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Palladium-Catalyzed Cyclization of Propargylic Compounds

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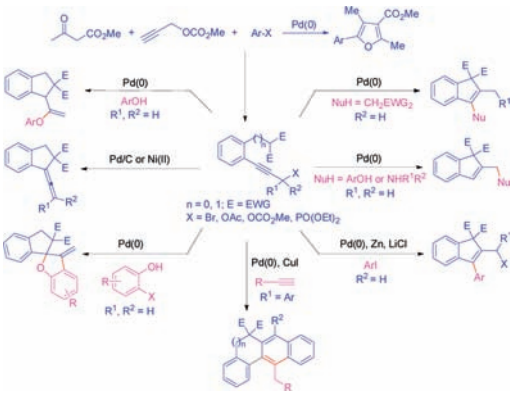
CONSPECTUS

Many groups have explored the scope of the palladium-based cyclization of propargylic compounds since Tsuji's first report in 1985. Through the proper positioning of an internal nucleophilic center and the judicious selection of an appropriate external nucleophile, the synthetic chemist can effectively assert control over the course of the reaction and its products. However, initial investigations were very limited: only heterocyclic compounds were originally synthesized. We have found the palladium-catalyzed cyclization of propargylic compounds to be a very efficient method for producing both carbocyclic and heterocyclic compounds. In this Account, we discuss the cyclization reactions of functionalized propargylic compounds with a variety of nucleophiles that we have developed over the past few years. We also review similar reactions reported by other groups.



We focus here on the cyclization of functionalized propargylic compounds containing a carbon nucleophilic center that is in close proximity to the propargylic moiety. We conducted a detailed investigation of their cyclizations with carbon nucleophiles, with nitrogen nucleophiles, with oxygen nucleophiles, and without nucleophiles. We have developed several efficient and useful methods for the synthesis of indenes, naphthalenes, polycycles, and spirocyclic compounds. All of these reactions proceed satisfactorily under very mild conditions; high regio- and stereoselectivity have been observed as well. In the course of our studies, we provided the first demonstration of a novel tandem C−H activation/bis-cyclization reaction of propargylic compounds with terminal alkynes.

In addition, we used external nucleophiles to investigate the cyclization of functionalized propargylic compounds that bear an unsaturated carbon−carbon or carbon−heteroatom bond. We presented the first report of the use of external nucleophiles to initiate a novel cyclization of functionalized propargylic compounds containing an electrophile. This revelation provided a fresh perspective through the discovery of a new type of domino cyclization of propargylic compounds.

Metal-catalyzed cyclization of propargylic compounds can provide indenes, cyclopentanones, cyclic carbonates, benzofurans, and a range of other cyclic molecules. A thorough understanding of the mechanisms involved in this class of reaction affords exceptional synthetic control, as shown here by our development of efficient procedures and reagents for palladium-catalyzed propargylic cyclizations.

1. Introduction

Propargylic compounds comprise one of the most important and most useful substrates; these can undergo several types of transformations promoted by palladium catalysts that obtain different kinds of allene, alkene, alkyne, and enyne derivatives (Scheme 1).[1] However, studies on the analogous reactions of propargylic compounds have been conducted much later and less extensively than those on allylic compounds, because the compounds are less reactive and the products of the reactions are unstable. Recently, the transition-metal-catalyzed reaction of propargylic compounds with various nucleophiles has emerged as a powerful tool for constructing carbon−carbon and carbon−heteroatom bonds.[2] In this work, we summarize the recent developments

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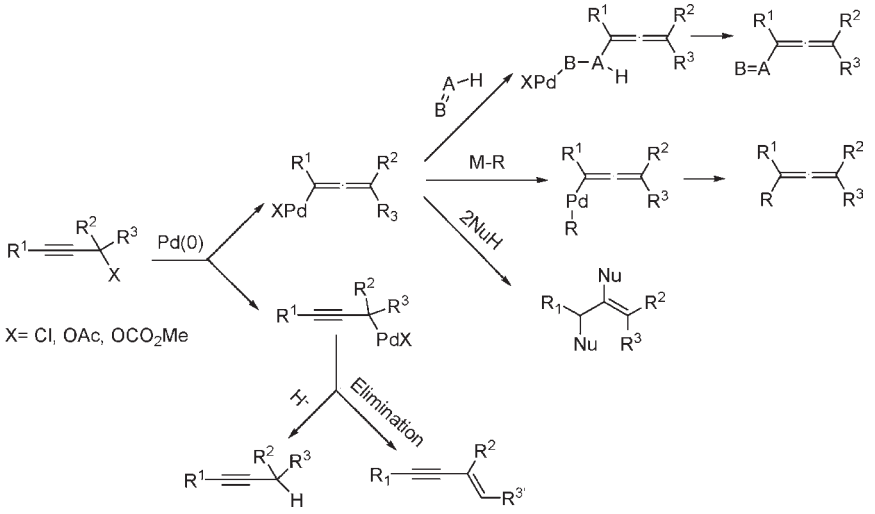
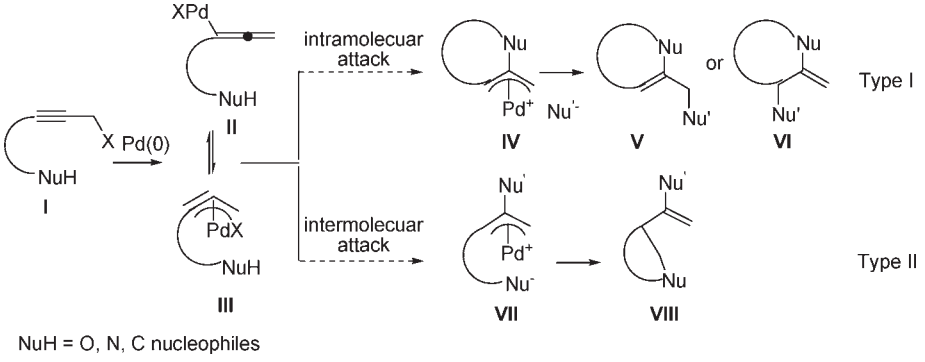
SCHEME 1. Mechanisms for the Formation of Allene, Alkene, Alkyne, and Enyne Derivatives



SCHEME 2. Mechanisms for the Cyclization of Functionalized Propargylic Compounds with Nucleophile



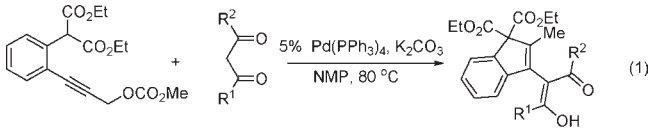
on the palladium-catalyzed cyclization of propargylic compounds and nucleophiles. We also highlight our remarkable advancements on the carboannulation of propargylic compounds.

2. Cyclization of Propargylic Compounds Bearing a Nucleophilic Moiety

The transition-metal-catalyzed cyclization of propargylic compounds that bear an internal nucleophilic center with an appropriate external nucleophile has become a powerful tool for constructing various cyclic compounds, such as indenes,[3−5] cyclopentanones,[6] cyclic carbonates,[7,8] benzofurans,[5,9] and indoles.[10,11] According to their mechanisms, we classified these cyclization reactions into Type I and II (Scheme 2). In Type I, the intramolecular cyclization occurs before the intermolecular nucleophilic attack, furnishing the cyclized π-allylpalladium complex **IV** that, in turn, further cyclizes to yield product **V** or **VI**. In contrast to Type I, if the intermolecular nucleophilic attack occurs first, π-allylpalladium complex **VII** is formed, which undergoes the secondary nucleophilic attack to obtain product **VIII**.

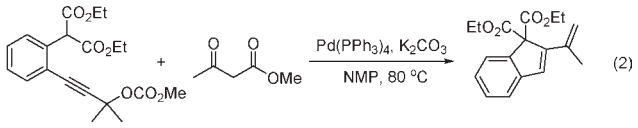
2.1. Cyclization with Soft Nucleophiles. As part of our ongoing research on palladium-catalyzed carboannulation,[12] we designed the propargyl carbonate **1**; it possesses a carbon nucleophilic center in close proximity to the propargylic moiety. We then investigated its respective cyclization with carbon, oxygen, and nitrogen nucleophiles (eqs 1 and 3).[3,4] At the beginning of the research, we studied the reaction of propargyl carbonate **1** with β-keto esters and β-diketones (eq 1).[3] After several trials, we found that the cyclization reactions proceeded satisfactorily in the presence of $Pd(PPh_3)_4$, obtaining regioselectively a series of 2,3-disubstituted indenes **3** in moderate to good yields. In this reaction, the existence of one keto-group is very crucial. No reactions have been observed when using dimethyl malonate and malononitrile as nucleophiles. Like Type I

(Scheme 2), this reaction has undergone a cyclization; however, the intermolecular nucleophilic attack occurs regioselectively at the more hindered side of the π-allyl systems.[13]



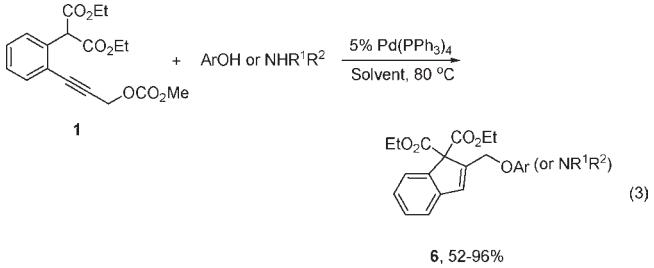
1 2 3, 34-83% (1)

Additionally, this cyclization reaction may also be extended to secondary propargylic carbonates, although the yields are relatively lower. Unfortunately, for tertiary propargylic carbonate **4**, only the 2-substituted indene **5** is isolated at the 73% yield due to steric hindrance (eq 2).



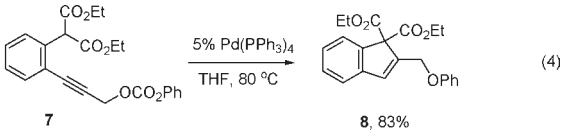
4 5, 73% (2)

Next, we studied the cyclization of carbonate **1** with various phenols and amines (eq 3).[4] Surprisingly, 2-substituted indenes **6** have been isolated as single products in good to excellent yields. The results are dramatically different from those of carbon nucleophiles mentioned above. We believe that, similar to Type I (Scheme 2), this reaction has also undergone a cyclization procedure; the difference is that the intermolecular phenoxide attacked regioselectively at the less-hindered site of the π-allyl systems. This cyclization reaction proceeded smoothly for phenols under neutral conditions, whereas the base is considered essential when using amines as nucleophiles. Remarkably, the treatment of bisphenols, such as hydroquinone and bisphenol A, with 2.0 equiv of carbonate **1**, furnished the corresponding expected symmetrically disubstituted products with good yields.



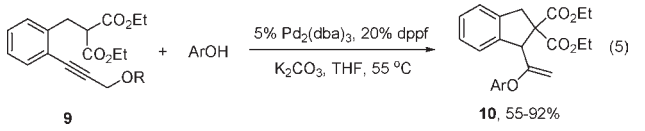
1 6, 52-96% (3)

Additionally, the propargylic carbonate **7** containing a latent nucleophilic phenolic moiety as a part of the carbonate leaving group also presented the 2-phenoxy substituted indene **8** with an 83% yield in the presence of palladium catalyst (eq 4). In this atom-economic cyclization reaction, the substrate **7** initially released the phenoxide. This, in turn, acted as a nucleophile that attacked the cyclized π-allyl complex to generate the product.

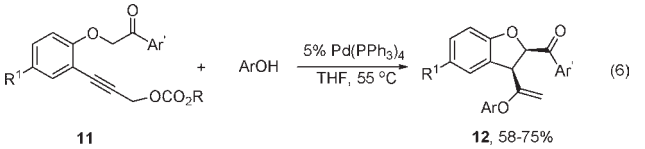


7 8, 83% (4)

To extend the scope of the reaction, the cyclization of functionalized propargylic compounds **9** and **11** with phenols was also examined (eqs 5 and 6, respectively).[5] In the presence of $Pd_2(dba)_3$ and dppf, propargylic compounds **9** (carbonate, acetate, benzoate, and phosphate) reacted with various phenols to obtain the substituted indenes **10** in good to excellent yields. Treatment of propargyl carbonates **11** with naphthols or 4-acetphenol resulted in benzo[*b*]furan **12** with moderate to good yields characterized by high regioselectivity and stereoselectivity. In these cyclization reactions, the intermolecular O-alkylation occurred before the intramolecular cyclization (Type II, Scheme 2).



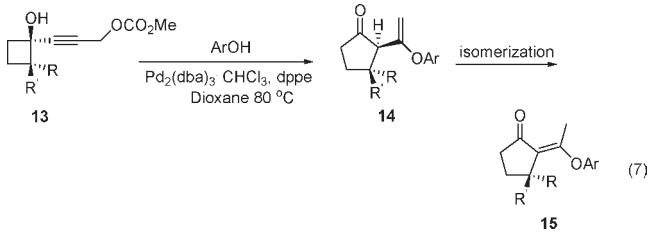
9 10, 55-92% (5)

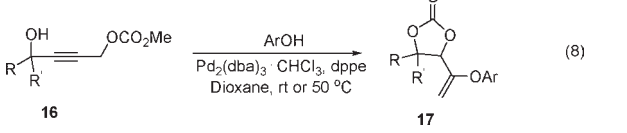


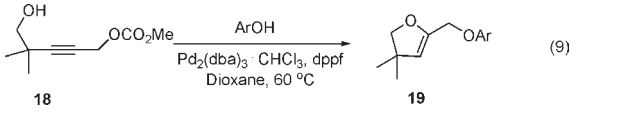
11 12, 58-75% (6)

The cyclizations of functionalized propargylic compounds which contain a heteronucleophilic center with an appropriate external nucleophile have been reported by other groups. Ihara and Yoshida et al. have conducted a detailed study on the cyclization of various propargylic carbonates that contain hydroxyl groups with phenols, and then synthesized different kinds of cyclic compounds (eqs 7−9).[6−9] These authors found that cyclobutanols **13** react with various substituted phenols in the presence of $Pd_2(dba)_3 \cdot CHCl_3$ and dppe at 80 °C in dioxane to afford phenoxy-substituted cyclopentanones **14**, which are sometimes isomerized to *endo*-**15** based on the structure of substrates **13** or the acidity of the phenols (eq 7).[6] Ihara and Yoshida et al. reasoned that this reaction has undergone a cascade intermolecular nucleophilic attack-ring expansion procedure. Furthermore, utilizing imides, such as phthalimide, in place of phenols also yielded similar results.[6b] Interestingly, aryloxy-substituted cyclic carbonates **17**

formed from the treatment of cyclic and acyclic substrates **16** with phenols in sealed tubes under the same palladium catalyst system at a low temperature (eq 8). Ihara and Yoshida et al. have also argued that the reaction involved a cascade intermolecular phenoxide attack, CO_2-elimination-fixation, and an intramolecular cyclization process.[7] They further found that the cascade reaction of chiral propargylic substrates with phenols occurred with complete transferring chirality. The results indicate that this cyclization reaction proceeded like Type II of Scheme 2, in which the π-allylpalladium complex **VII** has been formed by a π-propargylpalladium intermediate **III** with phenol through a palladacyclobutene complex.[7c] Additionally, the palladium-catalyzed reaction of propargylic oxiranes and phenols in the presence of carbon dioxide also yielded cyclic carbonates.[8] Propargylic compound **18** containing one more carbon chain than the carbonates **16** that reacted with phenols have led to substituted 2,3-dihydrofuran **19** as single product (eq 9).[9] This reveals that such a reaction has undergone an intramolecular cyclization and, consequently, an intermolecular nucleophilic attack procedure (Type I, Scheme 2), in which the phenoxide attacked regioselectively at the less hindered site.

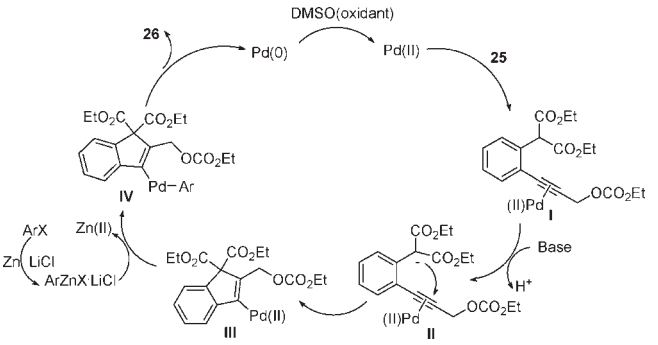




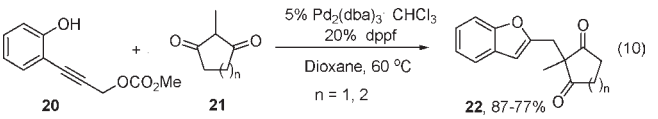


Meanwhile, Ihara and Yoshida et al. have likewise investigated the cyclization reaction of propargylic compound **20**, which includes a benzene ring with various phenols but failed. Luckily, using 2-methyldiketones **21** as nucleophiles, the cyclization reaction proceeded smoothly, leading to the corresponding 2-substituted benzofurans **22** in good yields

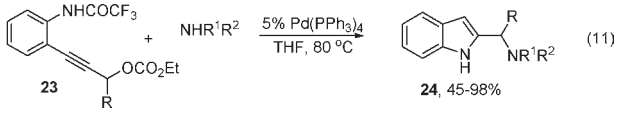
SCHEME 3. Proposed Mechanism for the Novel Cyclization/Coupling Process



(eq 10).[9] It is worthy to note that our result is very different from it when β-diketones were used as substrate (eq 1).[3]

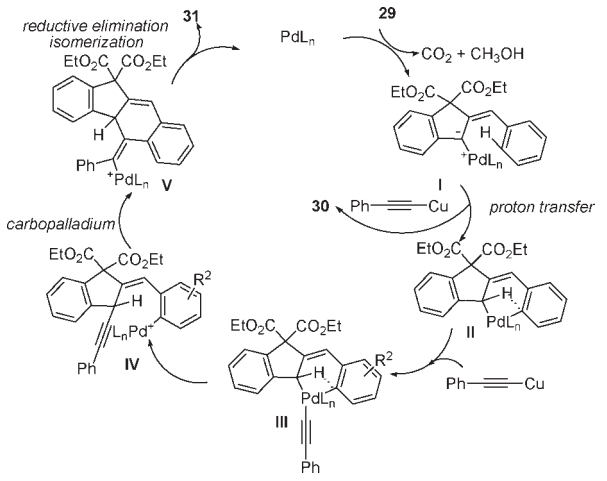


Furthermore, Cacchi et al. have reported that the carbonates **23** containing a nitrogen nucleophilic center in close proximity to the propargylic moiety reacted with various aliphatic amines to give a series of 2-(aminomethyl)indoles **24** in good to excellent yields (eq 11).[10] Notably, the acidity of the nitrogen–hydrogen bond played a crucial role and only a complex reaction mixture formed after the trifluoroacetyl group changed into an acetyl group. With regard to other nucleophiles (such as phenols and β-dicarbonyl compounds), these have not been thoroughly discussed in their paper. Meanwhile, Cacchi et al. also discovered that a series of free NH-indole 2-acetamides can be prepared easily using $Pd_2(dba)_3$ and dppf as catalytic systems under a high carbon monoxide atmosphere (40 atm).[11]

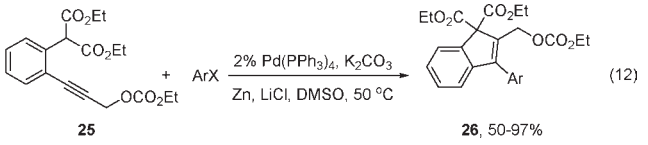


2.2. Cyclization with Hard Carbon Nucleophiles. Aside from soft nucleophiles, our group also investigated Pd-catalyzed cyclization of propargylic carbonate **25** with hard carbon nucleophiles. Interestingly, treatment of carbonate **25** with organozinc reagents generated in situ from the aryl iodides and zinc power[14] resulted in 2,3-disubstituted indenes **26** in good to excellent yields with remaining carbonate moiety (eq 12).[15] Remarkably, it is highly crucial to use dimethyl sulfoxide (DMSO) as solvent. This could be attributed to the fact that the Pd(0) was initially oxidized to Pd(II) by DMSO, after which the

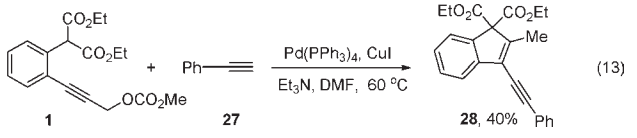
SCHEME 4. Proposed Mechanism for the Novel C−H Activation/Biscyclization Process



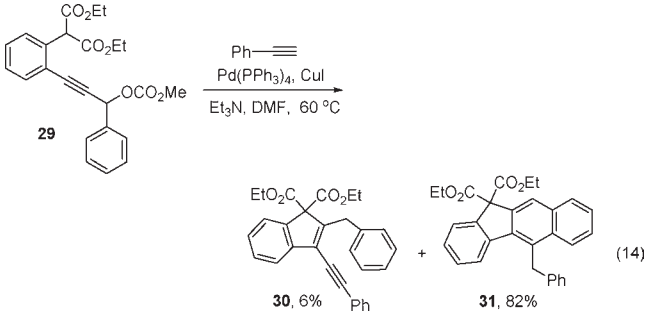
carbonate **25** underwent a Pd(II)-catalyzed cyclization/coupling process (Scheme 3)[16]



Furthermore, the cyclization of propargyl carbonate **1** with copper acetylide generated in situ was also investigated. Carbonate **1** reacted with phenylacetylene **27** in the presence of $Pd(PPh_3)_4$ (5 mol %) and co-catalyst CuI (10 mol %) at 60 °C in dimethylformamide (DMF) using Et_3N as a base, giving the desired 2,3-disubstituted indene **28** with 40% yield (eq 13). However, it was difficult to improve the yield even if different catalytic systems were screened.



Surprisingly, when the secondary propargylic carbonate **29**, which had a phenyl group in the propargyl position, was employed to the catalytic system mentioned above, an unexpected polycyclic compound **31** was isolated in 82% yield, together with the 2,3-disubstituted indene **30** in 6% yield (eq 14).[17] X-ray diffraction studies on the product and the deuterium-labeling tracer experiment both revealed that this reaction involved a tandem carboannulation, C−H activation (an intramolecular proton transfer played a very crucial role in this process), coupling, and C−C bond formation process (Scheme 4).

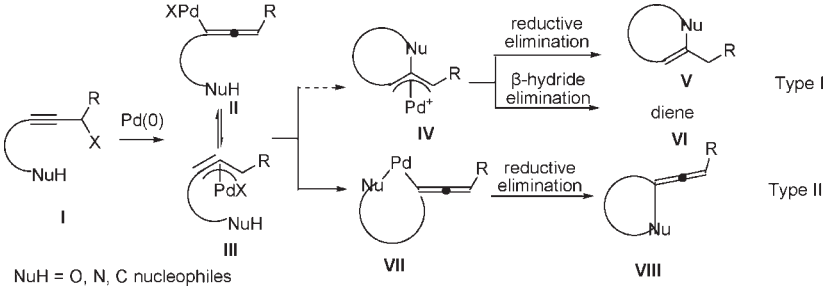


To our knowledge, this is the first report to have found that propargylic compounds can initiate a tandem biscyclization process involving a C−H functionalization of benzene, heteroaromatic rings, or simple C−C double bonds in the presence of a palladium catalyst. We also successfully applied this novel catalytic system to the synthesis of benz[*a*]anthracene derivatives.[18]

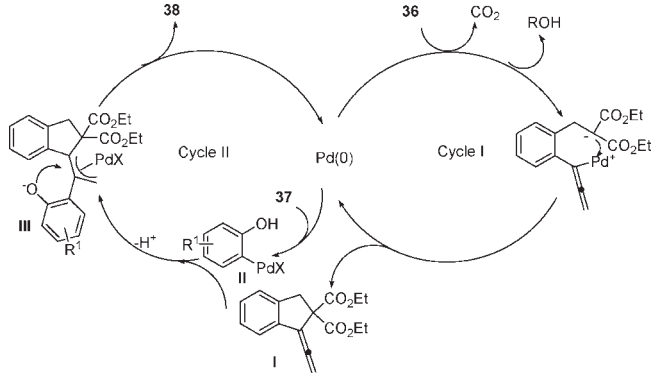
2.3. Cyclization without Nucleophiles. Propargylic compounds containing a carbo- or heteronucleophilic center, which is in close proximity to the propargylic moiety, can also undergo intramolecular cyclization to generate various cyclic compounds. Based on the length of the chain between the nucleophilic center and the propargylic moiety, the functionalized propargylic compound undergoes two types of cyclization procedures (Scheme 5). In Type I, the nucleophile attacks selectively the central carbon of the allenyl/π-propargylpalladium complex (**II** or **III**) to form (π-allyl)-palladium complex **IV**, which then undergoes reductive elimination or β-hydride elimination to give the cyclized product **V** or diene **VI**. In Type II, the nucleophile attacks the palladium metal to yield the palladacycle **VII**. Reductive elimination of **VII** results in product **VIII**, which contains the ethenylidene group.

In connection with the research above, we examined the cyclization of propargylic compounds **32** (eq 15).[19] In the presence of 0.5 mol % Pd/C, the cyclization of propargylic compound **32** (such as carbonate, acetate, benzoate, and phosphate) proceeded smoothly to produce the indene derivatives **33**, including an allene functional group, with good to excellent yields that are characterized by high regioselectivity under ambient conditions of temperature and air. For tertiary propargyl compounds, $Pd_2(dba)_3$ presented better yields than Pd/C. Furthermore, we found that using inexpensive nickel salts, such as $Ni_3(PO_4)_2 \cdot 8H_2O$, instead of Pd/C obtained the same products; however, we

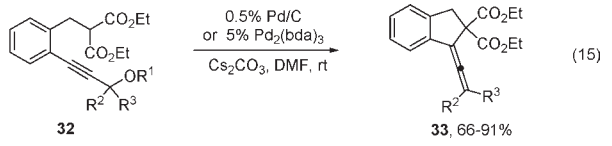
SCHEME 5. Mechanisms for the Cyclization of Functionalized Propargylic Compound



SCHEME 6. Mechanism for the Intermolecular Tandem Cyclization Reaction

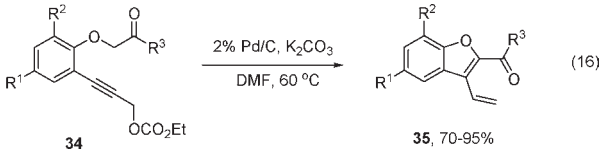


believe that there are large variations in the cyclization procedure.[20]



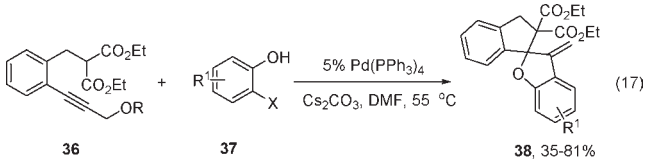
(15)

Similarly, propargylic carbonates **34** have been found to lead to a series of 2-aroyl (acyl or carboxyl)-3-vinyl benzo[*b*]furans **35** through a cyclization/isomerization procedure under the Pd/C system (eq 16).[21]



(16)

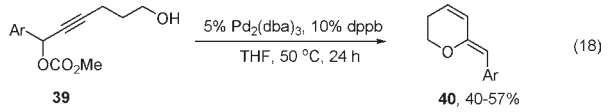
Allenes are highly useful moieties found in organic synthesis that have attracted significant attention in recent years.[22] Recently, some groups have reported that allenes reacted with 2-halophenols and 2-haloanilines in the presence of palladium catalysts, leading to cyclized products.[23] Encouraged by the easy formation of allenes,[19] we set out to investigate the cyclization of propargylic compounds **36** with 2-halophenols based on the notion that the allenes generated in situ could react further with 2-halophenols to give biscyclized products in the presence of palladium catalyst. The reaction of propargylic compounds **36** with a variety of 2-halophenols **37** resulted in the polycyclic products **38** with good yields and with high regioselectivities (eq 17).[24] These tetracyclic products **38** contained a unique aromatic *spiro* ring system, in which benzo[*b*]furan and indene rings share one carbon atom. We believe that the Pd(0) catalyst is simultaneously involved in two catalytic cycles in this tandem reaction (Scheme 6). In cycle I, propargylic compounds **36** reacted with Pd(0) to produce the allene **I**. In cycle II, oxidative addition of Pd(0) to 2-halophenols **37** resulted in the arylpalladium complexes **II** that, in turn, reacted with allene **I**, forming a π-allylpalladium complex **III**. The intermediate **III** underwent a regioselective intramolecular nucleophilic attack at the more hindered site to obtain spirocyclic compounds **38**.



(17)

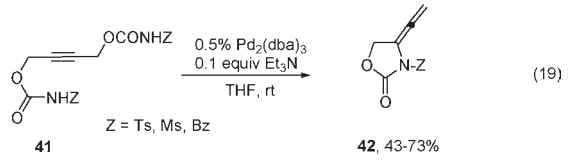
In addition, various heterocyclic compounds have also been synthesized by the direct cyclization of functionalized propargylic compounds. Sinou et al. have found that the treatment of 1-aryl-6-hydroxy-2-hexynyl carbonates **39** with the palladium complex in tetrahydrofuran (THF) at 50 °C yielded a series of unsaturated dihydropyrans **40** in moderate yields with high *Z*-stereoselectivity (eq 18).[25] They then proposed that this reaction has undergone a cyclization process, similar to Type I in Scheme 5. Surprisingly, no

cyclization occurred when the aromatic ring was replaced by an alkyl group.



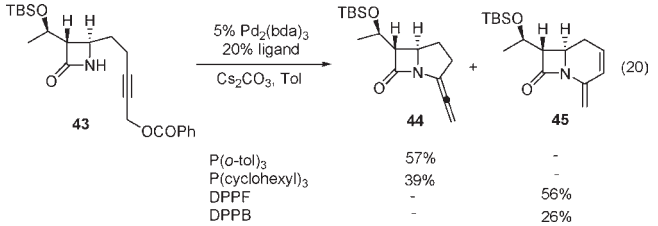
39 **40**, 40-57% (18)

Tamaru et al. have reported that the palladium-catalyzed aminocyclization of 2-butyn-1,4-diol biscarbamates **41** led to 4-ethenylidene-2-oxazolidinones **42** in good yields (eq 19).[26]



41 **42**, 43-73% (19)

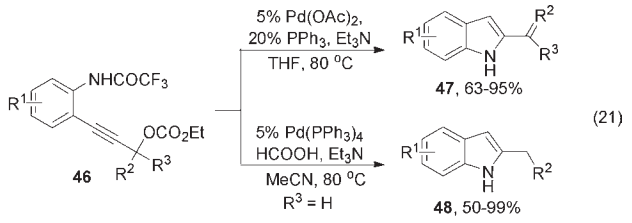
Subsequently, Mori and Kozawa have conducted a detailed investigation of the palladium-catalyzed cyclization of functionalized propargylic compounds containing a nitrogen nucleophilic center (lactam nitrogen or tosylamide nitrogen).[27] Interestingly, these authors have found that the type of ligand played an important role in determining the ring size of the cyclized products. For the cyclization of starting material **43**, the use of monodentate ligands, such as P(*o*-tol)$_3$ and P(Cy)$_3$, yielded carbapenam **44** as a single product; however, the use of bidentate ligands, such as dppf and dppb, only led to carbacepham **45** (eq 20).[27c] The regioselectivity is complete in this cyclization reaction. Mori and Kozawa reasoned that the propargyl compound **43** has undergone the Type II cyclization process in the presence of monodentate ligands. On the other hand, when the bidentate ligand was used, the reaction proceeded through the π-allylpalladium intermediate **IV** followed by β-hydride elimination to produce the carbacepham **45** (Type I, Scheme 5).



43 **44** **45** (20)

	44	**45**
P(*o*-tol)$_3$	57%	-
P(cyclohexyl)$_3$	39%	-
DPPF	-	56%
DPPB	-	26%

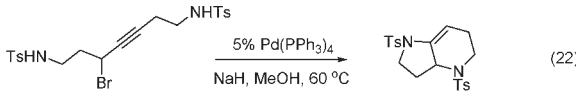
Recently, Cacchi and co-workers have investigated the cyclization of ethyl 3-(*o*-trifluoroacetamido-phenyl)-1-propargyl carbonates **46** under different palladium catalyst systems (eq 21).[28] In the presence of a combination of Pd(OAc)$_2$ and PPh$_3$, the reaction worked satisfactorily to present the 2-vinylic indoles **47** with good to excellent yields characterized by complete trans stereoselectivity. However, various 2-alkylindoles **48** have been obtained when a reductive reagent HCO$_2$H is added.



46 **47**, 63-95% **48**, 50-99% (21)

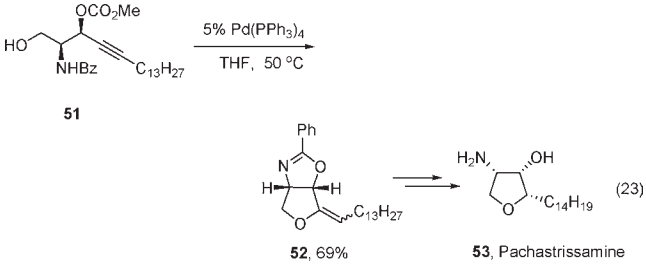
3. Cyclization of Propargylic Compounds Bearing Two Nucleophilic Moieties

Propargylic compounds that have two nucleophilic sites can also undergo a domino-effect cyclization to present fused or linked bicyclic products. Fujii, Ohno, and co-workers have reported that the domino cyclization of propargyl bromide **49**, which has one tosylamide group on each terminal carbon, worked satisfactorily under a palladium catalyst system, leading to fused bicyclic heterocycle **50** with an 89% yield (eq 22).[29] Using a mesylamide or nosylamide group, instead of a tosylamide group, also resulted in corresponding bicyclic products. However, in relation to changing both or one of the tosylamide groups to a hydroxy group, only the first cyclization reaction occurred and yielded furan derivatives.



49 **50**, 89% (22)

Furthermore, Ohno et al. have found that the treatment of propargyl carbonate **51** with Pd(PPh$_3$)$_4$ (5 mol %) also resulted in the desired bicyclic tetrahydrofuran **52** in good yield (eq 23).[30] The cyclic product **52** easily transformed to the pachastrissamine **53**, which displays remarkable cytotoxic activity against several tumor cell lines.

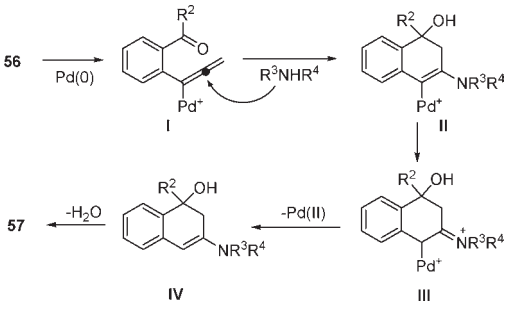


51 **52**, 69% **53**, Pachastrissamine (23)

4. Cyclization of Other Functionalized Propargylic Compounds

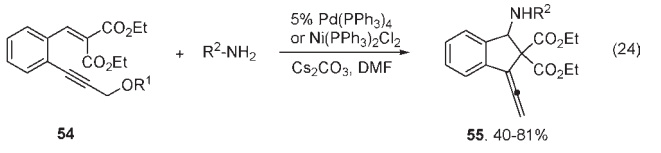
To further extend the scope of the cyclization reaction, the propargylic compounds containing other functionalized

SCHEME 7. Mechanisms for the Novel Cyclization of Propargylic Compound **56**

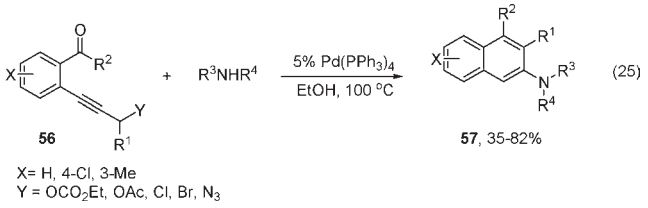


groups, such as unsaturated carbon−carbon or carbon−heteroatom bonds, were designed and investigated by our group.

Recently, the tandem Michael addition−cyclization reaction has been shown as an efficient method in generating various highly substituted cyclic compounds; this has attracted increased attention because it is efficient and atom-economic.[31] Thus, we prepared the propargylic compounds **54** containing a Michael acceptor, which is in close proximity to the propargylic moiety. We expect that it would undergo a tandem Michael addition−cyclization reaction with suitable nucleophiles to obtain cyclic compounds in the presence of palladium catalyst. Satisfactorily, we found that the treatment of propargylic compounds **54** with various primary aromatic amines in the presence of 5 mol % $Pd(PPh_3)_4$ led to the indene derivatives **55** bearing an allene group in good yields (eq 24).[32] Remarkably, using $Ni(PPh_3)_2Cl_2$ instead of $Pd(PPh_3)_4$ also resulted in the same desired product, but in slightly lower yields. Although the same products were obtained, we thought that they underwent different reaction routes.[19,20] Unfortunately, no desired product was obtained using phenols or diethyl malonate as nucleophile.



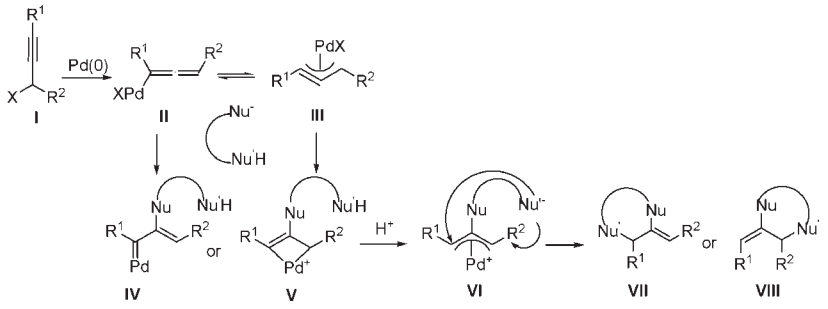
Interestingly, the reaction of propargylic compounds **56** bearing a carbonyl group with various aliphatic amines in the presence of 5 mol % $Pd(PPh_3)_4$ also worked satisfactorily in producing a series of substituted naphthylamine derivatives **57** (eq 25).[33] This is the first report on the Pd(0)-catalyzed transformation of propargyl carbonates containing an electrophile with external nucleophiles. This novel result indicates that the reaction should not proceed through iminium formation. We reason that this aminobenzannulation reaction proceeded through a 6-endocyclization process (Scheme 7). Herein, the alkenylpalladium complex **II** was formed instead of a π-allylpalladium complex.



5. Cyclization of Propargylic Compounds with Bisnucleophiles

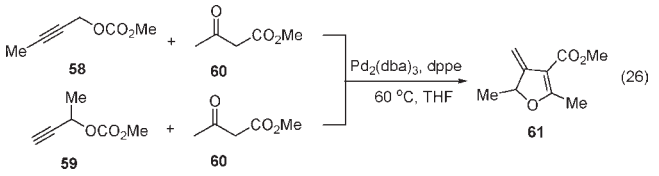
The cyclization of propargylic compounds with bisnucleophiles has also been shown as an efficient route to cyclic compounds. To date, two mechanisms have been proposed for these cyclization processes (Scheme 8). In the first step, propargylic compounds react with Pd catalysts to obtain an allenylpalladium complex **II** via the S_N2'-type reaction, which is in equilibrium with the π-propargylpalladium intermediate **III**.[34] Then, one nucleophilic center of the bisnucleophile attacks selectively the central carbon of the allenyl/π-propargylpalladium complex to form the π-allylpalladium complex **VI** through the palladium carbene complex **IV** or palladacyclobutene **V**, followed by a proton transfer. The other nucleophilic moiety of the bisnucleophile attacks the π-allyl complex **VI** at different positions, resulting in cyclized products **VII** or **VIII**. However, there is no clear

SCHEME 8. Mechanisms for the Cyclization of Propargylic Compounds with Bisnucleophile



evidence concerning either of these two mechanisms, especially with regards the nature of the complex obtained from the propargylic carbonate and the starting palladium (0) complex.

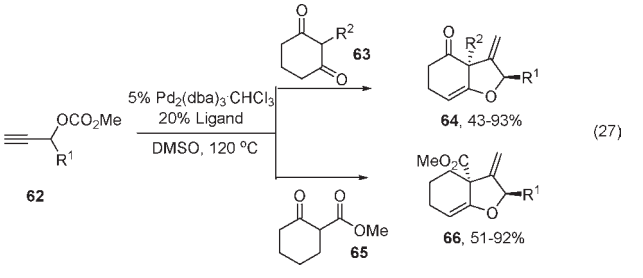
In 1985, Tsuji et al. presented the first report on the cyclization reaction of propargylic carbonates with β-keto esters and β-diketones that bear two active hydrogens with a 1:1 ratio to provide various substituted furan derivatives (eq 26).[35] In this reaction, C-alkylation and O-alkylation have both been observed. The intramolecular O-alkylation occurred regioselectively at the more substituted side of the π-allyl systems that furnish the *exo*-methylene dihydrofuran **61**, which has been isomerized to the corresponding furan under acidic conditions. This method has also been applied successfully to the synthesis of phenylthiomethyl-substituted furan, which is the precursor of the natural products such as neoliacine.[36] Furthermore, Tsuji and et al. have found that the 2-alkynyloxiranes can also undergo the same process to provide various tetra-substituted furan derivatives.[37]



(26)

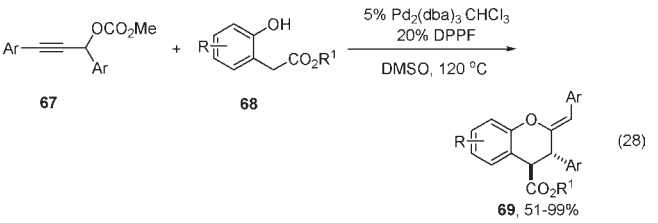
Since the initial report of Tsuji et al., various reactions in this family have been developed. The bifunctional carbon[38] and oxgen nucleophiles[39] were also investigated. A variety of carbocyclic and heterocyclic compounds have been prepared via the double C- or O-alkylation process, but with low regioselectivity. Tsuji et al. have already discussed it in detail.[1] Herein, we presented only the most recent examples.

Recently, Yoshida et al. have successfully applied the C-alkylation and O-alkylation of propargylic carbonates **62** with substituted β-dicarbonyl compounds **63** and **65** to the synthesis of tetrahydrobenzofuranones **64** and **66**. These are in good yield with high diastereoselectivities (eq 27).[40] These authors attributed the high diastereoselectivity to the result of steric factors.



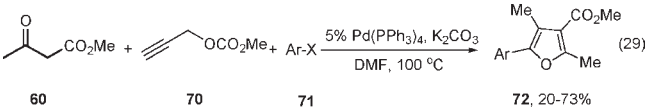
(27)

Furthermore, the treatment of propargylic carbonates **67** with 2-(2-hydroxyphenyl)acetates **68** provides substituted chromans **69** with high stereoselectivity (eq 28).[41] In this reaction, the O-alkylation process occurred before the C-alkylation process. Remarkably, optically active chromans have been obtained in 96% ee at 60 °C using (*S*)-SEGPHOS as ligand.



(28)

Multicomponent reaction (MCR) is an efficient ideal synthesis method, because it has the potential to generate molecular diversity in a single synthetic step from simple, readily available starting materials.[42] Likewise, MCR has emerged as a powerful tool for the synthesis of substituted furan derivatives.[43] Based on the pioneering work of Tsuji et al.,[35] we developed an efficient one-pot three-component reaction in the preparation of polysubstituted furans. Thus, we began our research by examining the cyclization reaction of β-keto ester **60**, primary propargylic carbonate **70**, and aryl halides **71** in the presence of palladium catalysts. We found that these coupling-cyclization reactions satisfactorily presented various tetrasubstituted furans **72** with excellent regioselectivities in the presence of $Pd(PPh_3)_4$ (5 mol %) using K_2CO_3 (2.0 equiv) as base (eq 29).[44] These results indicated that the intramolecular O-alkylation favored the more substituted side of the π-allyl system, which is consistent with the results presented by Tsuji et al. Unfortunately, a mixture of regioisomers formed when secondary carbonates were used.



(29)

6. Conclusion

Since the first report made by Tsuji in 1985, considerable efforts have been dedicated to the development of palladium-catalyzed cyclization of propargylic

carbonates. In this paper, we used mechanistic insight to guide the recent development of the palladium-catalyzed cyclization of propargylic compound and nucloephiles. In this field, we have established a series of useful and efficient methods to produce various carbocycles, polycycles, and spirocyclic compounds through the palladium-catalyzed carboannulation of functionalized propargylic compounds with nucleophiles. We first demonstrated some novel types of cyclization of propargylic compounds, such as tandem C−H activation/bicyclization and intermolecular tandem bicyclization reactions.

We would like to thank all the colleagues in this field and coworkers in our lab, whose names are cited in the references. Financial support from the Natural Science Foundation of China (NSF-20732002, NSF-20872052, and NSF-20090443) is gratefully acknowledged. Li−Na Guo and Xin-Hua Duan thank the Fundamental Research Funds for the Central Universities for financial support.

BIOGRAPHICAL INFORMATION

Li-Na Guo was born in 1981 in Shanxi, China. She received her B. S. from Taiyuan Normal College in 2003 and her Ph.D. from Lanzhou University in 2008, working with Professor Yong-Min Liang on the transition-metal catalyzed cyclization reaction. After her postdoctoral fellowship at the Alexander von Humboldt Foundation with Professor Paul Knochel at the Ludwig-Maximilians-Universität in München, Germany, she returned to China in 2010 and became an associate professor at the Xi'an Jiaotong University. Her research interests are asymmetric catalysis and new synthetic methodologies based on organometallic chemistry.

Xin-Hua Duan was born in 1977 in Ningxia, China. He obtained his Ph.D. from Lanzhou University in 2007 under the supervision of Professor Yong-Min Liang. He then worked as a postdoctoral research fellow with Professor Jieping Zhu at the Institut de Chimie des Substances Naturelles, CNRS, France (2007−2008), and with Professor Herbert Mayr at the Ludwig-Maximilians-Universität in München, Germany (2008−2010). He joined the Faculty of Science at Xi'an Jiaotong University in 2010. He is currently working on new synthetic methodologies, chemical kinetics, and equilibrium studies on reactive nucleophiles.

Yong-Min Liang was born in 1966 in Shanxi, China. He received his B.S. from Shanxi Normal University in 1989, and M.S. and Ph.D. from Lanzhou University in 1992 and 1998, respectively. He became an associate professor of Lanzhou University (2000−2003). After his postdoctoral research experience at National Tsing-Hua University with Professor Show-An Chen (2001−2002), he was promoted to full professor in 2003 at Lanzhou University. His current research interests are the development of new cascade reactions and new synthetic methodology based on transition-metal catalyzed transformations of organic compounds.

FOOTNOTES

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