Synthesis X.-H. Hu et al. Short Review

Recent Advances in Catalytic Stereocontrolled Cycloaddition with Terminal Propargylic Compounds

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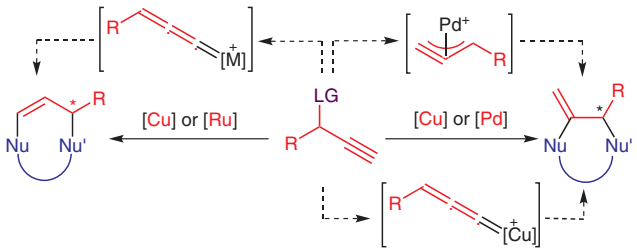

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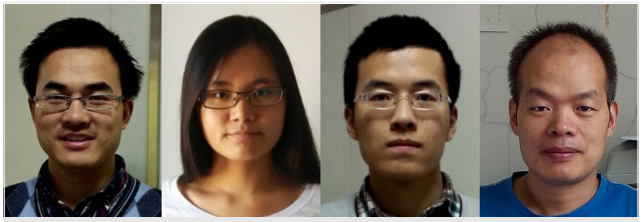
Abstract Terminal propargylic compounds containing an alkyne unit and an alcohol or ester group in the propargylic position have a fairly acidic acetylenic hydrogen atom; this makes them versatile substrates for further chemical transformation. Some transition metals such as ruthenium or copper exhibit specific affinity for terminal propargylic compounds, generating dielectrophilic ruthenium– or copper–allenylidene complexes that show high potential for stereoselective cycloaddition with various bis-nucleophiles. In this review, we highlight this emerging field of catalytic stereoselective cycloaddition with terminal propargylic compounds. Examples of ruthenium-, copper-, palladium-, and gold-catalyzed cycloaddition are given in the article, along with mechanistic considerations.

Key words cycloaddition, asymmetric catalysis, propargylic compound, ruthenium, copper, palladium, gold

1 Introduction

Stereoselective construction of complex cyclic frameworks from simple starting materials is one of the most challenging and longstanding tasks in organic synthesis. In this context, catalytic cycloaddition is one of the most efficient ways toward this end. Propargylic compounds contain two functional groups, a π-nucleophilic alkyne unit and an electrophilic propargylic position normally bearing an alcohol or ester group as the leaving group, and this makes them versatile substrates for a variety of chemical transformations.[1] In particular, the presence of a fairly acidic acetylenic hydrogen atom in terminal propargylic compounds provides specific reactivity in the formation of some new



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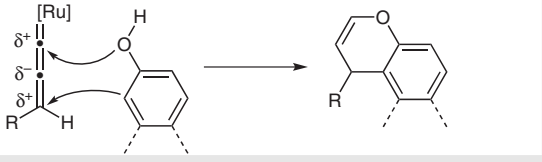
transition-metal intermediates, such as ruthenium– and copper–allenylidene complexes that show high potential as C2 or C3 synthons for cycloaddition with various bis-nucleophiles, especially in an enantioselective version.[2] Moreover, terminal propargylic compounds are easily accessible by the addition of acetylides to aldehydes. Although these compounds have been extensively employed in the construction of various cyclic structures, their application in stereoselective (including diastereo- and enantioselective) cycloaddition remains a less-explored area. This review aims to highlight the developments in this emerging field of catalytic stereoselective cycloaddition with terminal propargylic compounds, in which at least two carbon atoms of the propargylic moiety are incorporated into the newly formed cyclic ring. The review is classified according to the transition metal used.

2 Ruthenium–Allenylidene Complexes in Enantioselective Cycloaddition

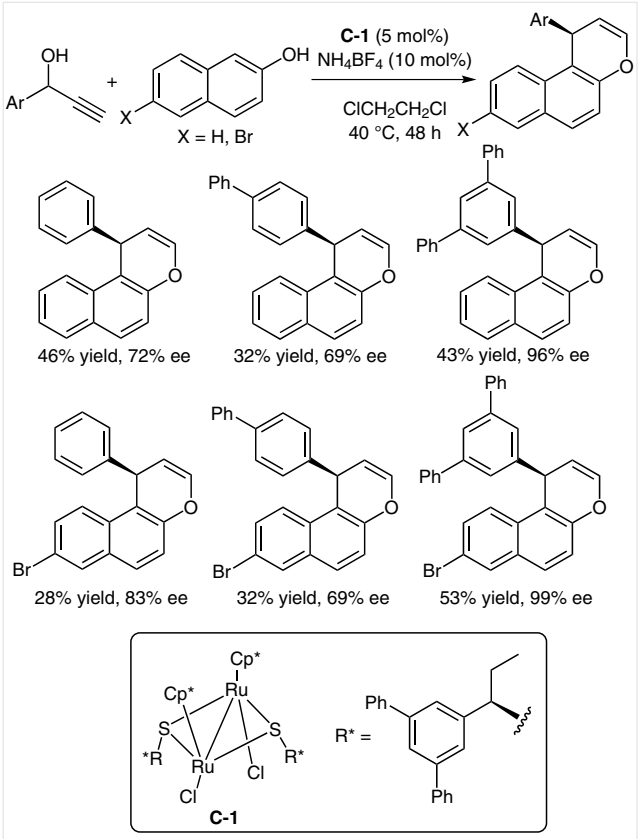
Propargylic alcohols or their ester derivatives can be readily transformed into transition-metal–allenylidene complexes; they have attracted much attention in the past decade as a new type of organometallic intermediate.[3] Some theoretical studies of allenylidene complexes indicate that the Cα and Cγ carbons of the allenylidene complexes are electrophilic centers, while the Cβ carbon is a nucleophilic center.[4] Therefore, the reaction of allenylidene complexes with bis-nucleophiles would lead to cyclized products in which allenylidene complex works as a C3 synthon.

In 2002, Nishibayashi and co-workers disclosed a novel ruthenium-catalyzed [3+3] cycloaddition of propargylic alcohols with 2-naphthols and phenols bearing electron-donating groups to regioselectively afford the corresponding 1*H*-naphtho[2,1-*b*]pyrans and 4*H*-1-benzopyrans in moderate to excellent yields, where ruthenium–allenylidene complexes serve as key intermediates.[5] In this reaction, both of electrophilic Cα and Cγ carbons in the allenylidene complex are subjected to attack by nucleophiles (Scheme 1).



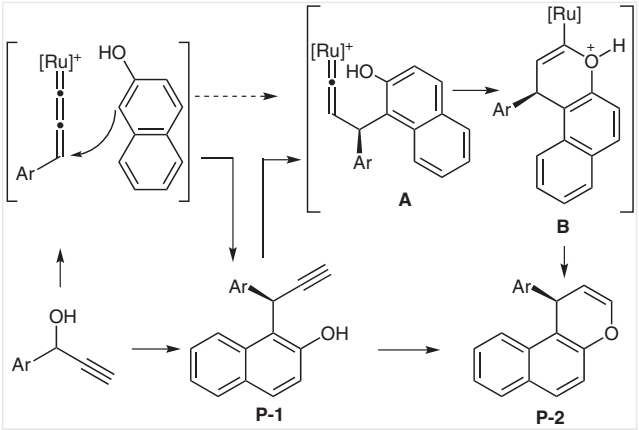
Scheme 1 Ruthenium-catalyzed [3+3] cycloaddition via metal–allenylidene complexes

Following this pioneering work, Nishibayashi and co-workers developed an enantioselective version by employing an optically active thiolate-bridged diruthenium complex **C-1**.[6] Reaction of various propargylic alcohols with 2-naphthols in the presence of 5 mol% of **C-1** and 10 mol% of ammonium tetrafluoroborate in 1,2-dichloroethane at 40 °C for 48 hours gave the corresponding naphthopyran derivatives in moderate yields with high enantioselectivity (Scheme 2). This reaction provides a new and efficient access to a variety of chiral naphthopyran compounds.



Scheme 2 Ruthenium-catalyzed enantioselective [3+3] cycloaddition between propargylic alcohols and 2-naphthols

The reaction is considered to proceed via stepwise propargylation and intramolecular cyclization as shown in Scheme 3, where ruthenium–allenylidene and –vinylidene complexes work as key reactive intermediates, respectively. Initially propargylation of 2-naphthol with propargylic alcohol gives the corresponding (*R*)-propargylated naphthol **P-1** with low to moderate enantioselectivity. Then, the cyclization of (*R*)-**P-1** proceeds enantioselectively to afford (*R*)-**P-2** with high enantioselectivity, in which a kinetic resolution of **P-1** occurs efficiently. The process from **P-1** to **P-2** may involve the ruthenium–vinylidene complex **A** and the corresponding alkenyl complex **B**.

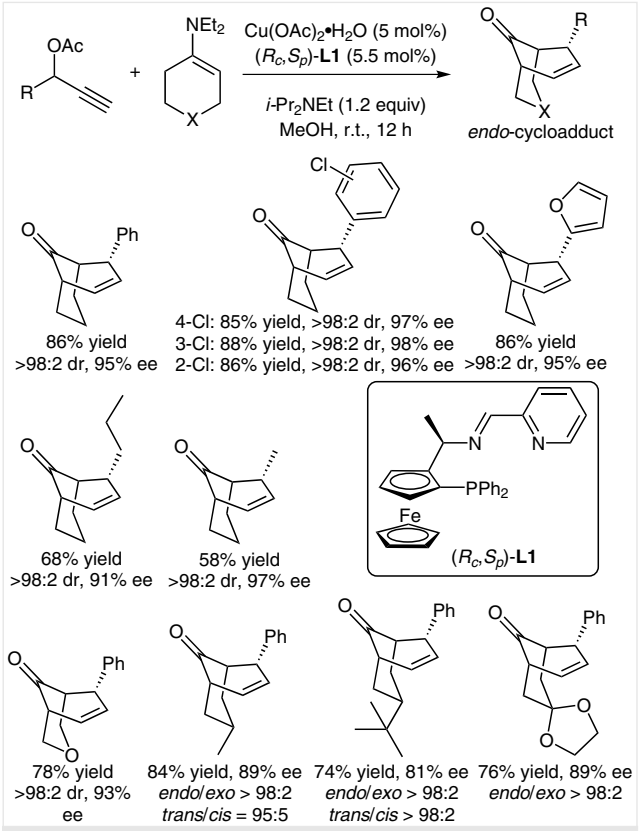


Scheme 3 Proposed reaction route for ruthenium-catalyzed asymmetric [3+3] cycloaddition

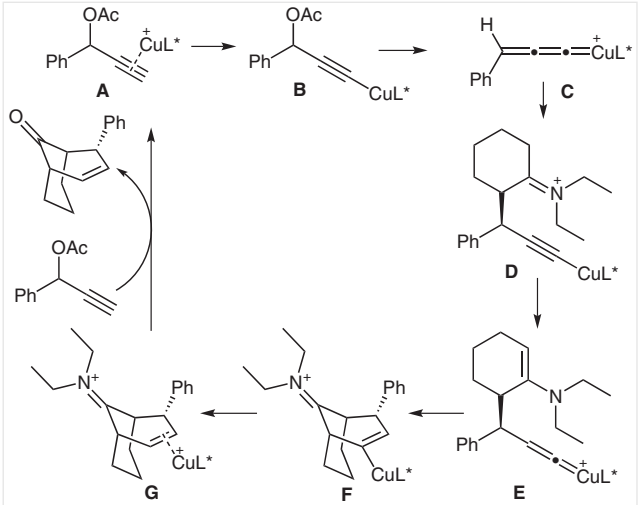
3 Copper–Allenylidene Complexes in Enantioselective Cycloaddition

Copper-catalyzed asymmetric propargylic substitution has recently made much progress.[7] The reaction is considered to proceed via copper–allenylidene complexes as key intermediates because only terminal propargylic esters serve as suitable substrates. Therefore, cycloaddition of propargylic esters as dielectrophilic C3 synthons with bis-nucleophiles in the catalysis of copper complexes would also be possible. In 2012, Hu and co-workers reported the first example of a highly diastereo- and enantioselective copper-catalyzed [3+3] cycloaddition of cyclic enamines with propargylic esters as C3 synthons employing a chiral ferrocenyl P,N,N-ligand.[8] Under mild conditions and for a wide range of substrates, perfect *endo* selectivity (*endo*/*exo* >98:2) and excellent enantioselectivity (up to 98% ee) for *endo*-cycloadducts was achieved (Scheme 4). The mild conditions, broad substrate scope, good yields, and high diastereo- and enantioselectivity makes this process highly useful in the synthesis of optically active bicyclo[n.3.1] frameworks.

A plausible mechanism is proposed in Scheme 5. Initially a copper–π-complex **A** is formed from propargylic acetate; deprotonation of **A** with a base gives the copper acetylide **B**. By the loss of an acetyl group from the copper acetylide **B**, the copper–allenylidene complex **C** might be formed. Nucleophilic attack of Cβ of the enamine to Cγ of the copper–allenylidene complex **C** gives the corresponding copper–acetylide complex **D**, which should be the key step for stereoselection. A hydrogen atom shifts to Cβ of the copper–acetylide complex to give a copper–vinylidene complex **E**. An intramolecular nucleophilic attack of Cβ of the enamine to Cα of the copper–vinylidene complex **E** affords alkenyl complex **F**, which is then converted into the cycloadduct.



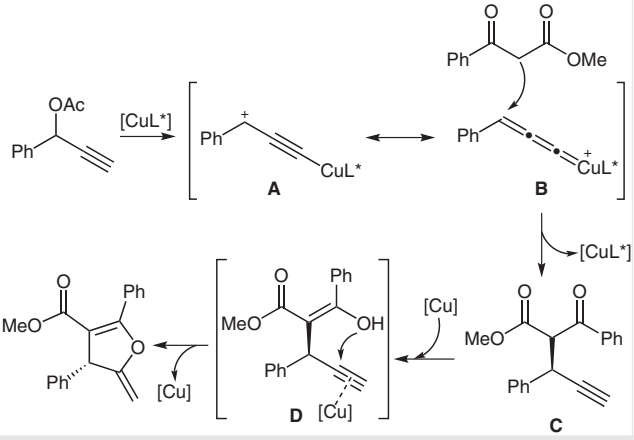
Scheme 4 Copper-catalyzed asymmetric [3+3] cycloaddition between propargylic esters with cyclic emanines



Scheme 5 Proposed reaction mechanism for [3+3] cycloaddition of propargylic acetates with cyclic enamines

The use of β-keto esters, a kind of versatile *O*,*C*-bis-nucleophile, for the copper-catalyzed asymmetric cycloaddition with propargylic esters, however, did not lead to the expected [3+3] cycloadducts. Instead, a formal [3+2] cyclo-

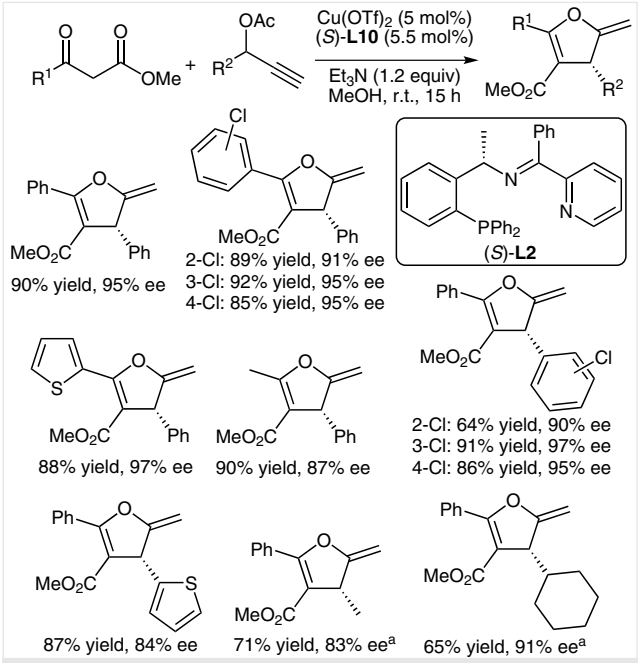
addition took place as reported by Hu and co-workers very recently.[9] The reaction proceeds via catalytic sequential propargylation/cyclization process as proposed in Scheme 6.[10] The copper–acetylide complex **A** bearing a cationic γ-carbon or its resonance structure, the copper–allenylidene complex **B**, should be generated in the initial step. Subsequent attack of the nucleophilic carbon of the β-keto ester to Cγ of the copper–allenylidene complex gives γ-alkynyl β-keto ester **C**. Coordination of cationic copper(II) to the alkyne forms the π-alkyne–copper complex **D** and enhances the electrophilicity of the alkyne. Subsequent 5-*exo*-*dig* nucleophilic attack of the hydroxy group on Cβ of the copper(II)–alkyne complex **D** followed by protonolysis generates the dihydrofuran product, a formal [3+2] cycloadduct.



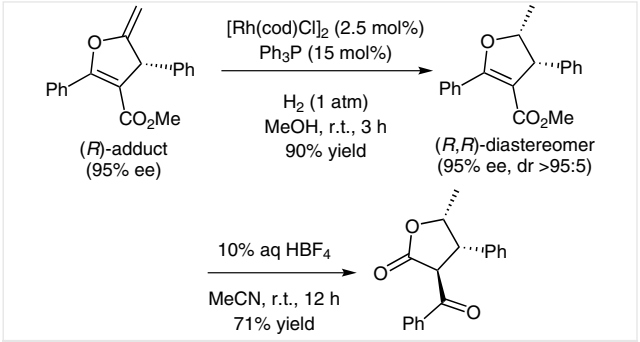
Scheme 6 Proposed reaction mechanism for [3+2] cycloaddition of propargylic acetates with β-keto esters

The employment of a bulky and structurally rigid chiral ketimine-type P,N,N-ligand **L2** was critical for the good performance of this reaction. A range of substitution patterns on the β-keto ester and propargylic acetate were well tolerated, generating optically active 2,3-hydrofurans bearing an exocyclic C=C bond in high yields and enantioselectivity (up to 97% ee, Scheme 7). It was noted that the reaction worked well for aliphatic propargylic substrates when aliphatic pentafluorobenzoates were used instead of the corresponding acetates.

Importantly, the exocyclic methylene group in the resulting [3+2] cycloadducts could be readily hydrogenated in a highly diastereoselective fashion (dr >95:5) without loss of enantioselectivity by catalysis using a combination of $[Rh(COD)Cl]_2$ and triphenylphosphine, predominantly giving the *cis*-diastereomer in high yield. The resulting hydrogenation product can be easily converted into the corresponding optically active γ-lactone by treatment with aqueous tetrafluoroboric acid at room temperature (Scheme 8).

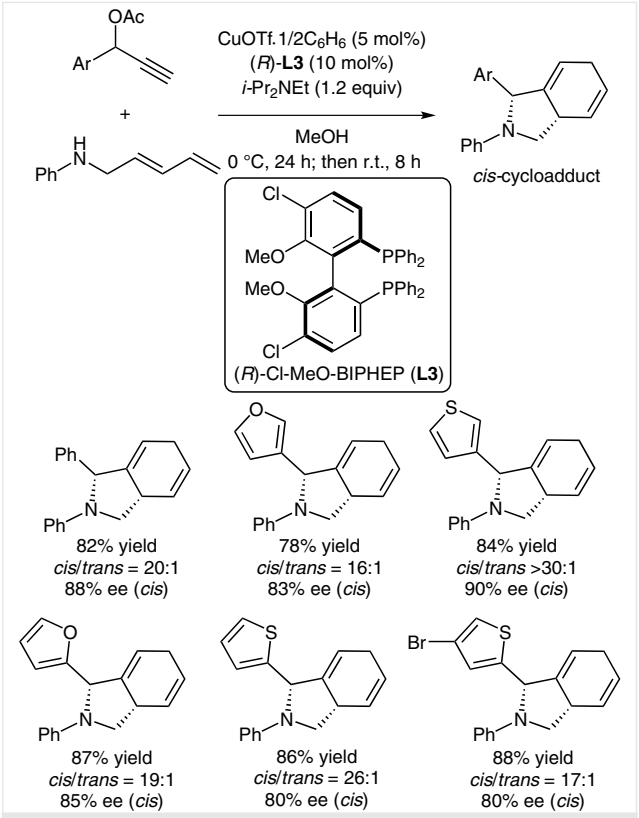


Scheme 7 Copper-catalyzed asymmetric [3+2] cycloaddition of propargylic acetates with β-keto esters. [a] The pentafluorobenzoate was used instead of the corresponding acetate.

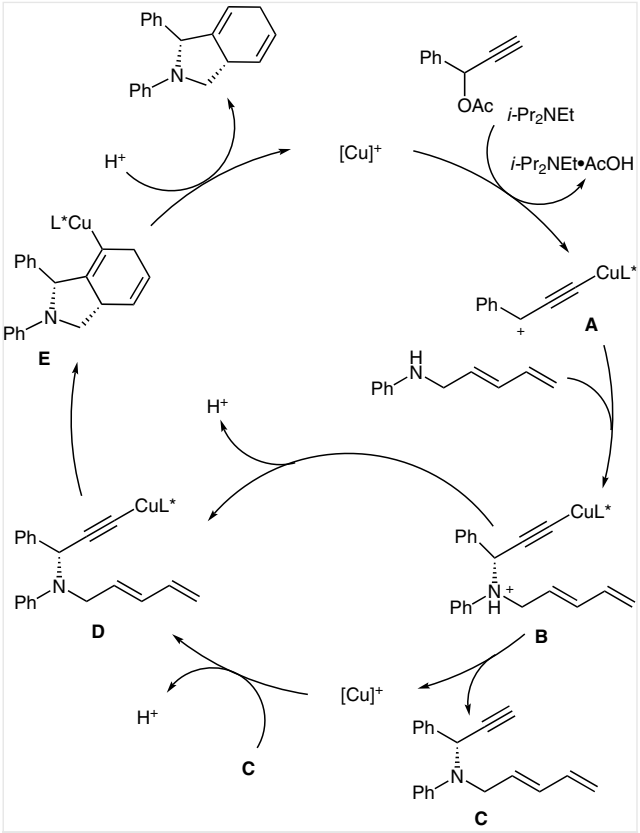


Scheme 8 Synthetic utility of the [3+2] cycloadduct

The copper-catalyzed sequential propargylic substitution/cyclization has also been reported by Nishibayashi and co-workers.[11] In 2010, they disclosed a copper-catalyzed diastereo- and enantioselective sequential propargylic amination/[4+2]-cycloaddition reaction of propargylic acetates with *N*-[(*E*)-penta-2,4-dienyl]aniline to give the corresponding optically active 1,2-disubstituted tetrahydroisoindoles in high yields with high diastereo- and enantioselectivity (up to >30:1 dr, up to 90% ee), in which only a single copper catalyst is required (Scheme 9). Although only limited substrate scope was examined, this reaction represents a novel synthetic approach to chiral tetrahydroisoindoles, which have been found as inhibitors of cyclooxygenase isoenzyme and thrombin.[12]



Scheme 9 Copper-catalyzed sequential asymmetric propargylic amination/[4+2]-cycloaddition reactions

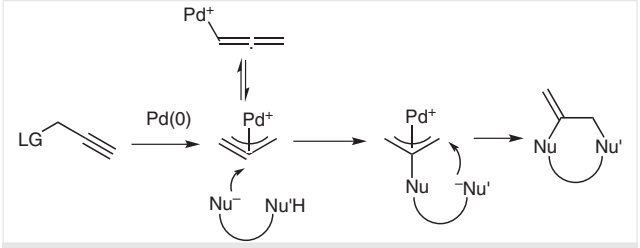


Scheme 10 Proposed reaction mechanism for sequential propargylic amination/[4+2]-cycloaddition reactions

A proposed reaction pathway is shown in Scheme 10. At first, *N*-[(*E*)-penta-2,4-dienyl]aniline attacks the copper acetylide complex **A** bearing a cationic γ-carbon atom from the *re* face to give **C** with high enantioselectivity. Then, the intramolecular [4+2] cycloaddition reaction occurs via the copper acetylide complex **D**, which is formed from **C** and the chiral copper complex. The direct transformation from **B** to **D** without the formation of **C** as a reactive intermediate may also be conceivable in the sequential reactions.

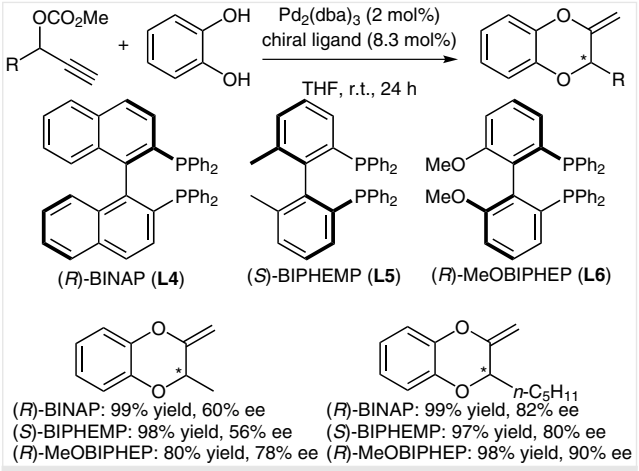
4 Palladium–π-Propargyl Complexes in Stereoselective Cycloaddition

Different to ruthenium or copper complexes, the reaction of propargylic esters or halides with palladium complexes leads to π-propargylpalladium and allenylpalladium complexes, which might be attacked consecutively by a bis-nucleophile to give the cyclization product (Scheme 11). In the reaction, propargylic esters are generally used as a C2 synthon. The use of a terminal propargylic ester is not essential, but could certainly simplify the outcome of the reaction. Pioneering work in the palladium-catalyzed [3+2] cycloaddition of terminal propargylic carbonates with β-keto esters to produce substituted dihydrofurans was reported by Tsuji and co-workers in 1985.[13] However, until recently the stereochemistry of the reaction was rarely examined.



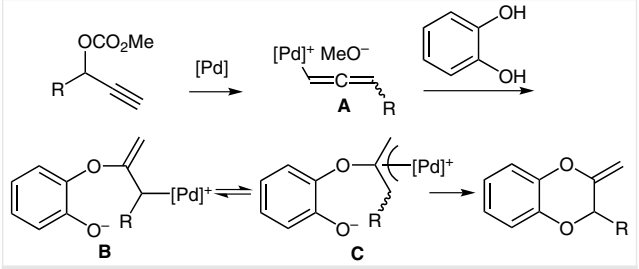
Scheme 11 Palladium-catalyzed cyclization of propargylic compounds with bis-nucleophiles

In 2000, Sinou and co-workers reported the palladium-catalyzed cyclization of various propargylic carbonates with benzene-1,2-diol using some atropoisomeric diphosphines as chiral ligands, affording 2-alkylidene-3-alkyl-2,3-dihydrobenzo[1,4]dioxins in quite good yields and high enantioselectivity (Scheme 12).[14] Besides terminal propargylic carbonates, internal propargylic carbonates were also examined and showed good performance.[15]



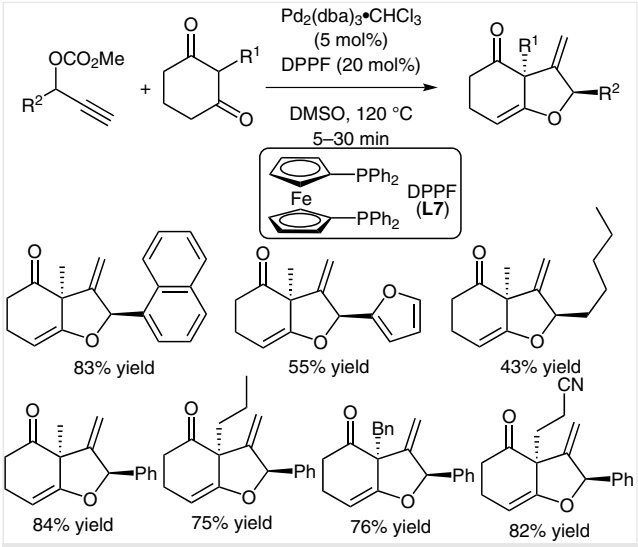
Scheme 12 Palladium-catalyzed asymmetric [4+2] cycloaddition of propargylic carbonates with benzene-1,2-diol.

The proposed mechanism is shown in Scheme 13. Initially, the reaction of racemic carbonates with the chiral palladium catalyst generates two diastereomeric enantiopure allenylpalladium intermediates **A**. Attack of the benzene-1,2-diol on the central sp carbon of these two intermediates gives palladium complex **B**, in equilibrium with the η^3-allyl complex **C**, probably in rapid σ↔π↔ σ interconversion. Intramolecular attack of the oxo nucleophile on the more substituted terminus of this allyl complex, which could be explained on the basis of electronic factors as shown previously by Larock and co-workers,[16] gives the cyclized compounds.



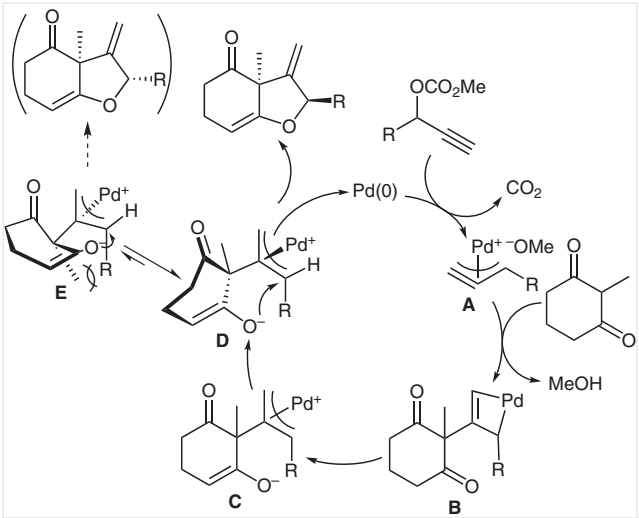
Scheme 13 Proposed reaction mechanism for [4+2] cycloaddition of propargylic carbonates with benzene-1,2-diol

In 2008, Yoshida and co-workers developed the palladium-catalyzed formal [3+2] cycloaddition of propargylic carbonates with 2-substituted cyclohexane-1,3-diones,[17] generating cyclized products containing two asymmetric centers, including a quaternary carbon, in a highly diastereoselective manner (*trans*-cycloadduct as a single diastereomer) (Scheme 14). The best results were obtained using 5 mol% of $Pd_2(dba)_3$·$CHCl_3$ and a diphosphine ligand (DPPF). However, an enantioselective version of this reaction was not examined.



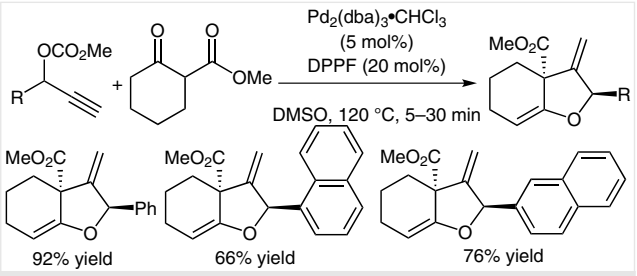
Scheme 14 Palladium-catalyzed [3+2] cycloaddition of propargylic carbonates with 2-substituted cyclohexane-1,3-diones

A possible mechanism for the reaction is outlined in Scheme 15. Initially the propargylic carbonate undergoes decarboxylation to give the π-propargylpalladium complex **A**, which subsequently reacts with cyclohexane-1,3-dione to give the π-allylpalladium intermediate **C**. Intramolecular attack of the enolate to π-allylpalladium complex produces a tetrahydrobenzofuranone. The observed high diastereoselectivity can be explained by steric interactions, in which the transition state **D** has lower energy because of the absence of steric repulsion between the methyl and R groups in the transition state **E**.



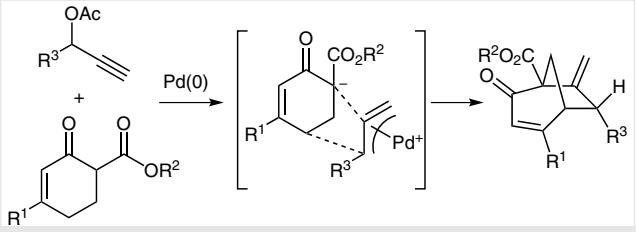
Scheme 15 Proposed reaction mechanism for [3+2] cycloaddition of propargylic carbonates with 2-substituted cyclohexane-1,3-diones

Other β-dicarbonyl compounds, such as 2-oxocyclohexanecarboxylic esters also proved to be suitable reaction partners for the reaction.[18] Under the optimal reaction conditions, tetrahydrobenzofuran derivatives having two asymmetric centers were obtained in moderate to high yields with the *trans*-cycloadduct as the single diastereomer (Scheme 16).



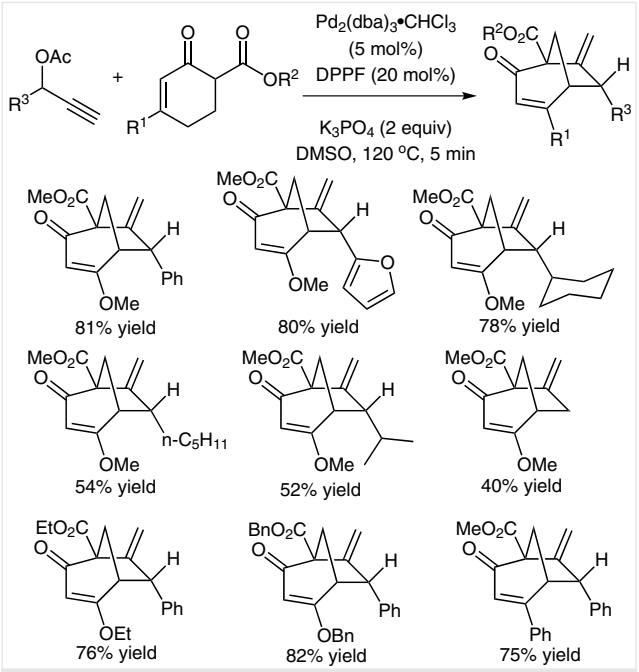
Scheme 16 Palladium-catalyzed [3+2] cycloaddition of propargylic carbonates with 2-oxocyclohexanecarboxylic esters

Although various heterocycles can be synthesized via the palladium-catalyzed cycloaddition of propargylic esters with bis-nucleophiles, few examples have been reported on the construction of carbocyclic molecules. In 2011, Yoshida and co-workers described a palladium-catalyzed cycloaddition of propargylic acetates with 2-oxocyclohex-3-enecarboxylates,[19] in which the α-carbon of the keto ester moiety and the γ-carbon of the enone moiety could act as the nucleophile (Scheme 17).



Scheme 17 Proposed reaction pathway for [3+2] cycloaddition of propargylic acetates with 2-oxocyclohex-3-enecarboxylates

Under the optimized conditions, a variety of propargylic acetates and 2-oxocyclohex-3-enecarboxylates were subjected to this palladium-catalyzed reaction, giving functionalized bicyclo[3.2.1]octenones in a highly stereoselective manner (obtained as a single diastereomer) (Scheme 18). Since various natural products have a bicyclo[3.2.1]octane structure,[20] this methodology provides a new protocol for the synthesis of these compounds with high efficiency.

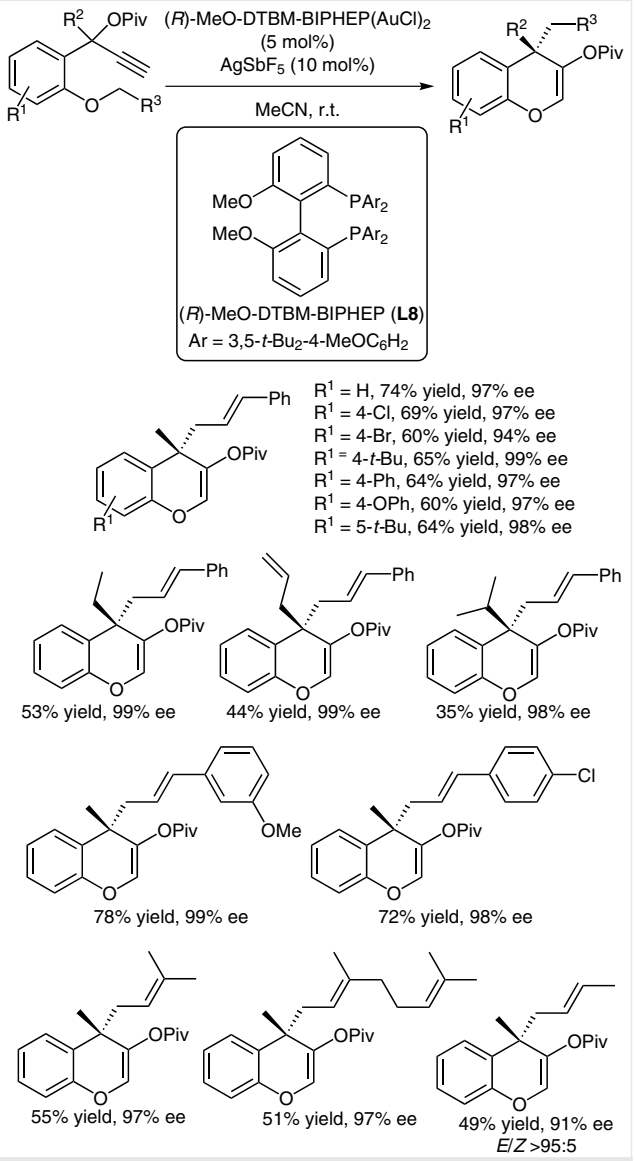


Scheme 18 Palladium-catalyzed [3+2] cycloaddition of propargylic acetates with 2-oxocyclohex-3-enecarboxylates

Besides β-dicarbonyl derivatives, Yoshida et al. also investigated the application of 2-(2-hydroxyphenyl)acetates as *C*,*O*-bis-nucleophiles in palladium-catalyzed asymmetric cycloaddition.[21] Since only internal propargylic carbonates were examined, it is not included in this review.

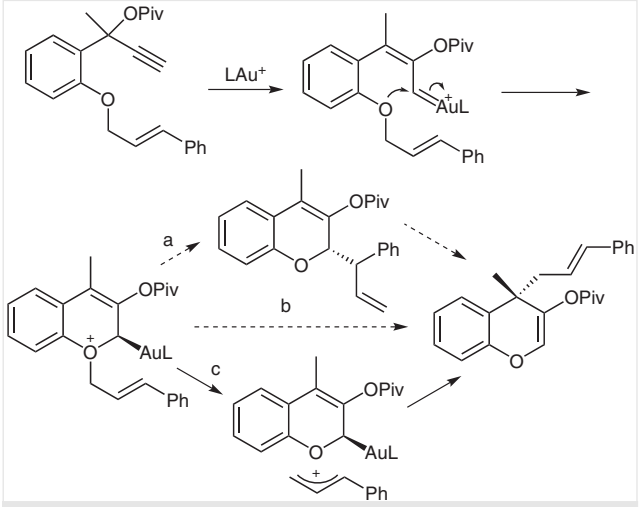
5 Gold–Carbenoid Complexes in Stereoselective Cycloaddition

The gold-catalyzed 1,2-acyloxy migration of propargylic esters generates gold carbenoid intermediates that can undergo a wide range of transformations[22] such as nucleophilic attack,[23] annulation,[24] subsequent acyloxy rearrangement,[25] and olefin cyclopropanation.[26] However, the application of this strategy in the stereoselective construction of complex cyclic rings has been rarely described. In 2009, Toste and co-workers reported a gold(I)-catalyzed intramolecular carboalkoxylation reaction of propargylic esters, leading to benzopyrans containing quaternary stereocenters with excellent enantioselectivity (Scheme 19).[27] The substitution on the aryl ring was well tolerated; however, a bulkier substituent in the propargylic position decreased the rate of the reaction. The migrating ether substituent showed significant impact on the reactivity and enantioselectivity. The substitution in cinnamyl ether did not interfere with the reaction, while an unsubstituted allyl group did not undergo the desired transformation.



Scheme 19 Gold-catalyzed asymmetric intramolecular carboalkoxylation reaction of propargylic esters

A plausible mechanism for the gold-catalyzed asymmetric rearrangement is shown in Scheme 20. Initial 1,2-acetoxy migration promoted by the gold(I) complex gives a gold(I)–carbenoid, which subsequently undergoes nucleophilic attack of the ether oxygen to generate an oxonium intermediate that can rearrange into benzopyran in several possible ways. However, a mechanism involving the formation of an allyl cation with a chiral allylgold(I) intermediate seems most likely on the basis of some experimental evidence.

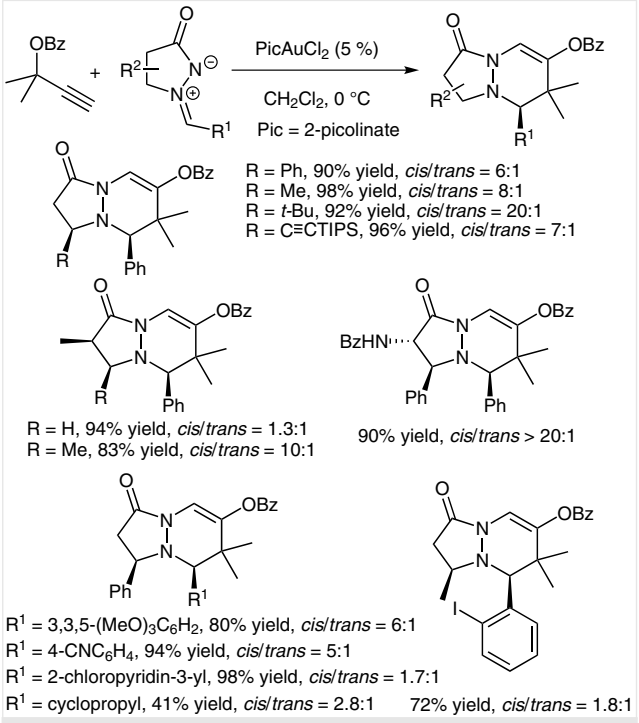


Scheme 20 Proposed mechanism for intramolecular carboalkoxylation reaction of propargylic esters

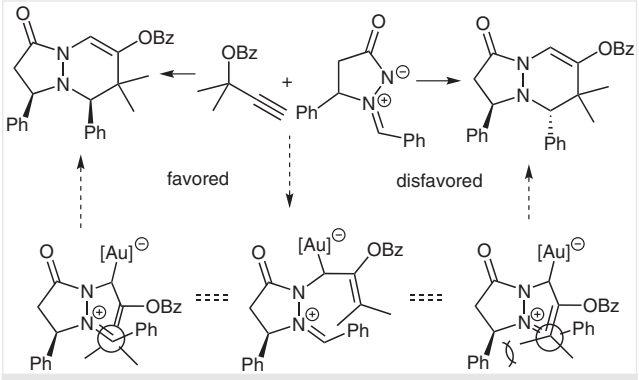
The gold-catalyzed 1,2-rearrangement of propargylic esters is believed to proceed through an alkenylmetal–carbenoid. On the basis of this discovery, Toste et al. developed a gold(III)-catalyzed [3+3] cycloaddition of propargylic esters and azomethine imines for the synthesis of diazabicycles (Scheme 21),[28] which is proposed to proceed via stepwise cycloaddition with a gold(III)–carbenoid intermediate. High 1,2-*cis* stereoselectivity results from the *cis*-imine geometry and the preferred *trans* geometry of the proposed gold–carbenoid intermediate, as well as steric interactions between the propargylic ester methyl group and the β-substituent in the ring-closing transition state (Scheme 22).

In 2011, Nevado and co-workers developed a reaction sequence starting with propargylic esters and dienes,[29] in which the gold catalyst not only catalyzed the 1,2-acetoxy migration and subsequent cyclopropanation, but also reactivated the in situ generated vinyl acetate, thereby triggering a formal homo-Cope rearrangement to give seven-membered rings in a highly stereoselective manner, affording only *cis*-cycloheptenyl acetates as the major product (Scheme 23, path a). Furthermore, if alkenes were used, highly substituted cyclopentenyl acetates could be obtained upon cyclopropyl ring opening. The reaction was also highly diastereoselective, and in most cases only *trans*-2,3-disubstituted cyclopentenyl derivatives were observed (Scheme 23, path b).

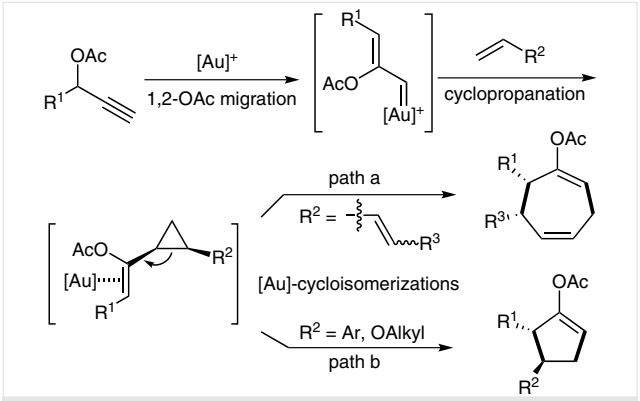
An enantioselective synthesis of the core of the frondosins,[30] marine norsesquiterpenoids with promising biological activity, was examined with this methodology.[29] Treatment of 1-(2,5-dimethoxyphenyl)prop-2-ynyl pivaloate and 6,6-dimethyl-1-vinylcyclohexene with (*S*)-MeO-DTBM-BIPHEP–gold(I) complex afforded quantitatively the corresponding bicyclic cycloheptenyl pivaloate. In situ hydrolysis



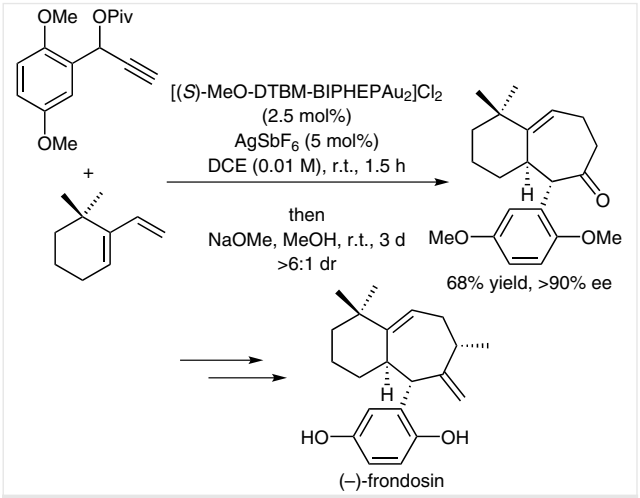
Scheme 21 Gold(III)-catalyzed [3+3] cycloaddition of propargylic esters with azomethine imines



Scheme 22 Ring-closing transition state for high 1,2-*cis* stereoselectivity



Scheme 23 Gold-catalyzed 1,2-acyloxy-rearrangement/cyclopropanation/cycloisomerization cascades



Scheme 24 Synthetic utility of gold-catalyzed cycloheptannulation cascades

and subsequent equilibration with sodium methoxide in methanol yielded the thermodynamically favored ketone in 68% yield and more than 90% ee (Scheme 24).

6 Summary and Outlook

This review summarizes the progress in the emerging field of catalytic stereoselective cycloaddition with terminal propargylic compounds. As illustrated above, many transition-metal complexes including ruthenium, copper, palladium, and gold have been reported for this type of transformation. In particular, ruthenium and copper catalysts show specific affinity for terminal propargylic compounds, generating dielectrophilic ruthenium– and copper–allenylidene intermediates that can possibly undergo highly diastereo- and enantioselective cycloaddition with various bis-nucleophiles. For palladium- and gold-catalyzed cycloaddition, terminal propargylic compounds might not be essential to promote the cycloaddition. However, the employment of terminal propargylic compounds simplifies the outcome of the cycloaddition, and in many cases, shows high specificity. Despite much progress, catalytic stereoselective cycloaddition with terminal propargylic compounds remains an underdeveloped area. The scope of the bis-nucleophile for ruthenium– or copper–allenylidene complex mediated enantioselective cycloaddition is very narrow. Few enantioselective examples of palladium-catalyzed cycloaddition are available although the corresponding diastereoselective reactions have been extensively studied by Yoshida and co-workers. We foresee that in the near future the scope of enantioselective cycloaddition with terminal

propargylic compounds will expand by the disclosure of more efficient catalytic systems or chiral ligands, and its synthetic utility for the construction of complex ring systems will be extensively explored due to its simplicity.

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