 2] Cycloaddition between Norbornadiene and Haloalkynes: A mixture of nobornadiene (3–5 equiv), and haloalkyne (1 equiv) in THF (0.5 mmol/mL) was added via a cannula to an oven-dried screw-cap vial containing Cp*RuCl(COD) (10 mol%) under nitrogen. The reaction mixture was stirred in the dark at 25–65 °C for 1–168 h. The crude product was purified by column chromatography to give the cycloadduct.



Scheme 3.46 Ru-catalyzed [2 + 2] cycloaddition between norbornadiene and haloalkynes



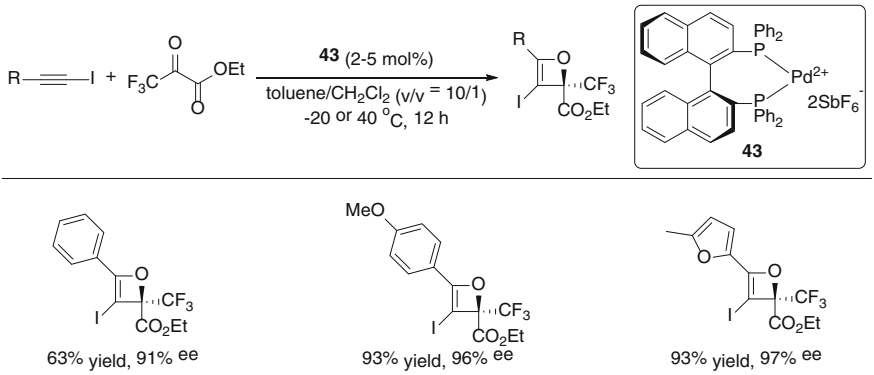
Scheme 3.47 Cycloaddition of haloalkynes and cyclooctene

In sharp contrast, the [2 + 2] cycloaddition of monocyclic alkenes with alkynes continues to represent a synthetic challenge. In 2011, Jiang and coworkers discovered that cyclooctene, a flexible alkene rather than the strained norbornene, reacted with haloalkyne could lead to a four-membered ring system via [2 + 2] cycloaddition pathway under mild conditions (Scheme 3.47, path B), while the 3-propynyl halide derivatives were not detected (Scheme 3.47, path A) [101]. This approach was another representative example of haloalkynes for carbocycle formation under Pd catalysis. Importantly, 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 delivered the corresponding cycloadducts in moderate to good yields. However, cyclododecene was found to be completely ineffective under the optimized conditions, while cycloheptene afforded an inseparable mixture including the Alder-ene products. These observations indicated that the ring size of the cyclicalkene was crucial for the formation of the desired cyclobutene derivatives.

General Procedure for the Cycloaddition of Haloalkynes and Cyclooctene: To a Schlenk tube (25 mL) was successively added $Pd(OAc)_2$ (5 mol%), CH_3CN (2 mL), cyclooctene (1.3 mmol) and haloalkyne (1 mmol). The resulting mixture was stirred at 30 °C for 10 h. Then, the mixture was filtered through a small amount of silica gel. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel preparative TLC (*n*-hexane) to give the desired product.

Additionally, a unique example was reported by Mikami in 2011 [199]. The catalytic asymmetric [2 + 2] cycloaddition reaction of 1-iodoalkyne with ethyl trifluoropyruvate was realized in the presence of a palladium catalyst **43**. Although the author only presented three substrates, this reaction indeed represented the first example of catalytic asymmetric [2 + 2] cycloaddition reaction of haloalkyne with a carbonyl group (Scheme 3.48).

General Procedure for Pd-Catalyzed Asymmetric [2 + 2] Cycloaddition Reaction of 1-Iodoalkyne: To a solution of (*S*)-BINAP-$PdCl_2$ (2 mol%) in CH_2Cl_2 (2 mL) was added $AgSbF_6$ (2.2 mol%) at room temperature under argon atmosphere. After stirring for 30 min, ethyl trifluoropyruvate (1 mmol) and iodoalkyne (0.5 mmol) were added to the mixture at −20 °C for 12 h, and then the reaction



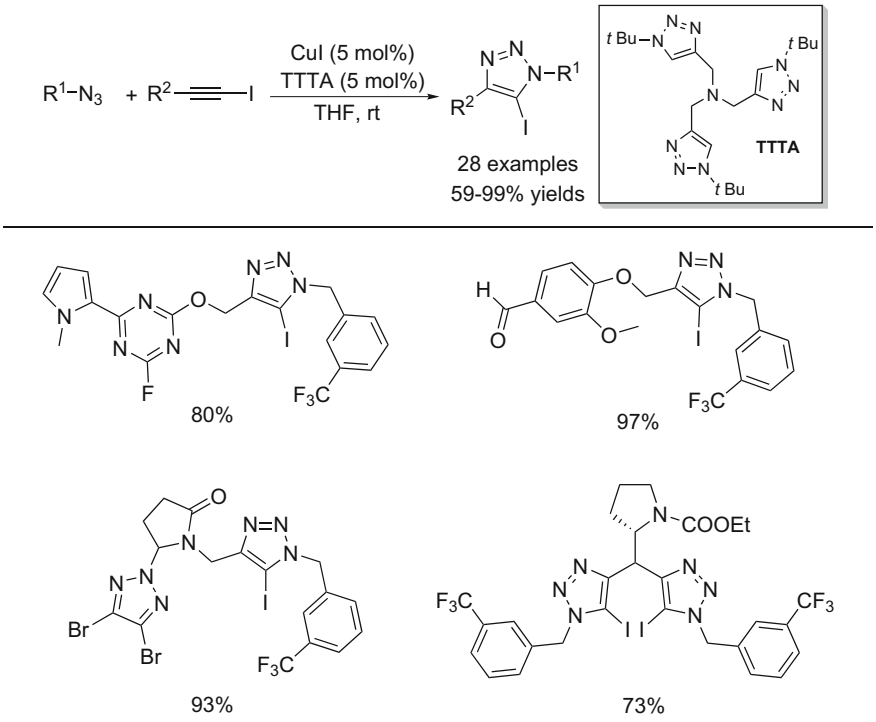
Scheme 3.48 Pd-catalyzed asymmetric [2 + 2] cycloaddition reaction of 1-iodoalkyne

mixture was directly loaded onto a short silica-gel column to remove the catalyst. Purification by silica-gel chromatography gave the corresponding oxetene product. And the enantiomeric excess was determined by chiral HPLC analysis.

3.2.2.2 [3 + 2] Cycloaddition

The Cu-catalyzed azide–alkyne [3 + 2] cycloaddition reaction has been widely investigated in the field of synthetic and medicinal chemistry, polymer chemistry, and materials science [200]. However, the efficiency and selectivity of this transformation depend on the reactivity of *in situ* generated Cu^{I} acetylides. Therefore the reaction partners are usually limited to terminal acetylenes, which provide only 1,4-disubstituted triazoles. In this regard, a general and practical protocol for the regio-controlled construction of different substituted triazoles would be a valuable complement to the "click chemistry". One outstanding example is that the efficient method reported by Hein and Fokin et al., for the chemo- and regioselective synthesis of iodotriazoles from organic azides and iodoalkynes (Scheme 3.49) [201]. This reaction featured a broad substrate scope, excellent functional group and solvent tolerance, and also remarkably high reaction rates. The employment of TTTA as ligand was the key to achieve this transformation, because no reaction was observed when TTTA was omitted, and the chemoselectivity as well as the observed rate of the reaction were strongly dependent on the nature of the ligand. As an additional benefit, the 5-iodo-1,2,3-triazole adducts are versatile synthetic intermediates, which are amenable to further functionalization. Later, García-Álvarez [202], Rowan [203], Zhu [204], and Díez-González [205] independently reported the cycloaddition of azides with haloalkynes under copper catalysis.

General Procedure for Copper-Catalyzed Cycloaddition of Azides with 1-Iodoalkynes: CuI (5 mol%) and TTTA (5 mol%) were stirred in THF (4.5 mL) at room temperature for 20 min, after which time a homogeneous solution was obtained. Organic azide (1 mmol) and 1-iodoalkyne (1 mmol) were dissolved in

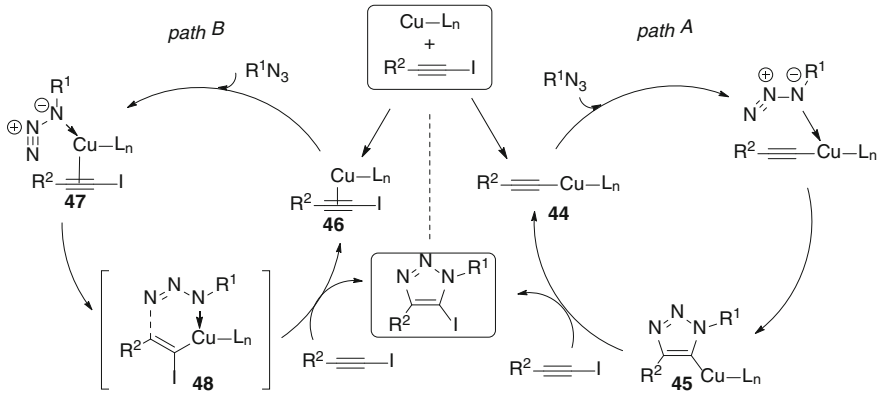


Scheme 3.49 Copper-catalyzed cycloaddition of azides with 1-iodoalkynes

THF (0.5 mL) and added in a single portion to the catalyst solution. The reaction mixture was stirred for 45 min, and then quenched by adding 10% NH_4OH solution (1 mL). The volatile components were removed by evaporation, and the resulting residue was suspended in water and diethyl ether. A precipitate formed upon vigorous stirring and was isolated by filtration to give the triazole as white powder.

Base on the experimental results and previous literatures [206, 207], the authors outlined their mechanistic proposals in Scheme 3.50. In path A, firstly, σ-acetylide complex **44** was formed. Then, key intermediate **44** coordinated to the proximal nitrogen center and subsequent cyclization to afford the cuprated triazole **45**. Finally, copper exchanged with iodoalkyne via σ-bond metathesis to provide the iodotriazole product and regenerate the acetylide **44**. On the other hand in path B, copper might activate the iodoalkyne through the formation of a π-complex intermediate **46**, which would engage the azide to deliver complex **47**. Then the complex **47** underwent cyclization through a vinyldiene-like transition state **48** to produce the triazole product.

The isoxazole moiety is also an attractive pharmacophoric element which is found in various useful therapeutic agents [208, 209]. The [3 + 2] cycloaddition of nitrile oxides with haloalkynes is an efficient route to facile access halo substituted isoxazole compounds, which could be further functionalized. Although this reaction

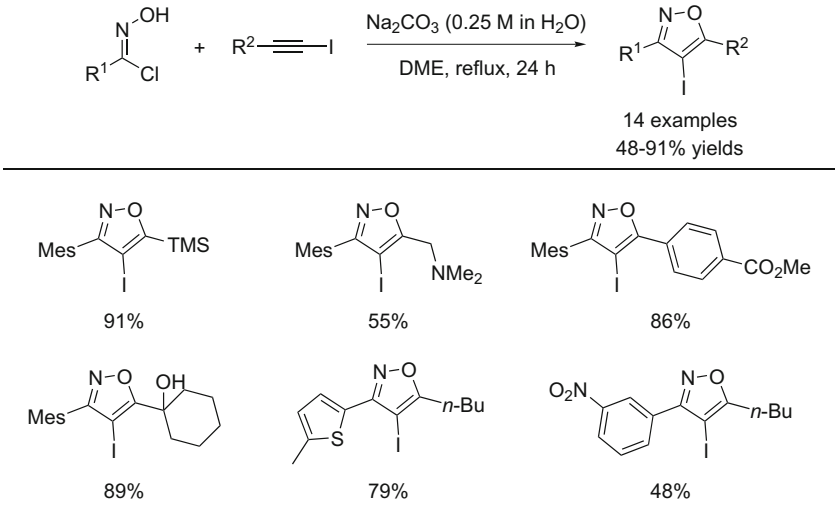


Scheme 3.50 Proposed mechanism for the copper-catalyzed azide-iodoalkyne cycloaddition

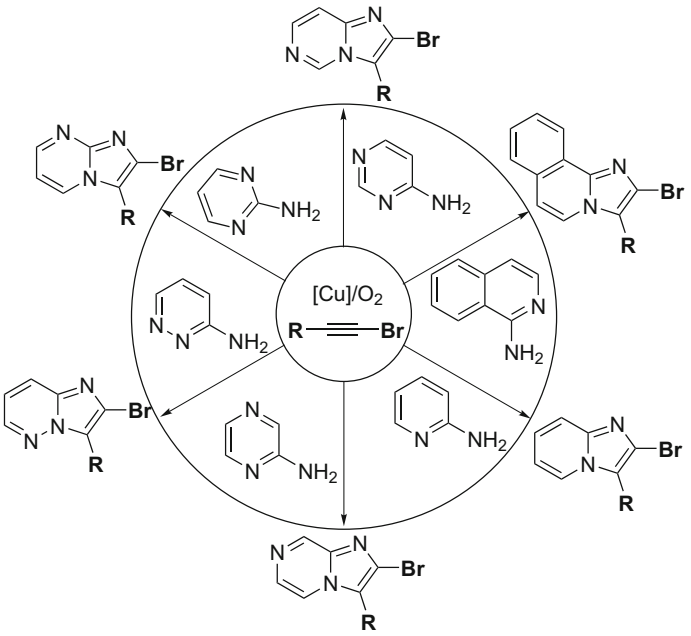
was investigated early in 1989, it suffered limited substrate scope or poor yields [210, 211]. In 2010, Browne and co-workers reported a thermally promoted cycloaddition of iodoalkynes with in situ generated nitrile oxides from chloro-oximes. This method has a broad substrate scope with respect to both iodoalkynes and chloro-oximes, and delivered the corresponding isoxazole products in good yields with excellent regioselectivity (Scheme 3.51) [212].

General Procedure for the Cycloaddition of 1-Iodoalkynes and Nitrile Oxides: The chloro-oxime (0.5 mmol), iodoalkyne (1 mmol), and DME (3 mL) were added to a two-necked round-bottom flask, which was then equipped with a suba seal and a condenser. The mixture was heated to 100 °C for 24 h with syringe pump addition of a Na_2CO_3 aqueous solution (2.1 mL, 0.25 M in water). Then the reaction was cooled, extracted with DCM, dried with $MgSO_4$, filtered, and concentrated. The residue was purified by column chromatography on silica gel.

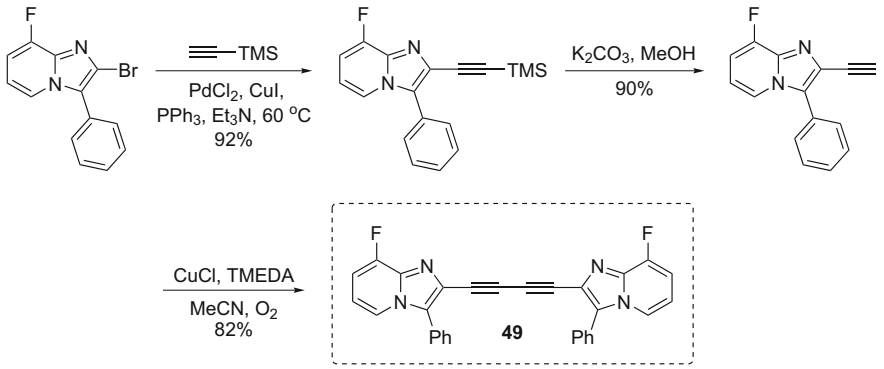
Imidazo-containing motifs are versatile building blocks in natural products and bioactive compounds that have great significance in the area of pharmaceuticals [213, 214]. Undoubtedly, the intermolecular oxidative diamination of haloalkynes via a transition metal-catalyzed nucleophilic addition/C–N bond formation cascade process is an attractive approach to synthesize imidazo derivatives, in which the reactive halogen substituent of the haloalkynes was retained. In 2012, Jiang and co-workers revealed a new and direct approach to construct 2-halo-substituted imidazo[1,2-a]pyridines through the Cu-catalyzed oxidative cyclization reaction of *o*-aminopyridines and haloalkynes. Various 2-halo-substituted imidazopyridine, imidazopyrazine and imidazopyrimidine products were obtained with high regioselectivity under mild reaction conditions (Scheme 3.52) [215]. Furthermore, the resultant 2-halo-substituted products could be easily functionalized via elegant cross-coupling reactions. A highly conjugated structure **49** was successfully constructed after three-step synthesis. The practicality of this Cu-catalyzed oxidative cyclization reaction exhibited its potential utilities for the construction of optoelectronic materials (Scheme 3.53).



Scheme 3.51 The synthesis of isoxazoles



Scheme 3.52 Cu-catalyzed of synthesis of imidazopyridine structures



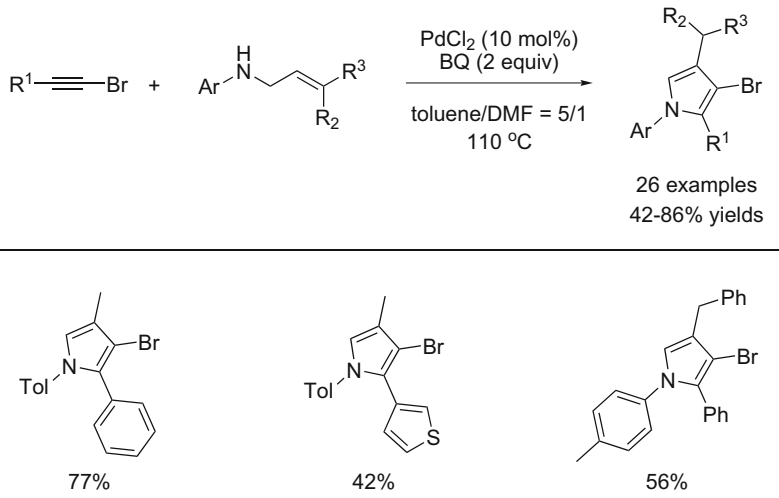
Scheme 3.53 Synthetic applications of imidazopyridine products

General Procedure for Cu-Catalyzed of Synthesis of Imidazopyridine Structures: A mixture of 2-aminopyridine (0.3 mmol), haloalkyne (0.2 mmol), and $Cu(OTf)_2$ (20 mol%) was stirred in MeCN (2 mL) at 60 °C under an oxygen atmosphere for 12 h. Then, water (10 mL) was added to quench the reaction. The aqueous solution was extracted with diethyl ether (10 mL × 3) and the combined organic layers were dried with $MgSO_4$, filtered and concentrated in vacuum. The residue was separated by flash column chromatography on silica gel to give the imidazopyridine products.

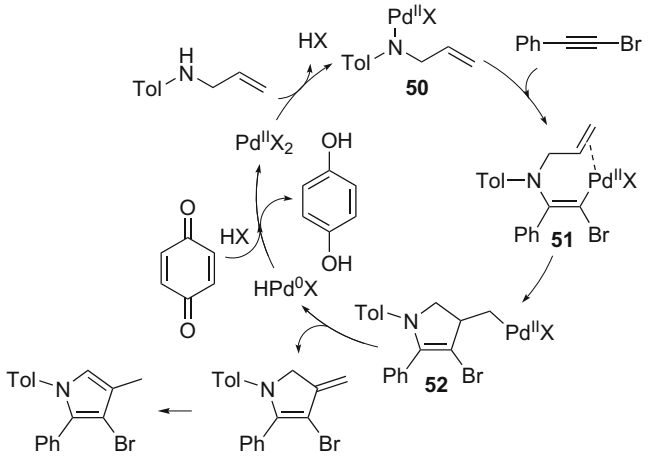
Pyrroles represent an interesting class of nitrogen-containing heterocycles that exhibit diverse therapeutic and biological activities [216–218]. Among them, 3-halo-substituted pyrroles are quite appealing as they provide a facile method for the deravatization at the 3-position of pyrroles. However, the examples for their efficient synthesis are still very rare. [219, 220]. In 2015, Jiang's group documented a novel palladium-catalyzed oxidative cyclization of bromoalkynes with *N*-alkylamines via cascade formation of C–N and C–C bond [221]. A wide spectrum of 3-bromopyrroles were obtained in moderate to excellent yields. Furthermore, the resultant 3-bromopyrroles could be easily functionalized via elegant cross-coupling reactions (Scheme 3.54).

General Procedure for Pd-Catalyzed of Synthesis of 3-Halo-Substituted Pyrroles: *N*-Allylamine (0.2 mmol), bromoalkynes (0.2 mmol), $PdCl_2$ (10 mol%) and BQ (2 equiv) were added to a solution of toluene/DMSO (2 mL, v/v = 5/1). The mixture was stirred under air at 110 °C. Upon completion, water (15 mL) was added and the resulting mixture was extracted with ethyl acetate (15 mL × 2). The combined organic phase was dried over Na_2SO_4, filtered and concentrated. The residue was eventually purified by flash column chromatography on silica gel with petroleum ether/ethyl acetate as eluent to afford the corresponding pyrroles.

On the basis of experimental data and previous reports [222, 223], a tentative reaction mechanism for this transformation was proposed in Scheme 3.55. Initially, the intermediate **50** was generated by the reaction of palladium(II) and *N*-allyamine. Subsequently, an intermolecular *cis*-insertion of bromoalkyne into the N-Pd bond gave the intermediate **51**, which underwent 1,2-migratory insertion, delivering the



Scheme 3.54 Pd-catalyzed of synthesis of 3-halo-substituted pyrroles



Scheme 3.55 Proposed mechanism

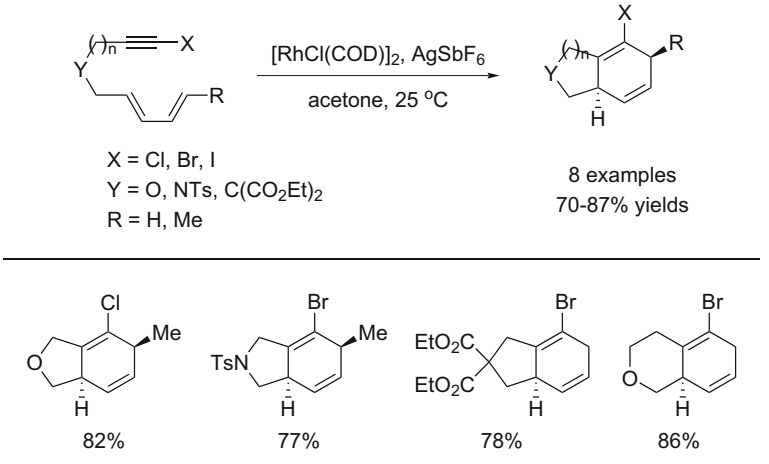
species **52**. A sequence of β-hydride elimination and isomerization afforded the desired 3-bromopyrrole adducts. In the meantime, palladium(0) species was reoxidized to palladium(II) species by BQ (1,4-benzoquinone).

3.2.2.3 [4 + 2] and [2 + 2 + 2] Cycloadditions

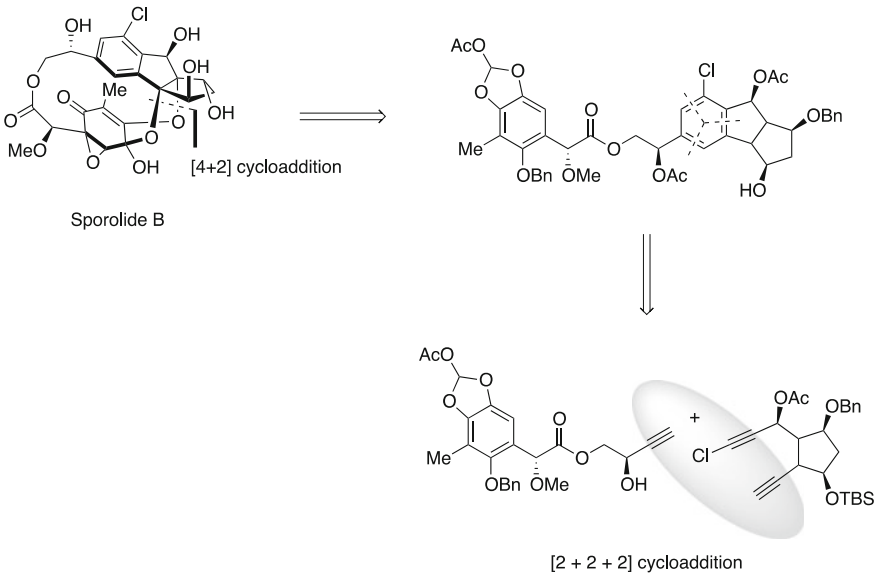
Transition metal-catalyzed [4 + 2] cycloaddition represents one of the most straightforward and efficient methods for the construction of six-membered rings [224, 225]. Due to the diverse transformation of the carbon carbon triple bond motif, haloalkynes have also exhibited their applications in transition metal-catalyzed [4 + 2] cycloaddition reactions [226]. In 2005, Tam's group [227] documented the first example of cationic Rh-catalyzed intramolecular [4 + 2] cycloaddition reaction of diene-tethered alkynyl halides (Scheme 3.56). The halide unit was found to be compatible under this catalytic system. Significantly, the halogen-containing cycloadducts could be converted into various products of synthetic usefulness.

General Procedure for Rh-Catalyzed [4 + 2] Cycloaddition of Diene-Tethered Alkynyl Halides: Inside an inert atmosphere (Ar) Glove Box, $[RhCl(COD)]_2$ (2.5 mol%) and $AgSbF_4$ (5 mol%) was added to an oven-dried vial and dissolved in acetone (3 mL). The reaction mixture was allowed to stir for 30 min and then added to another oven-dried vial containing the diene-tethered alkynyl halide (0.2 mmol) dissolved in acetone (6 mL). The reaction mixture was stirred at room temperature for 30 min. The crude reaction mixture was purified by column chromatography (EtOAc:hexanes = 1:9) to provide the desired product.

Additionally, another alternative method for the synthesis of six-membered rings is the [2 + 2 + 2] cycloaddition reaction [228]. In 2009, Nicolaou et al. [229] firstly reported the total synthesis of sporolides B, an unusual natural product isolated from the marine actinomycete *Salinospora tropica*. Crucially, they forged the chlorobenzenoid indane structural motif through a regio- and stereoselective Ru-catalyzed intermolecular [2 + 2 + 2] cycloaddition reaction between two acetylenic motifs, one of which bearing the chlorine residue (Scheme 3.57). This excellent work showed the prominent potential application of haloalkyne derivatives in the total synthesis of natural product.



Scheme 3.56 Rh-catalyzed [4 + 2] cycloaddition of diene-tethered alkynyl halides



Scheme 3.57 [2 + 2 + 2] Cycloaddition of haloalkyne in natural product synthesis

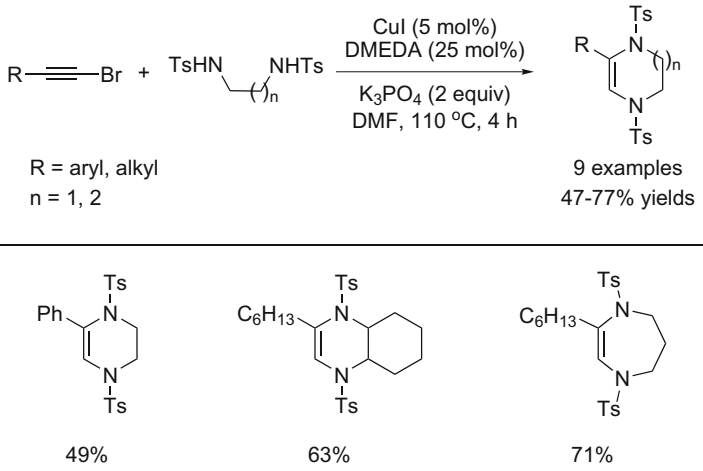
3.3 Transformations Involved Both Carbon-Halo Bond and Carbon-Carbon Triple Bond Motif

The development of efficient and practical methods for the construction of molecular complexity from simple and readily available reagents is an everlasting research topic in synthetic chemistry. The transformations of haloalkynes, involving both the carbon-carbon triple bond unit and the carbon-halo bond motif, have provided a valuable strategy to access various useful compounds.

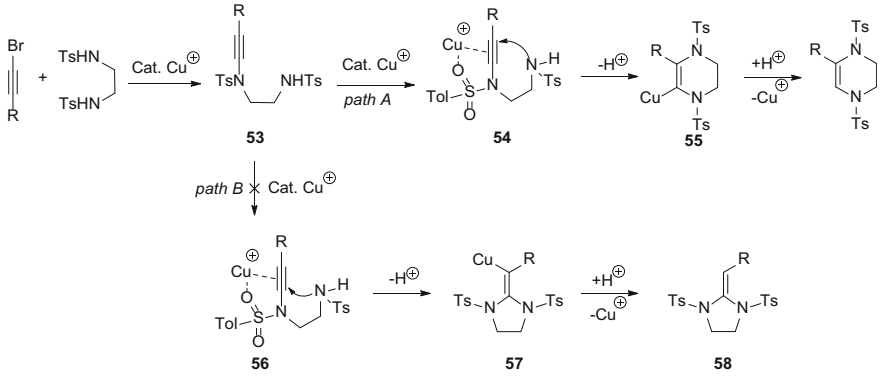
3.3.1 Initially Reacted at the Carbon-Halo Bond

Unsaturated heterocyclic compounds are important synthetic intermediate as well as prevalent structural motifs found in natural and artificial molecules [230]. In 2008, Urabe and co-workers reported 1,2-double amination of haloalkynes via copper catalysis, a concise route for the synthesis of protected tetrahydropyrazines and related compounds. This reaction exhibited reasonable generality for aliphatic and aromatic haloalkynes, delivering the corresponding tetrahydropyrazines in good yields (Scheme 3.58) [231].

General Procedure for Copper-Catalyzed Diamination of Haloalkynes: To a mixture of *N*,*N*′-di(*p*-toluenesulfonyl)ethylenediamine (0.4 mmol), powdered K_3PO_4 (0.8 mmol), and CuI (5 mol%) was added haloalkyne (0.4 mmol) in DMF (4 mL), followed by *N*,*N*′-dimethylethylenediamine (0.1 mmol) under argon.



Scheme 3.58 Copper-catalyzed diamination of haloalkynes



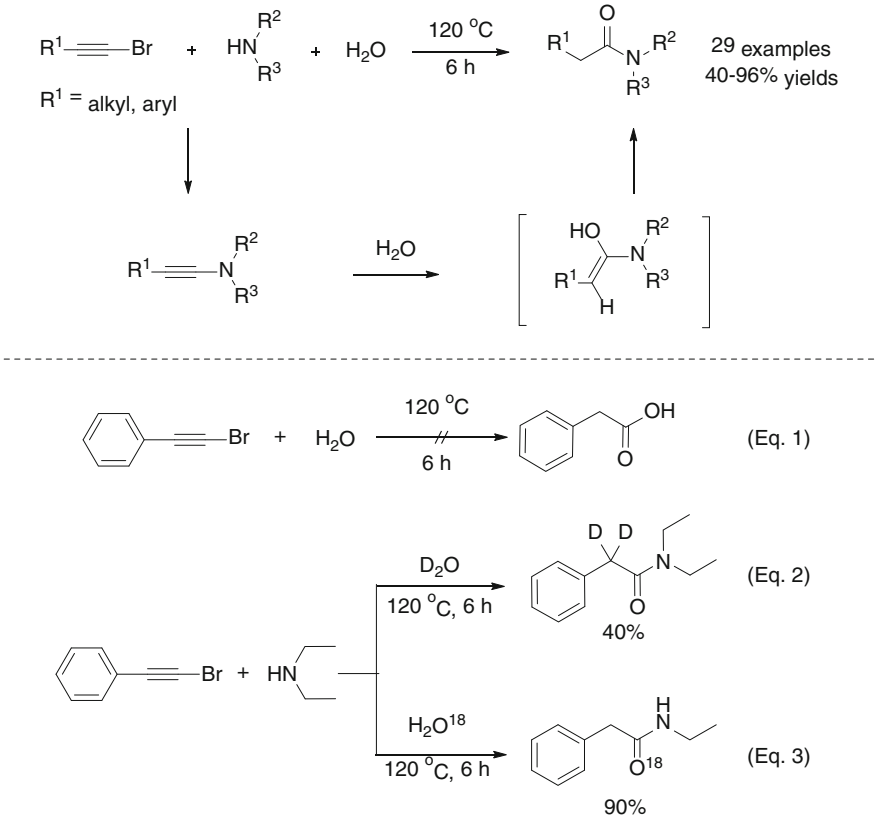
Scheme 3.59 Proposed reaction mechanism

The mixture was stirred in an oil bath maintained at 110 °C for 4 h. After being cooled to room temperature, the reaction mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give a crude oil, which was purified by column chromatography on silica gel.

The author also proposed the reaction mechanism as outlined in Scheme 3.59. Firstly, the alkynylation of sulfonamide gave the ynamide intermediate **53**, then the second amination of the acetylenic bond in **54** proceeded in a 6-*endo-dig* manner under copper catalysis to give cuprate **54**. Finally, protonation of the intermediate **54** provided the observed product and released the copper catalyst (path A). Importantly, the formation of isomeric tetrahydroimidazole **58** via the cyclization of 5-*exo-dig* mode (**56** to **57**, path B) was not observed. Interestingly, when

bromopropiolic acid derivatives were used, the 5-exo-dig type product could be obtained in good yield under transition-metal-free conditions [232]. Upon the diverse transformation abilities of ynamide, Jiang's group realized the synthesis of naphthalene-1,3-diamine derivatives from haloalkynes and amines under copper catalysis [233].

Amides are one of the most prevalent functional groups in natural products, pharmaceuticals, and polymers. In 2011, Jiang's group revealed a mild and efficient multi-component reaction for the construction of amides from bromoalkynes under transition-metal free conditions, which provided a wide range of secondary and tertiary amides in moderate to excellent yields (Scheme 3.60) [234]. The control experiments indicated that the alkynyl bromide should first react with amine to generate ynamine adduct and the isotopic labeling investigation clearly demonstrated that the oxygen atoms of the amide products originated from water [Scheme 3.60, Eqs. (1)–(3)]. Based on these observations, a mechanism involving ynamine intermediate formation and nucleophilic addition process was proposed. Later, they applied this method to construct thioamides [235].



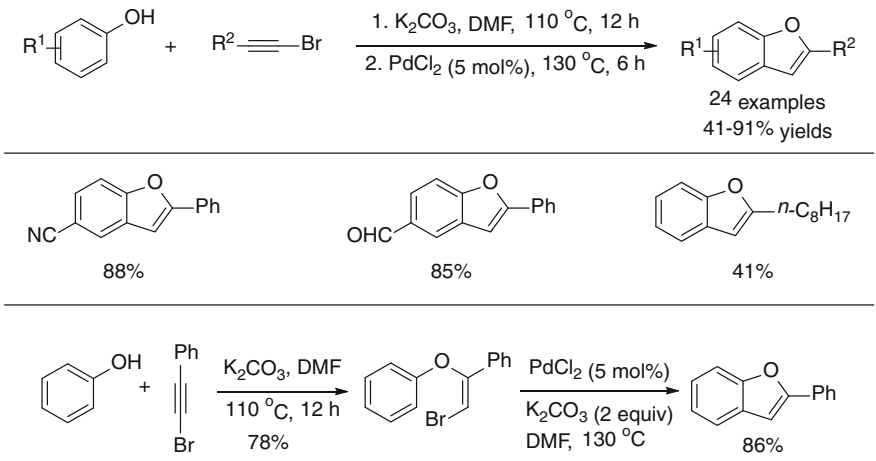
Scheme 3.60 Multi-component reaction for amides

General Procedure for the Synthesis of Amides: The mixture of 1-bromoalkyne (1 mmol) and amine (1.5 mmol) in water (2 mL) was stirred at 120 °C for 6 h in a Schlenk tube (25 mL). Upon completion of the reaction, water (8 mL) was added to the mixture. The resulting aqueous solution was extracted with diethyl ether (15 mL × 3). The combined organic phase was dried with anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography to give the corresponding amides.

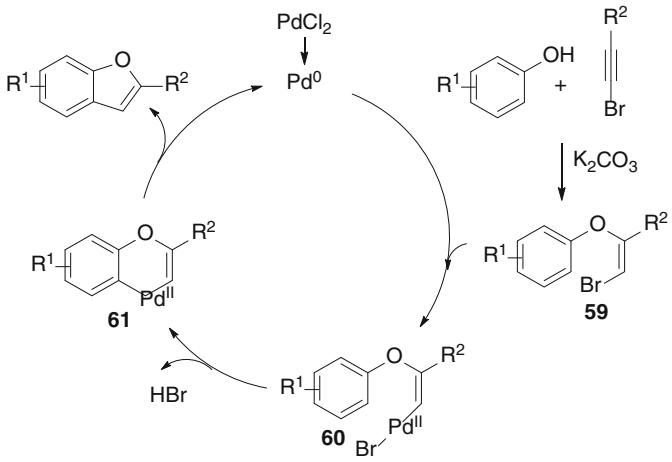
3.3.2 *Initially Reacted at the Carbon-Carbon Triple Bond*

Benzo[*b*]furans, are versatile synthetic blocks and significant structural motifs of natural products and potential drugs [236–238]. Due to their potential applications, the development of practical and efficient synthetic methods is highly demanded. In 2011, Wang and co-workers reported a sequential, one-pot reaction of phenols with bromoalkynes for the synthesis of benzo[*b*]furans [239]. This reaction tolerated diverse functional groups, and delivered the corresponding benzo[*b*]furan products in good yields. Importantly, the reaction intermediate could be isolated, and gave the desired product in high yield under the standard reaction conditions (Scheme 3.61).

General Procedure for the Synthesis of Benzo[b]furans: Under air atmosphere, a sealable tube equipped with a magnetic stirrer bar was charged with phenol (1.1 mmol), bromoalkyne (1 mmol), K_2CO_3 (2 mmol) and DMF (2 mL). The rubber septum was then replaced with a Teflon-coated screw cap, and the reaction vessel was placed in an oil bath at 110 °C for 12 h. Then $PdCl_2$ (5 mol%) was added and the reaction was performed at 130 °C for 6 h. After the reaction was completed,



Scheme 3.61 The synthesis of benzo[*b*]furans



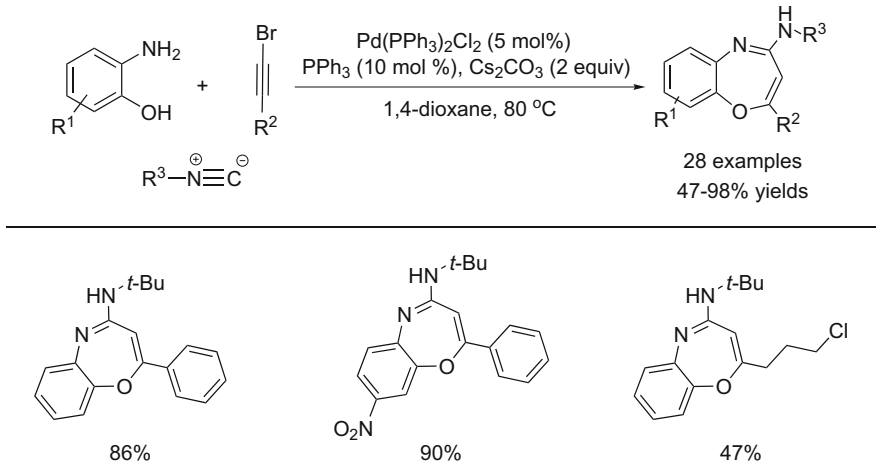
Scheme 3.62 Proposed mechanism

it was cooled to room temperature and diluted with ethyl acetate. The resulting solution was directly filtered through a pad of silica gel using a sintered glass funnel, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel to give the benzo[*b*]furan product.

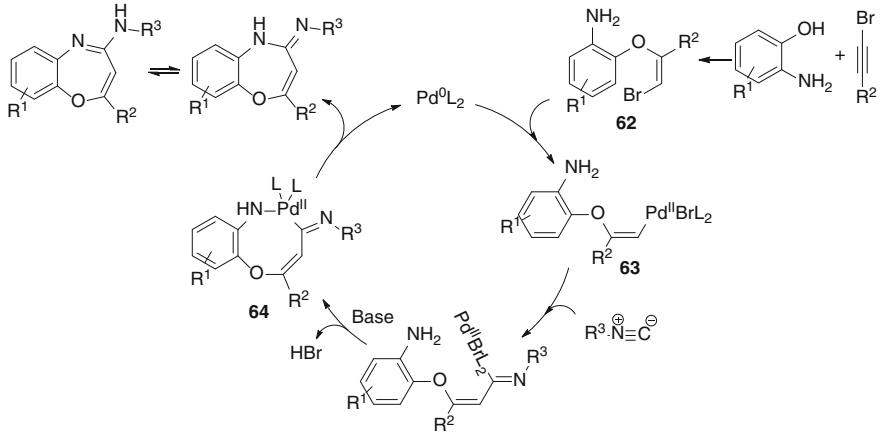
Based on these observations, the author proposed the possible reaction mechanism. Firstly, the intermolecular nucleophilic addition of phenol to bromoalkyne in the presence of base formed the (Z)-2-bromovinyl phenyl ether **59**. Then the intermediate **59** reacted with Pd^0 to give the Pd^{II} complex **60** via oxidative addition. Subsequently, an intramolecular electrophilic aromatic palladation of **60** generated the intermediate **61**, which was followed by a reductive elimination to provide the product and regenerate the Pd^0 catalyst (Scheme 3.62).

Except for furan derivatives [240], benzoxazepine derivatives, a very important kind of seven-membered ring, are the core building blocks with remarkable biological activities and pharmaceutical interests [241–243]. Unfortunately, multi-step synthesis is necessary for their preparation, which usually prevents them from constructing benzoxazepine analogues that are diverse in structure and electronic property. In 2012, Jiang and co-workers documented a robust route for the construction of substituted 4-amine-benzo[*b*] [1,4] oxazepines in a facile and convenient manner. This Pd-catalyzed cascade transformation of *o*-aminophenols, bromoalkynes and isocyanides underwent a selective C–O and C–N bond formation procedure and delivered the desired products in good to excellent yields (Scheme 3.63) [244].

General Procedure for Pd-Catalyzed Cascade Reaction for 4-Amine-benzo[b] [1,4] oxazepines: The mixture of 2-aminophenol (0.5 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol%) and PPh_3 (10 mol%) in 1,4-dioxane (1 mL) was placed in a Schlenk tube. Then, Cs_2CO_3 (1 mmol) and bromoalkyne (0.5 mmol) were added successively. The mixture was stirred for five min at room temperature. Subsequently, isocyanide



Scheme 3.63 Pd-catalyzed cascade reaction for 4-amine-benzo[*b*][1,4]oxazepines



Scheme 3.64 Proposed mechanism

(0.6 mmol) was added in one portion. The resulting mixture was stirred at 80 °C for 2 h. Upon completion, the reaction mixture was extracted with ethyl acetate (10 mL × 3), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexanes/EtOAc = 10/1) to give the corresponding product.

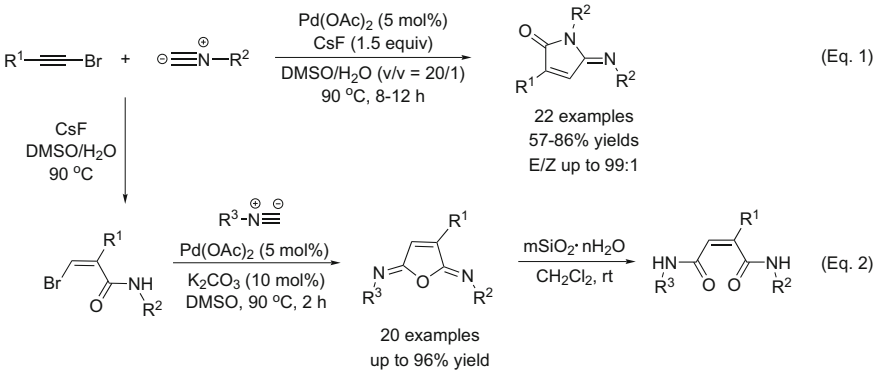
According to the mechanistic investigations, a possible catalytic cycle for this cascade reaction was illustrated in Scheme 3.64. Initially, nucleophilic addition of *o*-aminophenols to bromoalkynes delivered **62**, which underwent oxidative addition to Pd^0 species to form vinylpalladium(II) species **63**. Subsequently, migratory

insertion of isocyanide and release of HBr under basic conditions gave the eight-membered azapalladacyclic intermediate **64**. Finally, reductive elimination and isomerization provided the benzoxazepine product, as well as regenerating the active Pd^0 catalyst.

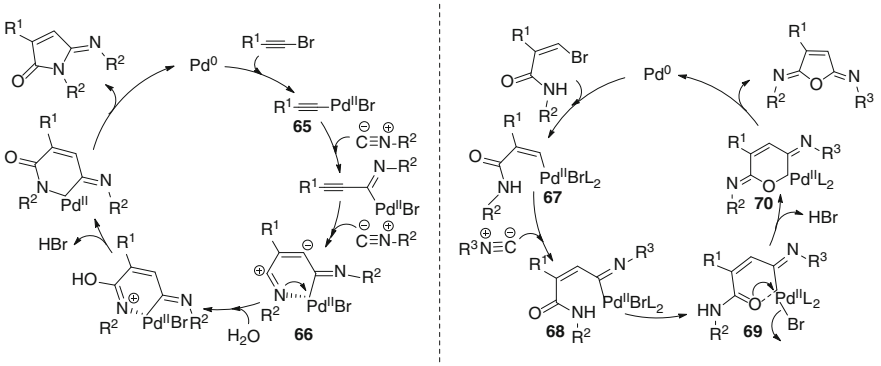
Besides oxygen, nitrogen [245] nucleophiles triggered cascade annulation reactions of haloalkynes, carbon nucleophiles could also be used to construct cyclic compounds. In 2014, Jiang's group reported the first Pd-catalyzed annulation reaction of bromoalkynes and isocyanides, which provided a direct and practical route to a wide range of 5-iminopyrrolones with excellent reigoselectivity [Scheme 3.65, Eq. (1)] [172]. This reaction could proceed smoothly under mild reaction conditions, and broad functional groups could be tolerated. Intriguingly, they observed the formation of 2,5-diimino-furan as side product, an isomer with the same molecular weight as 5-iminopyrrolone [Scheme 3.65, Eq. (2)]. Systematically condition screening revealed that base and the reaction time were crucial for the reaction pathway. CsF and longer reaction time (8–12 h) preferred the formation of 5-iminopyrrolones, while K_2CO_3 and shorter reaction time (2 h) were favored to deliver the 2,5-diimino-furan products [246]. Furthermore, the resultant furans could readily undergo hydrolysis to give maleamide skeletons, which might have further applications in synthetic and medicinal chemistry.

General Procedure for Pd-Catalyzed Synthesis of 5-Iminopyrrolones: A mixture of $Pd(OAc)_2$ (5 mol%), H_2O (0.1 mL), DMSO (2 mL), isocyanide (3 mmol), haloalkyne (1 mmol) and CsF (1.5 mmol) was added successively in Schlenk tube. The mixture was stirred at 90 °C for 12 h. Upon completion of the reaction, the mixture was cooled to room temperature, and the solution was filtered through a small amount of silica gel. The solvent was removed under reduced pressure, and the residue was purified by silica gel preparative TLC to give the desired 5-iminopyrrolones product.

General Procedure for Pd-Catalyzed Synthesis of 2,5-Diimino-furans: A mixture of CsF (1.2 mmol), H_2O (0.1 mL), DMSO (2 mL), isocyanide (2 mmol), and bromoalkyne (1 mmol) was successively added in a Schlenk tube (25 mL). After



Scheme 3.65 Pd-catalyzed synthesis of 5-iminopyrrolones and 2,5-diimino-furans



Scheme 3.66 Proposed mechanisms

stirring for 12 h at 90 °C, the starting materials were completely consumed as monitored by TLC and GC-MS analysis. Then, the reaction mixture was cooled to room temperature, filtered through a small amount of silica gel and concentrated. The residue was purified by silica gel preparative TLC to give the bromoacrylamide product.

A mixture of bromoacrylamide (0.2 mmol), isoacyanide (0.24 mmol), $Pd(OAc)_2$ (5 mol%), K_2CO_3 (0.4 mmol) and DMSO (2 mL) were added successively in a tube (10 mL). The resulting mixture was stirred at 90 °C for 2 h. Upon completion, the reaction mixture was extracted with ethyl acetate (10 mL × 3), and the organic layers were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by aluminum oxide basic preparative TLC to give the 2,5-diimino-furan product.

Based on these findings, the authors proposed the mechanisms of the two reactions. For the synthesis of 5-iminopyrrolones (Scheme 3.66, left pathway), they believed the procedure was first initiated by the oxidative addition of Pd^0 species to bromoalkyne affording alkynylpalladium complex **65**, followed by migratory insertion and nucleophilic addition of isocyanide delivered intermediate **66**, in which the nitrogen atom would simultaneously coordinate with the Pd center. Then hydrolysis led to the release of HBr and 5-iminopyrrolone product was finally constructed by the reductive elimination with the regeneration of Pd^0 catalyst. As to the 2,5-diimino-furan derivatives (Scheme 3.66, right pathway), they proposed that the initial oxidative addition of Pd^0 to bromoacrylamide provided the vinylpalladium species **67**, subsequent migratory insertion of isocyanide generated **68**. Then, the coordination of the amide oxygen atom with the Pd^{II} center gave intermediate **69**. Finally, under the treatment of base, HBr would be eliminated to form complex **70**, which underwent the reductive elimination to deliver the annulation adduct and regenerated the active Pd^0 catalyst. It was supposed that the different coordinated type with Pd catalyst might be account for the one-pot reaction affording the *N*-containing cyclization products, whereas the two-step procedure giving the *O*-containing heterocycles.

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Chapter 4
Conclusions and Outlook

Abstract The above three chapters have highlighted the robust reactivity and described the general preparation methods of haloalkyne reagents. Significantly, efforts have been made in elucidating the mechanisms of these chemical processes, which provide the researchers valuable insight of the haloalkyne compounds. In this chapter, we will summarize the book and also point out some challenges that need to be faced in the area of haloalkyne chemistry. We hope this book will not only ignite the interest of readers to the field of haloalkyne chemistry, but also inspire the researchers to answer the unsolved challenges and exploit new research areas of haloalkyne chemistry.

Keywords Insight and understanding · Unsolved challenges · Haloalkyne chemistry

This book has highlighted the robust reactivity and also summarized the general preparation methods of haloalkyne reagents. The diverse reactivity of haloalkynes allow these efficient transformations to deliver a variety of novel acyclic and cyclic structures representing prevalent and significant frameworks as well as being useful motifs for further transformations. Thus, haloalkynes have emerged as powerful and versatile building blocks in a diverse spectrum of synthetic transformations including natural product total synthesis. In addition, the efforts have been made in elucidating the mechanisms of these chemical processes, which provide the researchers valuable insight and understanding the reactivity of haloalkyne compounds.

Despite the great progress that has achieved, many challenges still need to be faced in the area of haloalkyne chemistry, such as, the catalytic asymmetric reactions and the carbon nucleophilic addition reactions of haloalkynes, as well as the development of more general, practical, efficient and green methods for the transformation of haloalkynes to access valuable molecules. We hope this book will not only ignite the interest of readers to the field of haloalkyne chemistry, but also inspire the researchers to answer the unsolved challenges and exploit new research areas of haloalkyne chemistry.

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