



HHS Public Access

Author manuscript

Acc Chem Res. Author manuscript; available in PMC 2021 January 21.

Published in final edited form as:

Acc Chem Res. 2020 January 21; 53(1): 231–243. doi:10.1021/acs.accounts.9b00477.

Rhodium-catalyzed (5+2) and (5+1) cycloadditions using 1,4-enynes as the five-carbon building blocks

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CONSPECTUS

Cycloaddition reactions are a hallmark in organic synthesis because they provide an efficient way to construct highly substituted carbo- and heterocycles found in natural products and pharmaceutical agents. Most cycloadditions occur under thermal or photochemical conditions, but transition metal complexes can promote reactions that occur beyond these circumstances. Transition metal complexation with alkynes, alkenes, allenes, or dienes often alters the reactivity of those π -systems and facilitates access to diverse cycloaddition products.

This Account describes our efforts toward the design of novel five-carbon synthons for use in rhodium-catalyzed (5+*n*) cycloadditions, which include 3-acyloxy-1,4-enynes (ACEs) for (5+1) and (5+2) cycloadditions and 3-hydroxy-1,4-enynes (HYEs) for (5+1) cycloadditions. Furthermore, this Account includes relevant computational information, mechanistic insights, and applications of these cycloadditions to synthesize various highly substituted carbo- and heterocycles.

The (5+*n*) cycloaddition reactions presented herein share the following common mechanistic features: the 1,2-migration of an acyloxy group in propargyl esters or an ionization of a hydroxyl group in propargylic alcohols, oxidative cyclization to form a metallacycle, insertion of the one- or two-carbon component, and reductive elimination to yield the final product.

In conjunction with a cationic rhodium catalyst, we used ACEs for the intramolecular (5+2) cycloaddition with tethered alkynes, alkenes, and allenes. In some cases, an electron-deficient phosphine ligand improved the reaction yields, especially when the ACE featured an internal alkyne. We also demonstrated that chirality could be efficiently transferred from a relatively simple starting material to a more complex bicyclic product. Products derived from ACEs with tethered alkenes and allenes contained one or more stereocenters, and high diastereoselectivity was achieved in most of these cases. For ACEs tethered to an allene, the reaction preferentially occurred at the internal alkene. We also switched the positions of the alkene and the alkyne in the 1,4-enyne of our original ACE to provide an inverted ACE variant, which produced products with complementary functionalities.

After we successfully developed the Rh-catalyzed intramolecular (5+2) cycloaddition, we optimized conditions for the intermolecular version, which required a neutral rhodium catalyst and

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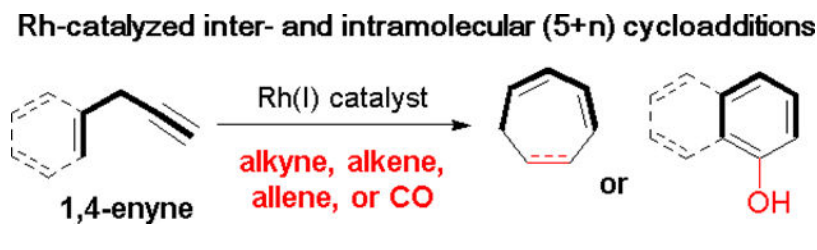
The authors declare no competing interest.

phosphine ligand. When a terminal alkyne was used as the two-carbon component, high regioselectivity was observed. While investigating the effect of esters on the rate of the intermolecular (5+2) cycloadditions, we determined that an electron-rich ester significantly accelerated the reaction. Subsequently, we demonstrated (5+1) cycloadditions undergo this rate enhancement as well in the presence of an ester.

Aside from ACEs, we synthesized HYEes in four steps from commercially available 2-aminobenzoic acid for use in the (5+1) cycloaddition. Mechanistically, HYEes were designed so that the aniline nitrogen could serve as the nucleophile and the –OH could serve as the leaving group. Using HYEes, we developed a novel method to make substituted carbazoles, dibenzofurans, and tricyclic compounds with a cyclohexadienone moiety.

Although the occurrence of transition-metal catalyzed acyloxy migrations has been known for decades, only recently has their synthetic value been realized. We hope our studies that employ readily available 1,4-enynes as the 5-carbon components in (5+n) cycloadditions can inspire the design of new two-component and multi-component cycloadditions.

Graphical Abstract



1. Introduction

Cycloaddition reactions are a mainstay in organic synthesis as they provide an efficient method to construct complex carbo- and heterocycles found in natural products and pharmaceutical agents. Forming at least two bonds in a single step, cycloadditions boast high atom-economy, improved step count efficiency, and often occur with a high degree of regio- and stereoselectivity.¹

Most cycloadditions occur under thermal or photochemical conditions, but transition metal complexes can also be used to promote reactions that occur beyond these circumstances.² Transition metal complexation with alkynes, alkenes, allenes, or dienes often alters the reactivity of those π -systems and facilitates access to diverse compounds.

Six-membered rings are easily formed via the Diels-Alder cycloaddition reaction, but a similarly ubiquitous cycloaddition for the formation of seven-membered rings has not been discovered, despite their presence in pharmaceutical agents and natural products (Scheme 1).³ To make seven-membered rings, only three types of two-component cycloadditions are possible: (6+1),⁴ (5+2)⁵ and (4+3).⁶ New methods for the formation of seven-membered rings could be expedited by the development of novel five- and three-carbon synthons.

This Account details our design and use of novel five-carbon components in rhodium-catalyzed ($5+n$) cycloadditions. These include 3-acyloxy-1,4-enynes (ACEs) for ($5+1$) and ($5+2$) cycloadditions and 3-hydroxy-1,4-enynes (HYEs) for ($5+1$) cycloadditions. Herein, our experimental findings, mechanistic insights, computational rationales, and application-based work will be presented, and an overview of the featured transformations can be found in Scheme 2.

It should be noted that IUPAC nomenclature defines a cycloaddition as a reaction in which two or more unsaturated molecules (or parts of the same molecule) combine to form a cyclic adduct in which there is a net reduction of the bond multiplicity. While the reactions presented here involve the migration of an acyloxy group to promote ring formation, we have simply referred to them as cycloadditions throughout the text.

2. ($5+2$) Cycloadditions

2.1 Background

Compared to other transition metal-catalyzed ($m+n$) cycloadditions, the ($5+2$) cycloaddition remains largely underdeveloped. Prior to our studies, vinylcyclopropanes (VCPs) were the only known five-carbon synthon for transition metal-catalyzed ($5+2$) cycloadditions.^{5,7,8}

In 1995 the Wender group reported the first transition-metal catalyzed intramolecular ($5+2$) cycloaddition between a VCP and a tethered alkyne using a $\text{RhCl}(\text{PPh}_3)_3$ catalyst.^{7a} The same group later used substituted cyclopropanes to investigate the regio- and stereoselectivity of this reaction.^{7b} Not long after, the Trost, Louie, and Fürstner groups determined that Ru-,⁹ Ni-,¹⁰ and Fe-based¹¹ catalysts promoted the intramolecular ($5+2$) cycloaddition of VCPs with alkynes as well. Intramolecular ($5+2$) cycloadditions of VCPs and alkenes¹² are more difficult reactions to execute because the alkene is less reactive than the previously used alkynes and diastereoselectivity issues can arise. However, the Wender group only observed formation of the cis-fused 5–7 bicyclic compounds. They also discovered that allenes could be tethered to the VCP to promote the ($5+2$) cycloaddition.¹³ Additionally, they examined the endo/exo selectivity and chirality transfer in this reaction. Finally, the Wender and Hayashi groups achieved the enantioselective intramolecular ($5+2$) cycloaddition of VCPs and alkynes or alkenes by using chiral BINAP¹⁴ or phosphoramidite ligands, respectively.¹⁵

In Diels-Alder [$4+2$] cycloadditions, a conjugated diene (the 4π system) reacts with an alkyne or alkene (the 2π system), as shown in Scheme 3. For a ($5+2$) cycloaddition, the 4π system needs to be a five-carbon component. We envisioned that an ester in the middle of a 1,4-enyne might be able to connect the separated alkene and alkyne through a 1,2-acyloxy migration. Inspired by this idea, we proposed a Rh-catalyzed homo-Diels-Alder ($5+2$) cycloaddition using a 3-acyloxy-1,4-enyne (ACE) as the five-carbon synthon (Scheme 3). The ester in **3.6** could promote this cycloaddition with an accompanying Rautenstrauch-type¹⁶ 1,2-acyloxy migration. The ($5+2$) cycloaddition should be thermodynamically favorable because this transformation involves the formation of two C-C σ -bonds and the cleavage of two C-C π -bonds. In addition, depending on the 2-carbon components, a product containing a conjugated triene or diene is formed.

However, when we ran this reaction with various alkynes and ACEs under thermal conditions, no product formation was observed. We reasoned that a transition metal catalyst might lower the kinetic barrier for the cycloaddition by coordinating to all three π -bonds in **3.7**. To further reduce the entropic cost, we decided to tether the five- and two-carbon components together and explore the intramolecular (5+2) cycloaddition first.

2.2 Intramolecular (5+2) Cycloaddition with Alkynes

We were pleased to find that the intramolecular (5+2) cycloaddition with a concomitant 1,2-acyloxy migration proceeded smoothly at room temperature with a variety of Rh(I) catalysts, even though cationic rhodium species $[\text{Rh}(\text{cod})_2]\text{BF}_4$ was superior (Scheme 4).¹⁷ The use of platinum or gold complexes did not form the desired products. Successful substrates included those with oxygen, nitrogen, or malonate tethers, esters adjacent to the C1 alkyne (e.g. **5.3**), and aryl or alkyl substituents adjacent to the C9 alkyne (e.g. **5.2**).

When an internal alkyne was the two-carbon component (e.g. **5.5**, Scheme 5), cationic rhodium catalysts alone resulted in only trace cycloaddition product formation. However, the addition of an electron-poor phosphite ligand $(\text{CF}_3\text{CH}_2\text{O})_3\text{P}$ significantly increased the reaction yields with these substrates. The alkyne within the 1,4-enyne could be terminal or internal, but internal alkynes required an electron-withdrawing substituent (e.g. **5.7**). The limiting factor of this reaction was the tether length; tethers greater than or equal to six atoms did not result in the desired cycloaddition products. This observation was not surprising since π systems separated by more than six atoms are known to be difficult in transition-metal-catalyzed intramolecular cycloisomerization and cycloaddition reactions.²

The resultant bicyclo[5.3.0]decaatriene skeletons from this reaction are found in many natural products (Scheme 1),¹⁸ and the cycloheptatriene moiety is prevalent in many natural products and pharmaceutical agents.¹⁹ Furthermore, the cycloheptatriene has three double bonds that can be easily functionalized. In some cases, we used the cycloheptatriene products to access di- and trisubstituted tropones, which have broad pharmacological activities.²⁰

2.3 Chirality Transfer for the Intramolecular (5+2) Cycloaddition of ACEs and Tethered Alkynes

The Rh-catalyzed intramolecular (5+2) cycloaddition between an ACE and a tethered alkyne provides rapid access to bicyclo[5.3.0]decane skeletons in a stereospecific fashion (Scheme 6).²¹ In most cases, any erosion of the enantiomeric ratio is minimal. In reactions where an *ee* loss was observed, the bicyclic products were resubjected to the reaction conditions, which resulted in no significant change in *ees*. These results suggested that any observed erosion of the enantiomeric ratio occurs before the final cycloaddition product is formed.

In certain cases, the chirality transfer efficiency is ligand dependent. We knew from previous intramolecular [5+2] cycloaddition research¹⁰ that substrates with internal alkynes, such as **6.3**, require phosphite ligands to work. However, we observed that phosphite ligands significantly decreased the degree of chirality transfer for most substrates. Nevertheless, we were able to obtain an 84% *ee* using a phosphite ligand for product **6.7**. As seen in the

formation of product **6.9**, adding $(\text{PhO})_3\text{P}$ gave a higher yield but a lower *ee* compared to the Rh catalyst alone. Overall, this work was the first time that bicyclo[5.3.0]decaatrienes were prepared in high *ees*.

Computational studies from the Houk group²² yielded insight into the chirality transfer mechanism. Their DFT calculations suggested the Rh catalyst coordinates to the alkynes and alkene in (*S*)-**7.1** anti to the acyloxy group to yield **7.2** (Scheme 7). The Rh-promoted 1,2-acyloxy migration and cyclization first forms the chiral Rh-allyl intermediate **7.3**, which readily interconverts with **7.4**. Alkyne insertion can proceed through either **7.3** or **7.4**. This syn-addition of the tethered alkyne leads to the formation of the eight-membered rhodacycle **7.5**. A final reductive elimination then yields (*S*)-**7.6**. Overall, the anti-addition of the Rh catalyst to the ACE and the syn-insertion of the alkyne to the Rh-allyl complex result in the observed stereochemistry for the intramolecular (5+2) cycloaddition.

2.4 Intramolecular (5+2) Cycloaddition of ACEs and Tethered Alkenes and Allenes

The intramolecular (5+2) cycloaddition also worked for ACEs with tethered alkenes (Scheme 8 and Scheme 9)²³ and allenes (Scheme 10)²⁴ as the two-carbon components. In each case, a neutral rhodium catalyst $[\text{Rh}(\text{coe})_2\text{Cl}]_2$ with an electron-deficient phosphine ligand $(3,5\text{-}(\text{CF}_3)_2\text{C}_6\text{H}_3)_3\text{P}$ provided the cycloaddition products, albeit the allene reactions generally resulted in lower yields.

For tethered alkenes, the two-carbon alkene component could be either terminal or 1,2-disubstituted with an aryl substituent. Chirality transfer from the substrates to the products was possible even for the formation of three contiguous stereogenic centers. Only one diastereomer was observed in each case.

Mechanistically, the Rh catalyst adds anti to the acyloxy group of the ACE to give **9.5** and promotes the 1–2 acyloxy migration and oxidative cyclization, which forms rhodacycle **9.6** (Scheme 9). The tethered alkene then inserts into the rhodacycle to form **9.7**. Subsequent reductive elimination of **9.7** forms cycloheptadiene product **9.8**. This mechanism is consistent with the observed absolute stereochemistry of propargylic ester **9.3** and bicyclic product **9.4**, which was confirmed by X-ray crystallography.

The yields for the (5+2) cycloaddition of allenes were lower than the corresponding reaction with alkenes. Under optimized conditions, the yields of the bicyclic products only ranged from 45–58% percent, due to the isomerization of the allene to dienes under the reaction conditions. The reaction preferentially occurred at the internal alkene.

The reaction begins with Rh addition anti to the acyloxy group to yield **10.3** (Scheme 10). Oxidative cyclization of **10.3**, accompanied by a 1,2-acyloxy migration, yields **10.4**. The tethered allene then inserts into the rhodium-carbon bond to yield **10.5**. Reductive elimination of the eight-membered rhodacycle results in **10.6**.

2.5 Inverted Intramolecular (5+2) Cycloaddition with Alkynes

Inspired by Yu's report²⁵ detailing the design of a new five-carbon building block by swapping the positions of key reaction components, we switched the positions of the alkene

and the alkyne in the 1,4-enyne of our original ACE to provide an inverted ACE variant (Scheme 11), which produced products with complementary functionalities.²⁶

Usually, propargylic esters that contain an internal alkyne favor a 1,3-acyloxy migration to form allenes when used with Rh(I) catalysts.²⁷ However, electron-withdrawing substituents conjugated with an alkyne can alter the selectivity to instead favor a 1,2-acyloxy migration when used in Pt-,²⁸ Rh-,²⁹ and Au-catalyzed reactions because the electron-withdrawing substituents make the C2 position more electrophilic than the C3 position.^{20a} Inverted ACEs **11.1** (Scheme 11) were used with various Rh (I) catalysts to promote the intramolecular (5+2) cycloaddition with tethered alkynes. While neutral Rh catalysts did not give the desired products, cationic Rh catalysts proved efficient for the reaction, and $[\text{Rh}(\text{COD})_2]\text{BF}_4$ was the best. The addition of ligands was ineffective at improving the reaction yields, and neither gold nor platinum catalysts could promote this transformation. The reaction was amenable to substituents on the internal position of the alkene, but no desired product was observed when the external position of the alkene was substituted. A tether length of six atoms decreased the reaction efficiency.

DFT calculations helped elucidate the mechanism of inverted ACE (5+2) cycloadditions. The Rh catalyst coordinates to the internal alkyne and terminal alkene to form **12.4** (Scheme 12). This coordination promotes a 1,2-acyloxy migration and oxidative cyclization that results in intermediates **12.5** and **12.6**. Alkyne insertion into the rhodium-carbon bond yields rhodacycle **12.7**. Reductive elimination gives **12.8**, and Rh catalyst dissociation yields final product **12.9**. Based on calculated enthalpies and Gibbs free energies, the 1,2-acyloxy migration is the rate determining step. This inverted ACE cycloaddition provides another way to prepare seven-membered rings, and these rings have complementary functionalities compared to our previous cycloaddition products.

2.6 Intermolecular (5+2) Cycloaddition

After developing the Rh-catalyzed intramolecular (5+2) cycloaddition, we turned our attention to the intermolecular version. Unsurprisingly, the intermolecular cycloaddition is more difficult because of potential reactivity, chemo- and regioselectivity issues that result from removing the tether between the two reactants. Conversely, it is easier to obtain the two separate reactants needed to execute the intermolecular version.

When we subjected **13.1** and **13.2** to the $[\text{Rh}(\text{COD})_2]\text{BF}_4$ catalyst used previously in the intramolecular (5+2) cycloaddition, the desired cycloaddition product **13.3** was not observed, regardless of the presence or absence of phosphite ligand $(\text{CF}_3\text{CH}_2\text{O})_3\text{P}$ (Scheme 13).³⁰ Palladium, platinum and gold complexes did not work either. We suspected two molecules of ACE could potentially coordinate to the cationic rhodium catalyst as bidentate ligands as shown in **13.4**, which would prevent the two-carbon alkyne component from coordinating to the rhodium. Indeed, only when using a neutral rhodium catalyst with three coordination did we observed the desired product. In most cases, Wilkinson's catalyst worked well also. The two-carbon alkyne could be either terminal or internal. Polar substituents on the propargylic or homopropargylic positions of the terminal alkynes formed highly regioselective products. Terminal alkynes were generally more reactive than internal

alkynes, and while internal alkynes still worked, they required an electron-withdrawing halogen, ketone, or ester as the terminal substituent.

Our intermolecular (5+2) cycloaddition method with concomitant 1,2-acyloxy migration was applicable to a wide variety of substrates, and it was amenable to scale up with high regioselectivity. About 0.76 g of compound **14.3** was obtained with a greater than 20:1 isomeric ratio (Scheme 14). Cycloheptatriene **14.3** could then be functionalized to yield **14.4**.

In collaboration with the Houk group, we performed DFT calculations and our data indicated a concerted cycloaddition mechanism was at work (Scheme 15).¹⁵ From ACE **15.1**, the rhodium coordinates anti to the acyloxy group, as shown in **15.3**. Proceeding through transition state **15.4**, rhodacycle intermediate **15.5** is formed. The 1,2-acyloxy migration is believed to be the rate-determining step (RDS). Four rhodacyclooctatriene intermediates can be proposed after the insertion of alkyne **15.2** to rhodacyclohexadiene intermediate **15.5**. Via pathway **A**, the alkyne could insert into either the sp³-carbon-metal bond to form **15.6** or **15.7**. Via pathway **B**, the alkyne could insert into the sp²-carbon-metal bond to form **15.8** or **15.9**. For a terminal alkyne, such as **15.2**, the R group could be either close (**15.6** or **15.9**) or distal (**15.7** or **15.8**) to the forming C-C bond. In Houk's previous computational studies on Rh-catalyzed reactions involving unsymmetrical alkynes, the bulkier alkyne substituent prefers to be distal to the forming C-C bond.³¹ From the mostly likely rhodacyclooctatriene intermediate **15.8**, final product **15.10** is formed via a reductive elimination step.

The Rh-catalyzed intermolecular (5+2) cycloaddition between an ACE and an alkyne, which is accompanied by a 1,2-acyloxy migration of a propargyl ester, provides an efficient method to synthesize seven-membered rings in only two steps from commercially available starting materials.

2.7 Effect of Esters on the Intermolecular (5+2) Cycloaddition

In a subsequent study,³² we examined the effect of various esters on the ACE C3-position in Rh-catalyzed intermolecular (5+2) cycloadditions (Scheme 16). By using the electron-donating ester *p*-dimethylaminobenzoate, the reaction rate was more than 46 times faster than the corresponding reaction with a phenyl ester. We reasoned that the electronic effect of the ester could facilitate the reaction in an early nucleophilic attack step or a late reductive elimination step. After computational calculations,¹⁵ we attributed the rate increase to the reductive elimination step.

Since the effect of the electron-donating ester on the rate of the reaction is determined by the barrier of 1,2-acyloxy migration, computational calculations were completed to determine whether the lower transition state energy resulted from the Rh being anti (**TS1**) or syn (**TS1'**) to the acyloxy group. We determined that during the concerted process of 1,2-acyloxy migration with the Rh catalyst, the Rh prefers to add in an anti-fashion because the activation free energy is 5.4 kcal/mol less than if the Rh would add in a syn-fashion. The ester's electron-donating ability also stabilizes the carbonyl carbon's positive charge (as shown in **15.4**) and lowers the transition state's energy in the rate-determining step. For

ACEs with a tertiary ester, the catalyst loading could be reduced to 0.5%. For ACEs with a secondary ester, the yield increased from 16% to 53% (**16.4a** to **16.4b**).

All of the previous research represents the first time that ACEs have served as the five-carbon component in Rh-catalyzed intra- and intermolecular (5+2) cycloadditions with alkynes, and in some cases, intramolecular cycloaddition with alkenes and allenes.

3. (5+1) Cycloadditions

Six-membered carbocycles are among the most prevalent ring compounds. Many two- and three-component cycloadditions have been designed to produce these structures, but difficulties associated with sourcing the five-carbon component hinder further progress of the (5+1) cycloaddition.

3.1 (5+1) Cycloaddition with an ACE and CO

The first Rh-catalyzed (5+1) cycloadditions of ACEs and CO were developed by Fukuyama, Ryu, Fensterbank and Malacria.³³ 1,3-Dihydroxybenzenes with additional one or two substituents were prepared. However, the reaction requires high pressures of CO (50 atm) and high temperature (80 °C). After discovering that the electron-donating ester can significantly accelerate the rate of the Rh-catalyzed (5+2) cycloaddition,³⁴ we examined the effect of the ester on (5+1) cycloaddition of ACE and CO.³⁵ Indeed, the (5+1) cycloaddition could run under lower temperature (room temperature to 50 °C) and much lower pressure of CO (1 atm) using ACEs that contained an electron-rich dimethylaminobenzoate ester.^{28,36}

3.2 Aryl Propargylic Esters as the Five-carbon Building Block in (5 + 1) Cycloadditions

Besides expanding the scope of (5+2) cycloadditions, we have also developed additional five-carbon synthons for (5+1) cycloadditions to access polycyclic compounds. We envisioned that if the alkene part of an ACE could be embedded in an aromatic system, aryl propargylic esters could then be used in a Rh-catalyzed benzannulation. To our delight, this new type of (5+1) cycloaddition indeed worked and allowed for the synthesis of highly substituted indoles at the C4–C7 positions, complementary to current techniques for indole preparation. We also extended this method to the synthesis of benzofurans, benzothiophenes, carbazoles, and dibenzofurans.³⁷

The DFT calculation supported mechanism is shown in Scheme 17. Starting with **17.1**, the Rh(I) catalyst coordinates to the alkyne to form **17.3**. This species undergoes the rate-determining stepwise 1,2-acyloxy migration to form **17.4**. Then zwitterion intermediate **17.5** forms, isomerizes to a four-membered rhodacycle **17.6**, undergoes CO insertion and subsequent reductive elimination to afford ketene intermediate **17.7**. Finally, a 6 π electrocycloaddition and aromatization yields benzofuran product **17.2**.

Based on the previous benzannulation of heteroaryl propargylic ester research, we were able to synthesize a variety of highly substituted benzofuran-containing natural products which include: amurensin H (or viniferifuran), malibatol A, shoreaphenol (or hopeafuran), fuliginosin A, and many other related bioactive heterocycles such as diptoindonesin G (Scheme 18).³⁸

3.3 3-Hydroxy-1,4-Enynes and Diaryl Propargylic Alcohols in (5 + 1) Cycloadditions

We then developed a second five-carbon synthon for (5+1) cycloadditions as shown in Scheme 19. We predicted a novel bicyclic rhodacycle intermediate would result if we replaced the acyloxy group in an ACE with a leaving group X and nucleophile Y, as seen in 1,4-enyne **19.4**. Through transition state **19.5**, the resulting novel rhodacycles **19.6** could result in new cycloadditions.

From commercially available 2-aminobenzoic acid, 3-hydroxy-1,4-enynes (HYEs) **19.7** in Scheme 19 or **20.1** in Scheme 20 were synthesized in four steps to test this hypothesis.³⁹ Mechanistically, HYE s were designed so the aniline nitrogen could serve as the nucleophile and –OH could serve as the leaving group. Using HYE s, we developed a novel method to make substituted carbazoles and carbazoles fused with various heterocycles.

Various Rh(I) catalysts were screened with substrate **19.7** in the presence of CO. The Wilkinson's catalyst and cationic Rh(I) catalysts provided complex mixtures or no desired product. [Rh(COD)Cl]₂ and [Rh(CO)₂Cl]₂ under one atmosphere of CO led to good yields of **19.9**, 81% and 88%, respectively. The CO pressure affected product yields as well, and one atmosphere of CO was optimal. The alkene termini could accommodate alkyl, cyclopropyl, and aryl groups. Bromine, methoxy, and trifluoromethyl substituents on the aromatic ring were all tolerated, and the electronic nature of these substituents did not appear to affect the tandem annulation [5+1] cycloaddition (Scheme 20). However, an internal alkyne did substantially decrease the final product yield. We were pleased to find that phenols could also be used as the nucleophile in these reactions.

We proposed two plausible reaction mechanisms in Scheme 21. From **21.1**, via pathway **A**, a concerted annulation and oxidative cyclization with the loss of water forms **21.3**. Insertion of CO and subsequent reductive elimination leads to **21.4**. Aromatization then yields carbazole **21.5**. Alternatively, the Rh-catalyst could coordinate to the substrate to form **21.6**, and then the aniline nitrogen could perform a nucleophilic attack on the alkyne in **21.6** to form **21.7**. The loss of water from **21.7** then results in Rh(I) carbene **21.8**. From here, a 6 π electrocyclization can form **21.3**, and CO insertion would go through **21.4** to form **21.5**. Otherwise from **21.8**, CO insertion could form ketene **21.9**, and 6 π electrocyclization of this compound would eventually lead to **21.5**. The isolation of by-product **21.14** could be explained through ketene **21.11**, but this by-product cannot rule out the possibility of either pathway **A** or pathway **B**, since the two pathways can be connected by the interconversion between **21.3** and **21.8**.

As opposed to traditional cycloadditions (where two bonds are formed), this reaction formed an additional C-N or C-O bond in conjunction with two other C-C bonds. To demonstrate the power of this method for the synthesis of polycyclic compounds, it was used to synthesize the natural products glycosinine and mahanimbine and achieve the formal synthesis of mukoenine-A and heptaphylline (Scheme 22).^{32,40}

After employing HYE s with a Boc-activated aniline nucleophile in (5 + 1) cycloadditions, we altered our five-carbon component by replacing the Boc-aniline nucleophile with a sulfonamide (Scheme 23). Boc-substituted compounds don't react well with certain two-

carbon units, such as furans, hence we replaced the aniline nucleophile with a sulfonamide. The reaction tolerated numerous substituents on the alkene termini and aniline ring, and it only appeared to be hampered when substituents were simultaneously present on the alkene and alkyne.

We also prepared a wide variety of substrates to test the ability of the tandem annulation (5+1) cycloaddition to prepare tetracyclic and even pentacyclic heterocycles fused with a carbazole (Scheme 24).^{32,33}

To form polycyclic heterocycles, the proposed mechanism begins with Rh(I) coordination to diaryl propargylic alcohol **24.3** to form **24.4**. Then nucleophilic addition of the nitrogen to the alkyne, followed by construction of the C–Rh bond in **24.5** occurs. Loss of a water molecule results in Rh(I) carbene **24.6**. Insertion of CO and displacement of rhodium forms ketene **24.7**. A 6π electrocycloaddition forms **24.8** (pathway a), and re-aromatization of both five- and six-membered rings yields final product **24.9**. Alternatively, Friedel-Crafts acylation followed by re-aromatization event can also provide final product **24.9** through intermediate **24.10** (pathway b).

The *de novo* synthesis of benzene rings continues to be a challenge for organic chemists. Of the few methods currently available, only a limited number are general enough to be extended to the synthesis of polycyclic heterocycles. The use of diaryl propargylic alcohols is a general, environmentally benign and atom-economical way to synthesize benzene rings that doesn't rely on stoichiometric amounts of toxic Fischer carbenes used in other methods.³⁶ Using this Rh(I)-catalyzed tandem reaction, the efficient synthesis of highly substituted carbazoles, furocarbazoles, pyrrolocarbazoles, indolocarbazoles, and thiophenocarbazoles can be achieved.

Conclusion

Transition-metal catalysis, specifically rhodium, has been shown to be an invaluable tool for the construction of complex ring systems. In addition, the design of novel five-carbon synthons from relatively simple starting materials has propelled the development of (5+*n*) cycloadditions. These cycloadditions largely share the common mechanistic features of rhodium coordination, 1,2-migration of an acyl group in propargylic esters or an ionization of hydroxyl group in propargylic alcohols, oxidative cyclization, and reductive elimination to form ring products that are often found in pharmaceutical agents and natural products. Although the occurrence of transition-metal catalyzed acyloxy migrations has been known for decades, only recently has their synthetic value in cycloadditions been realized.

The (5+*n*) cycloadditions we have developed so far do not have heteroatoms in the 5- or *n*-atom components. One of the future directions for this work is the introduction of heteroatoms to either of these two components for the preparation of diverse heterocycles. It is our hope that the work previously described, which uses readily available 1,4-enynes as the 5-carbon components in (5+*n*) cycloadditions, can be extended to other two-component and multi-component cycloadditions.

ACKNOWLEDGMENT

We would like to thank Dr. Peng Wen and Bethany J. McCarty for carefully proofreading the manuscript and thoughtful discussions. We also want to thank all coworkers involved in this research, particularly Dr. Xingzhong Shu, Dr. Xiaoxun Li, Dr. Wangze Song and Ms. Casi M. Schienebeck.

Funding Sources

We would like to thank the University of Wisconsin-Madison and NSF (CHE-1464754) for financial support. S.A.B. was supported in part by the NIH Chemistry-Biology Interface Training Grant (T32GM008505) and the NSF Graduate Research Fellowship.

Biographies

Stephanie A. Blaszczyk obtained her B.S. degree in Chemistry from Rockford University after working with Professor Matthew Bork. Following graduation, she worked for Geneva Laboratories and Tate & Lyle. Now a Ph. D. candidate at the University of Wisconsin-Madison, Stephanie develops new synthetic methods under professor Weiping Tang. She is also actively involved in science communication, most recently serving as a 2019 AAAS Mass Media Science & Engineering Fellow at the Milwaukee Journal Sentinel.

Daniel A. Glazier obtained his B.S. in chemistry from the University of Pittsburgh in 2014 after working with Paul Floreancig. He then enrolled as a Ph.D. student at the University of Wisconsin-Madison and joined the Tang Lab. He develops new synthetic methods and also uses DFT calculations to study the mechanism of these reactions. After receiving his PhD, he joined Arrowhead Pharmaceuticals.

Weiping Tang received his B.S. degree from Peking University, M.S. degree from New York University, and Ph.D. degree from Stanford University. He was a HHMI postdoctoral fellow at Harvard University. He is currently a professor in the School of Pharmacy and Department of Chemistry at the University of Wisconsin-Madison. His group is interested in developing new synthetic methods, medicinal chemistry and chemical biology.

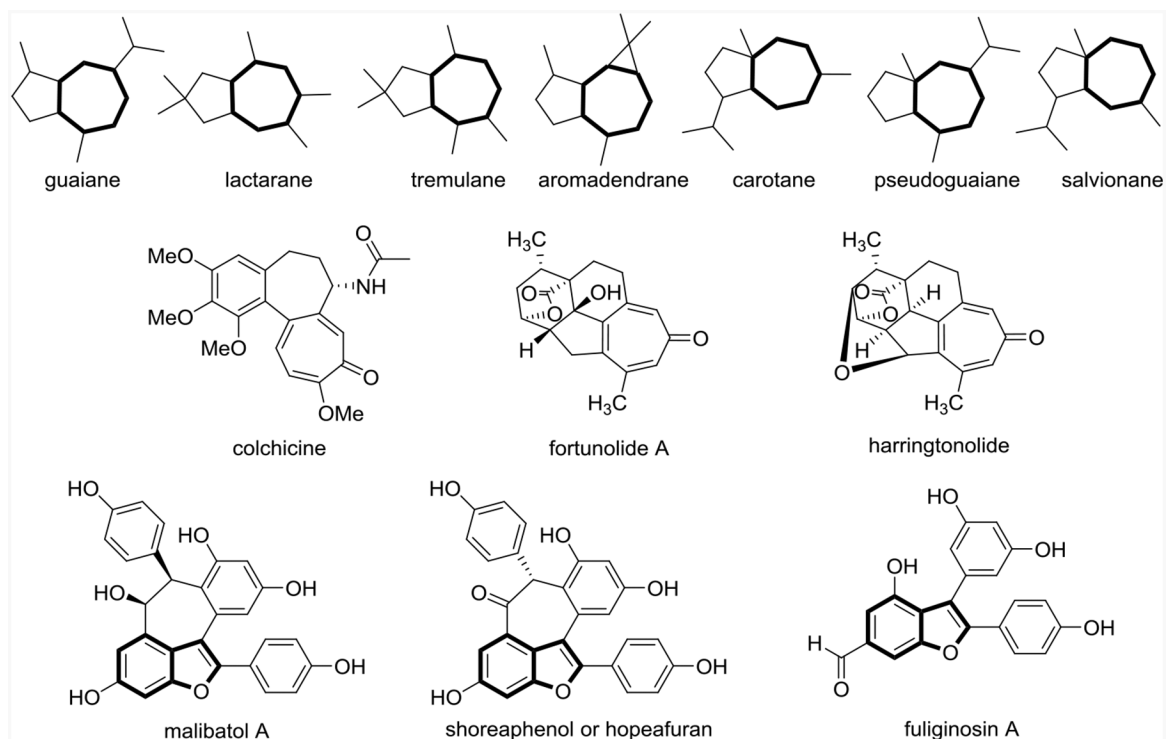
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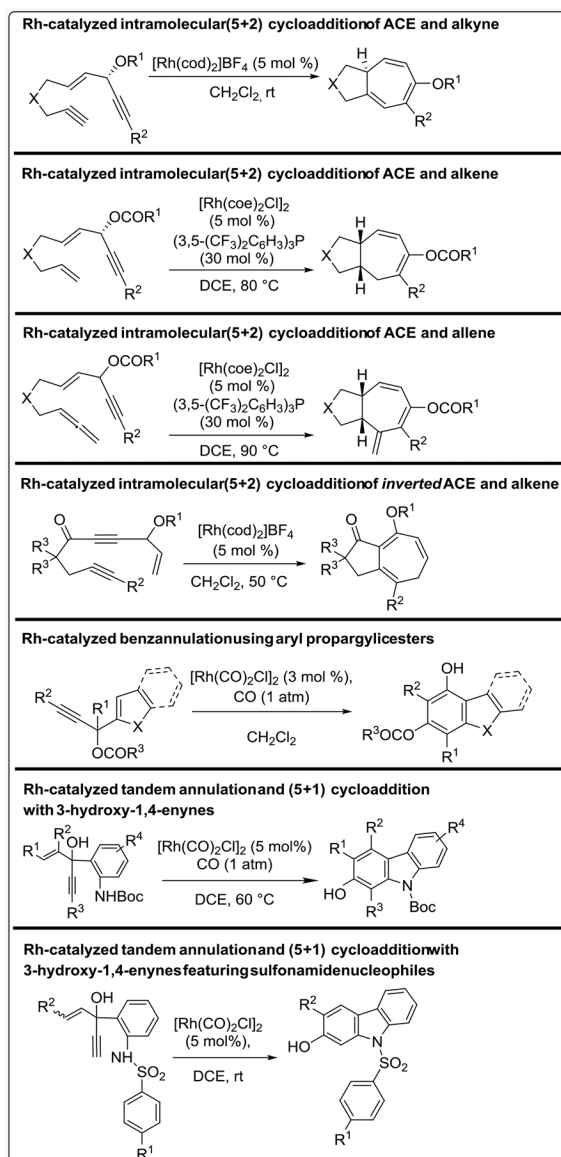
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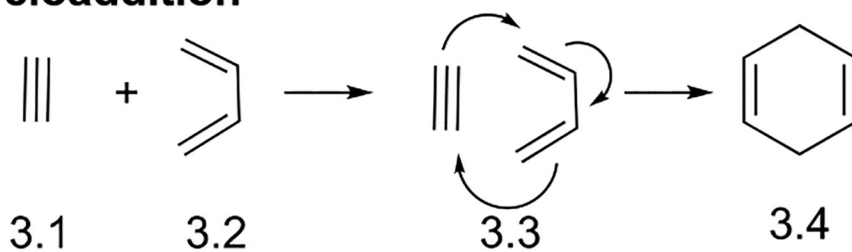
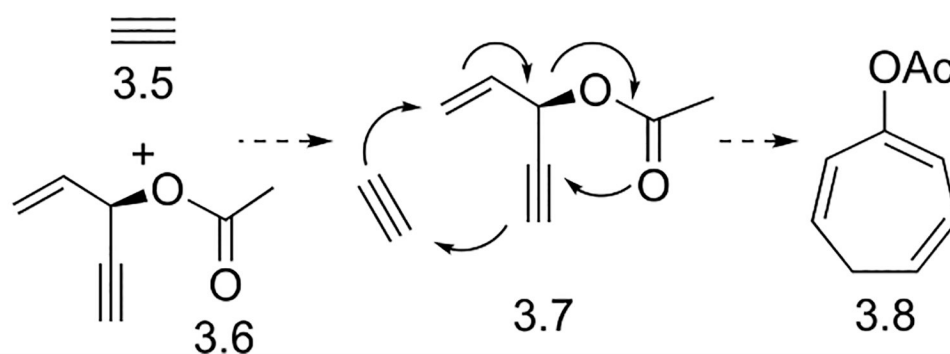
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**Scheme 1:**

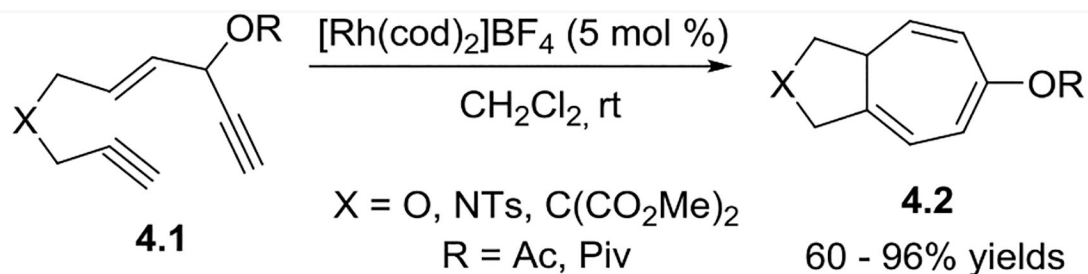
Selected 5–7 fused bicyclic skeletons in sesquiterpenoids and natural products featuring six- and seven-membered rings related to this Account



Scheme 2:
Summary of $(5+n)$ cycloadditions featured in this Account

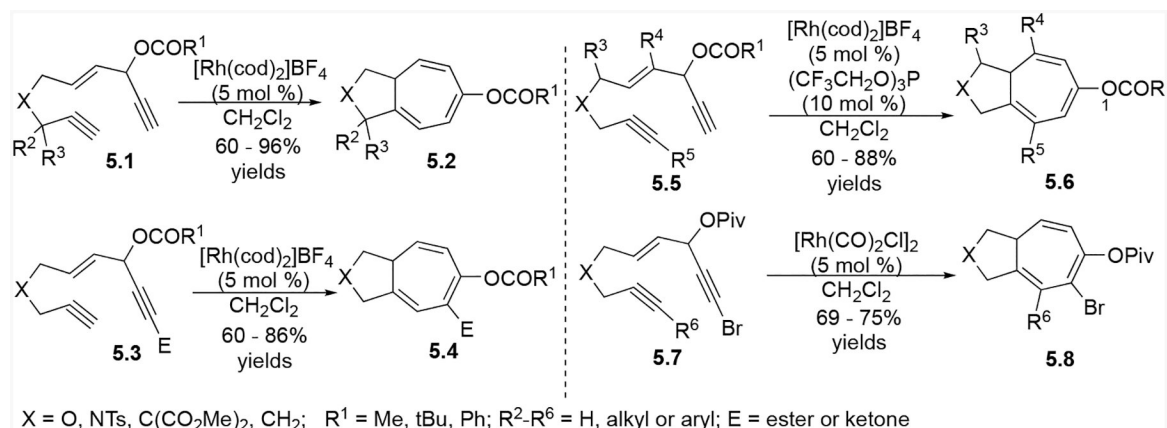
(4+2) cycloaddition**(5+2) cycloaddition**

Scheme 3:
Diels-Alder (4+2) cycloaddition and proposed (5+2) cycloaddition

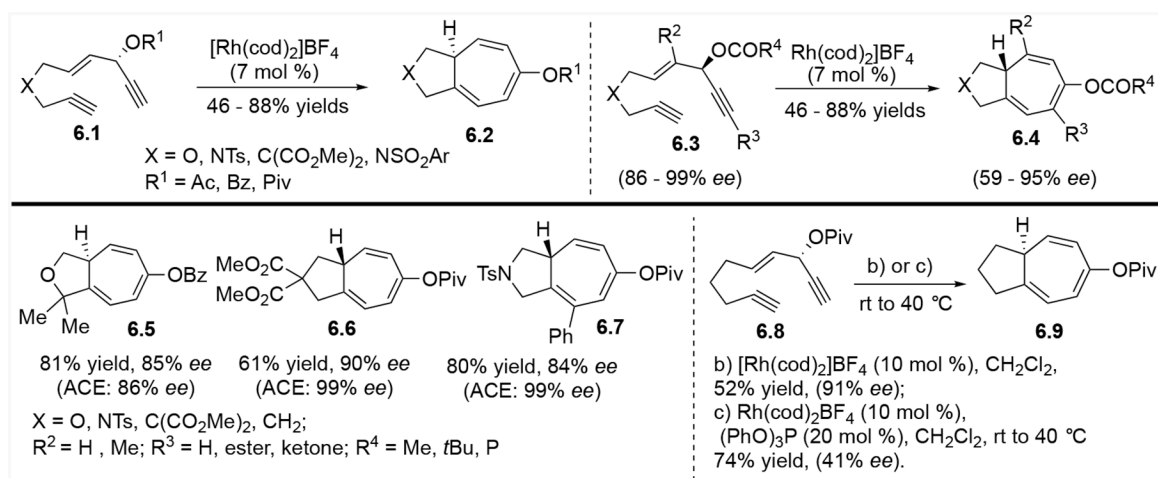


Substrate	Product	Yield (%)
		90
		96
		75
		80

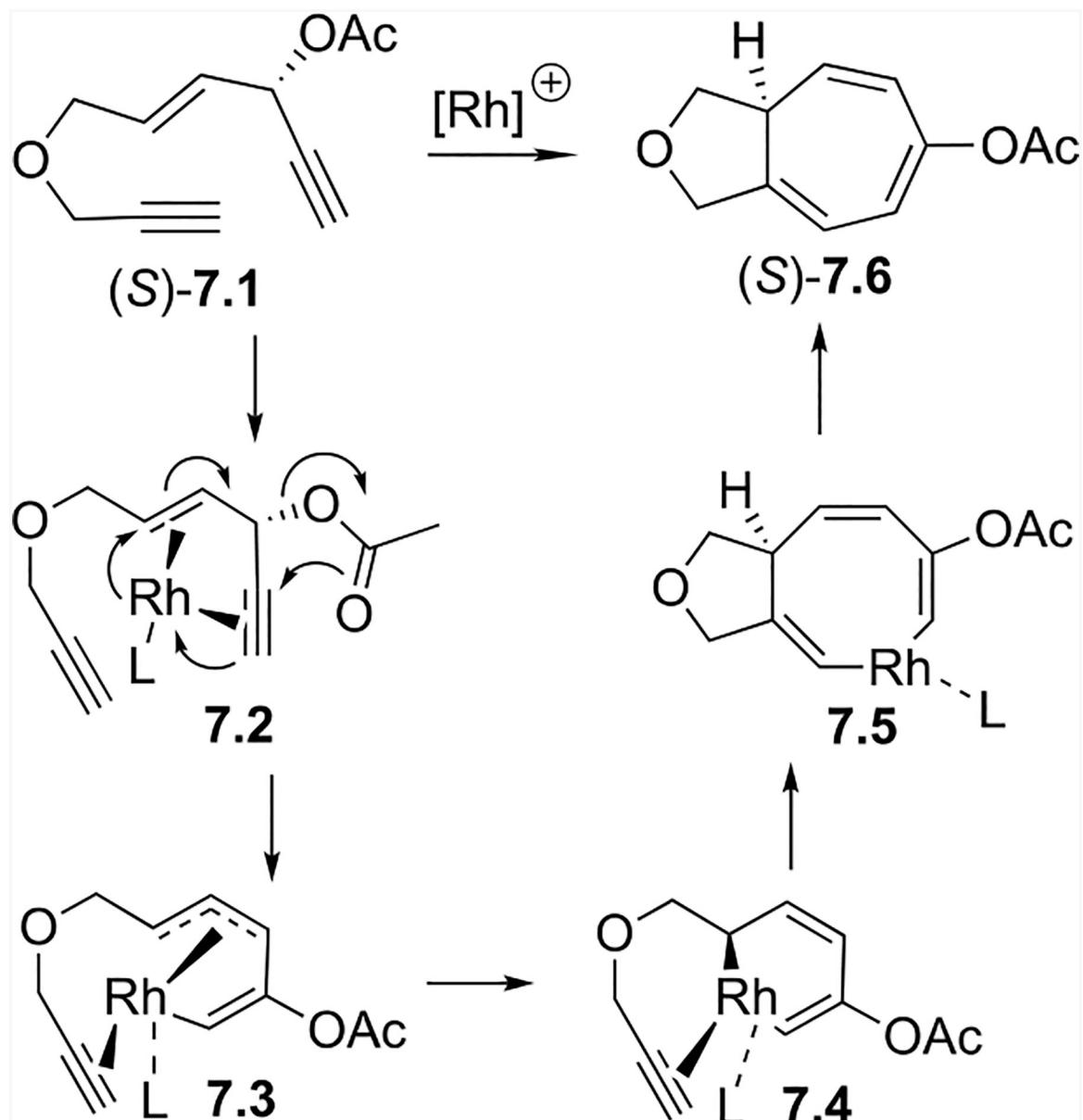
Scheme 4:
 Rh-catalyzed intramolecular (5+2) cycloaddition of ACE and alkyne

**Scheme 5:**

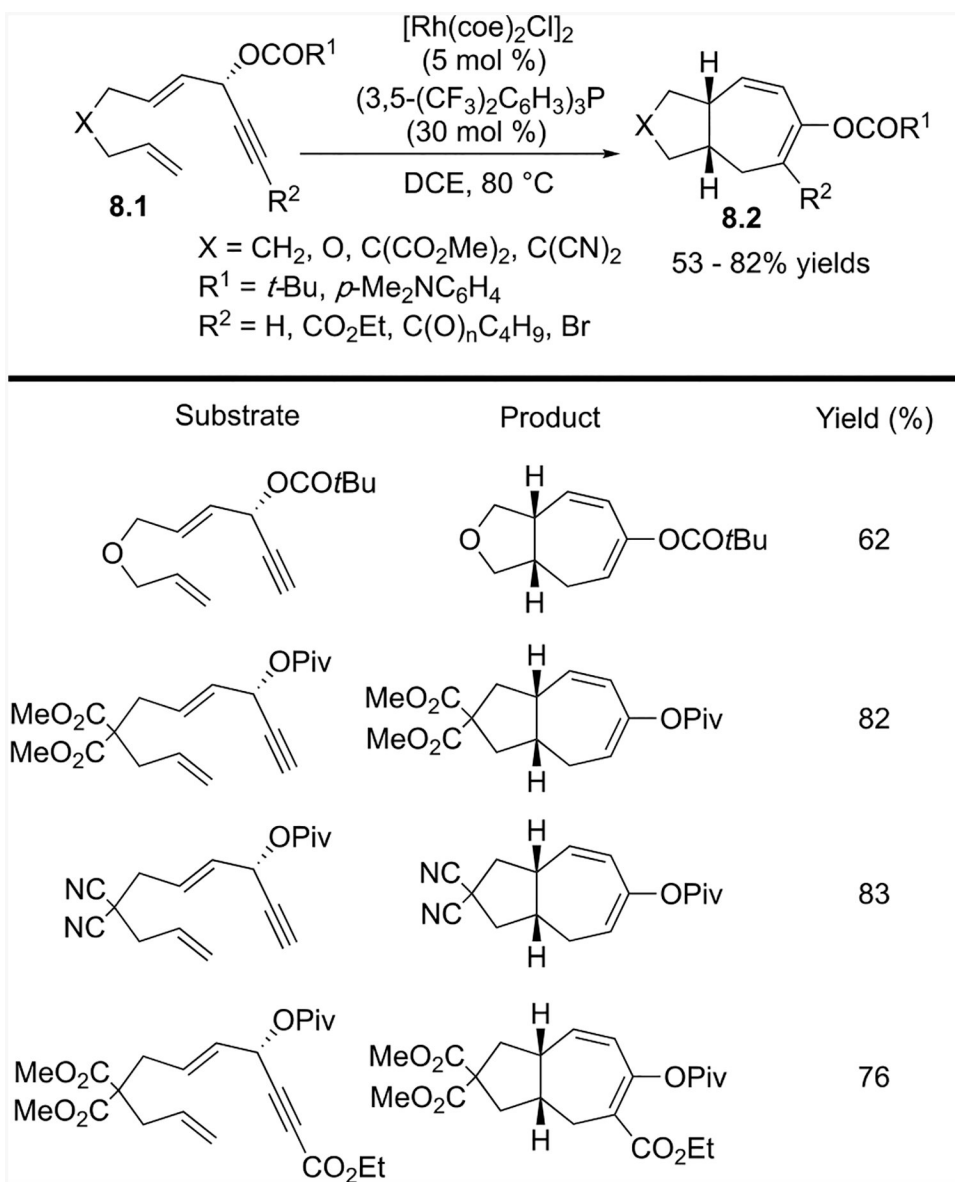
Substrate scope and reaction conditions intramolecular (5+2) cycloaddition between ACEs and tethered alkynes

**Scheme 6:**

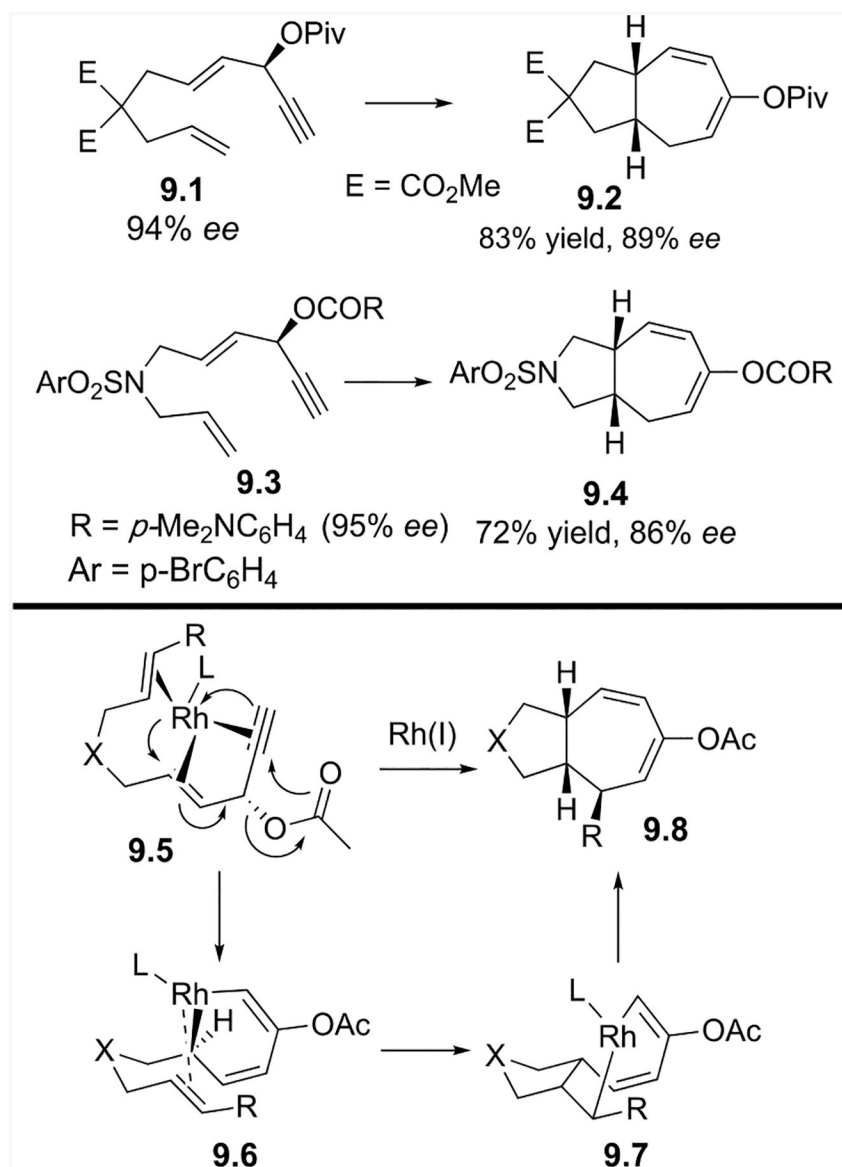
Transfer of chirality in the intramolecular (5+2) cycloaddition



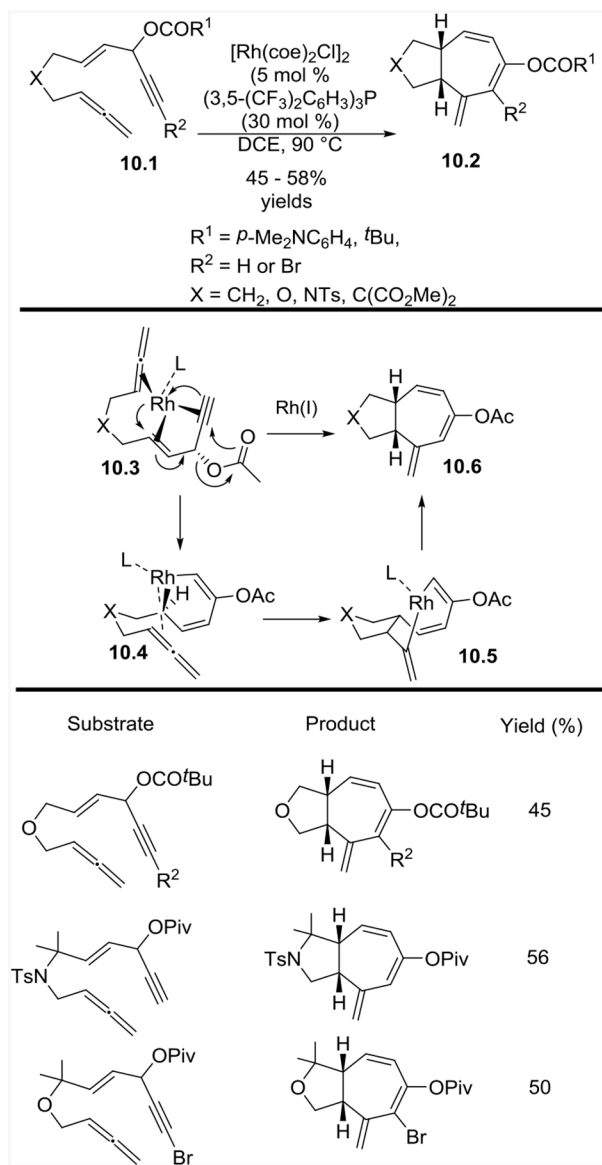
Scheme 7:
Proposed mechanism for chirality transfer in the intramolecular (5+2) cycloaddition



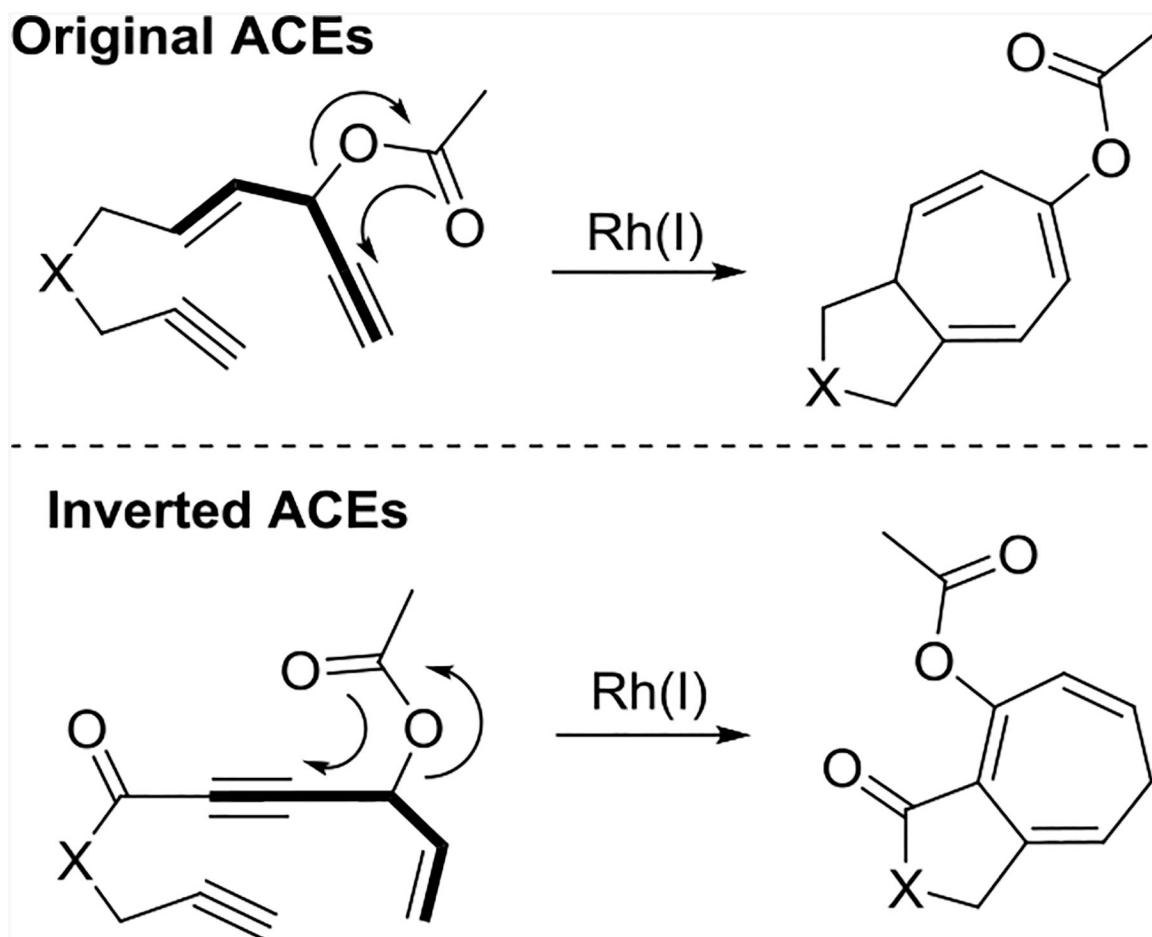
Scheme 8:
Intramolecular (5+2) cycloadditions with alkenes



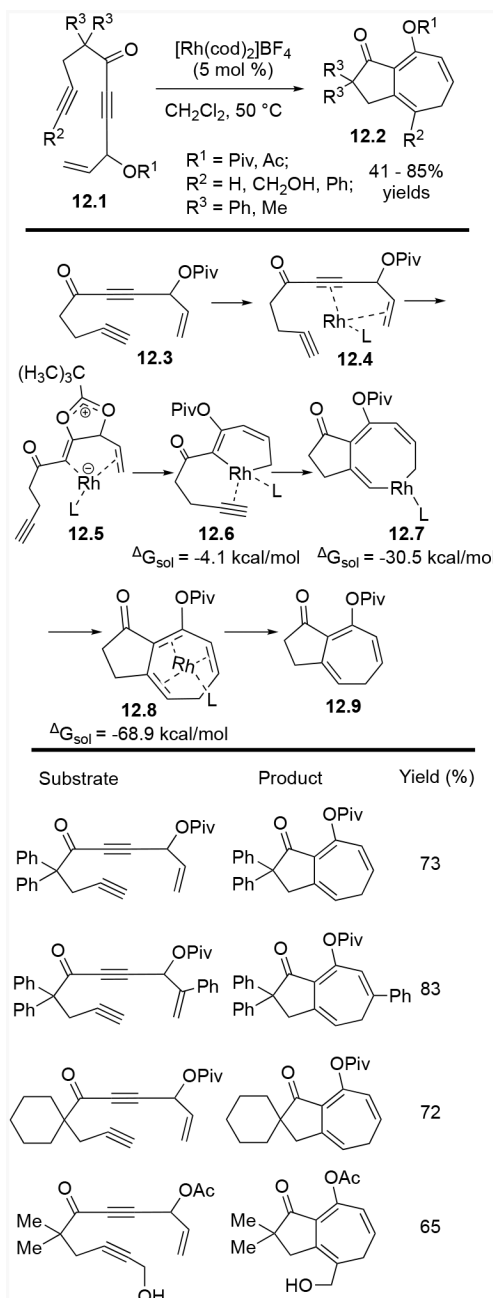
Scheme 9:
Chirality transfer in the intramolecular (5+2) cycloadditions with alkenes



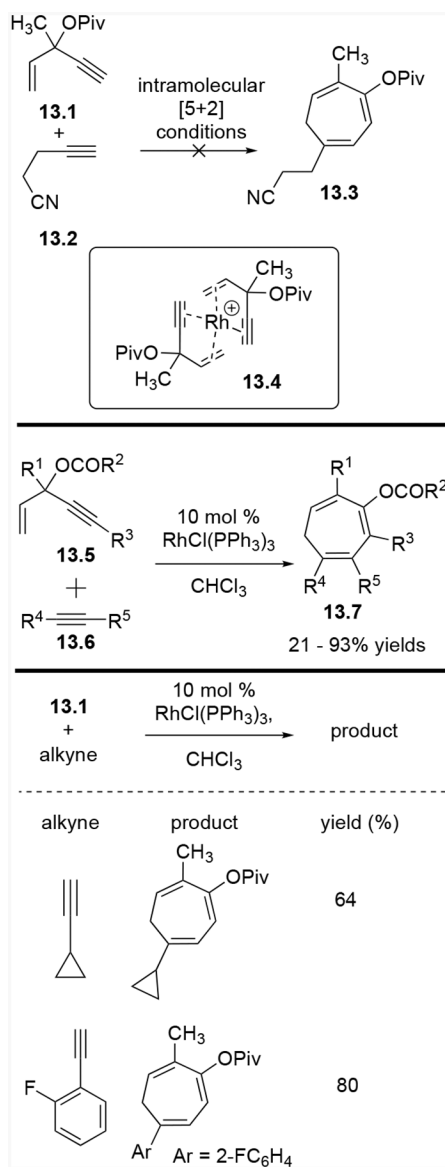
Scheme 10:
Intramolecular (5+2) cycloadditions with allenes



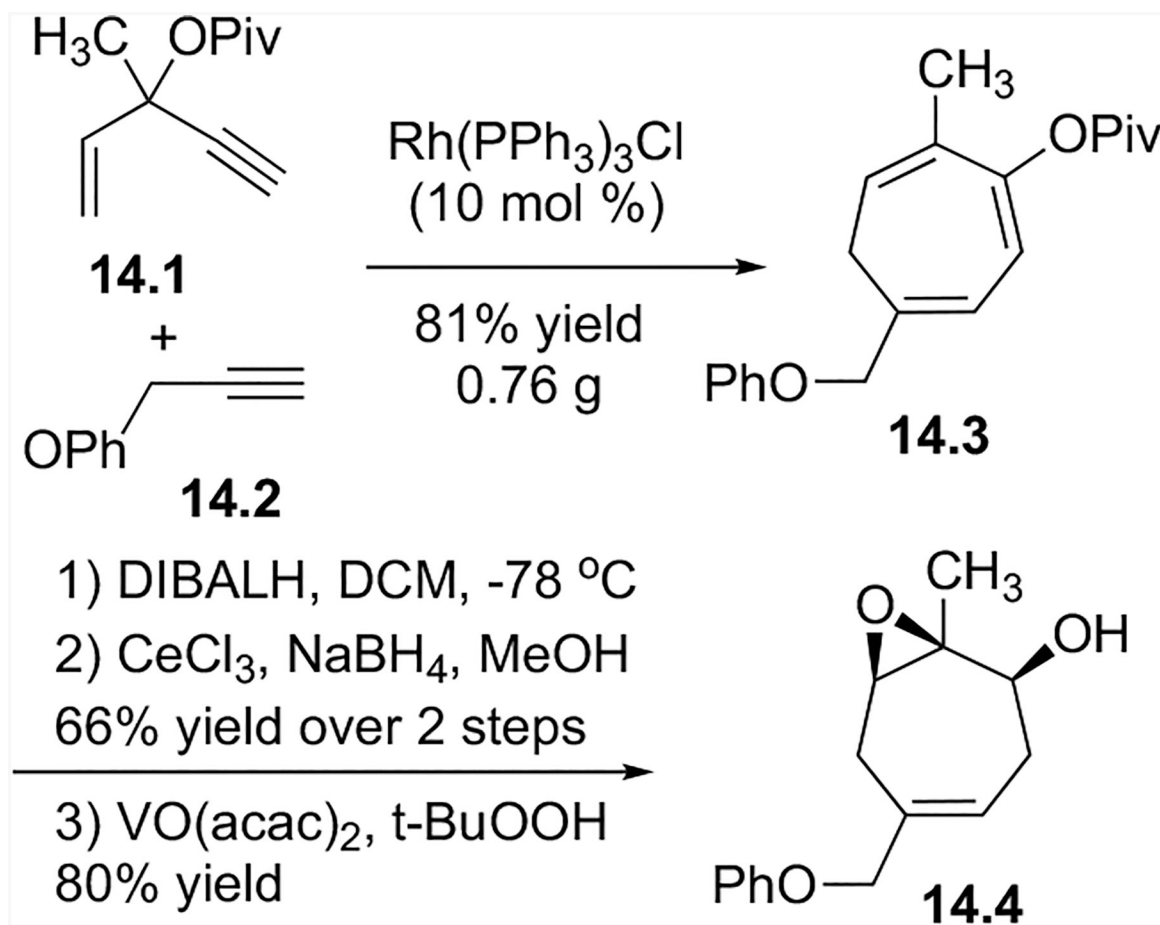
Scheme 11:
Original ACEs compared with inverted ACEs



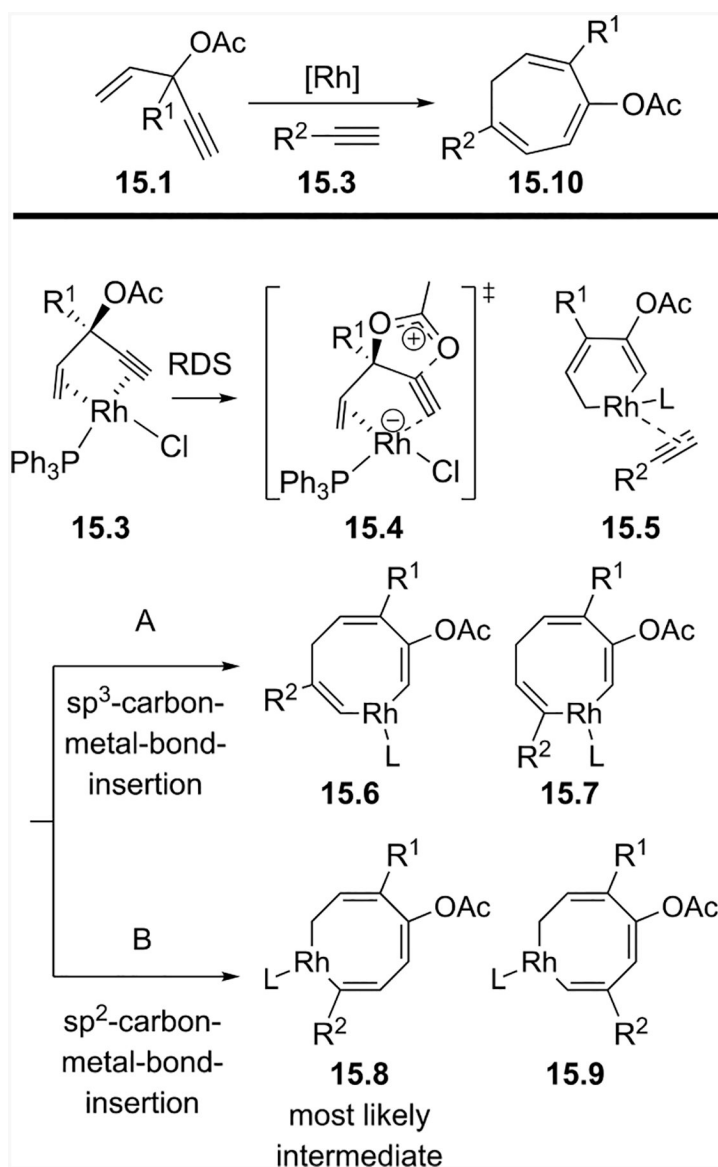
Scheme 12:
Intramolecular (5+2) cycloaddition with inverted ACEs



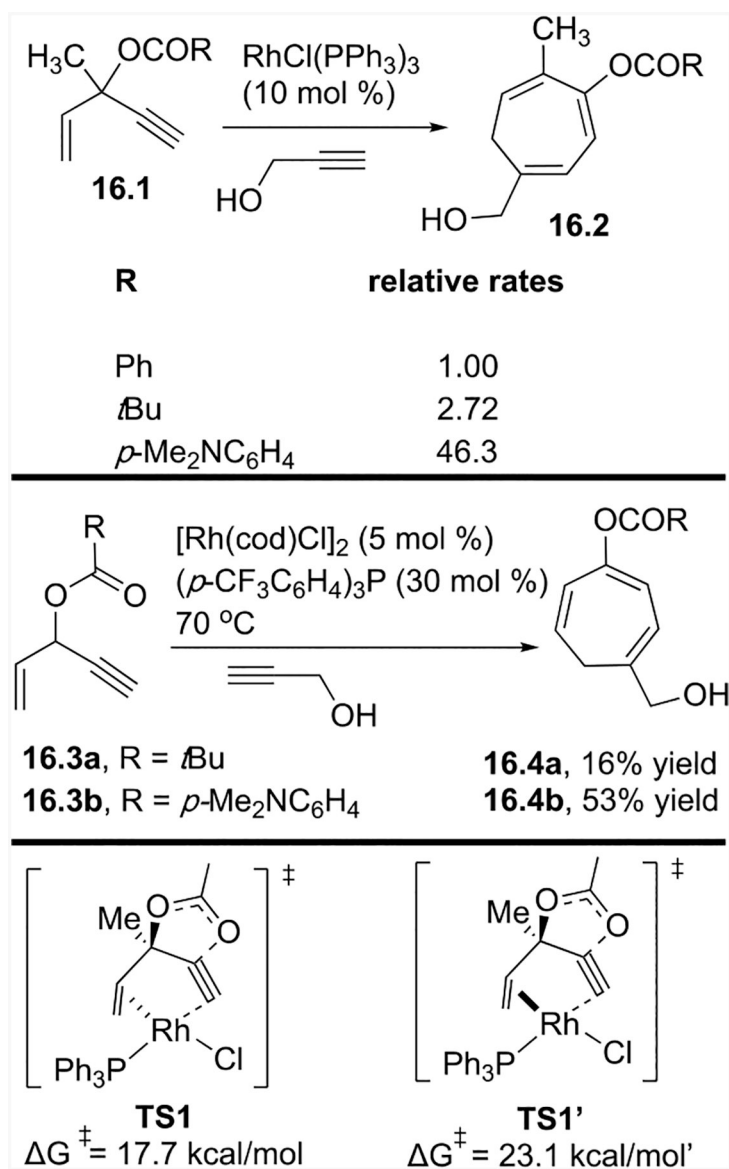
Scheme 13:
Scope for Rh-catalyzed intermolecular (5+2) cycloaddition of an ACE and an alkyne

**Scheme 14:**

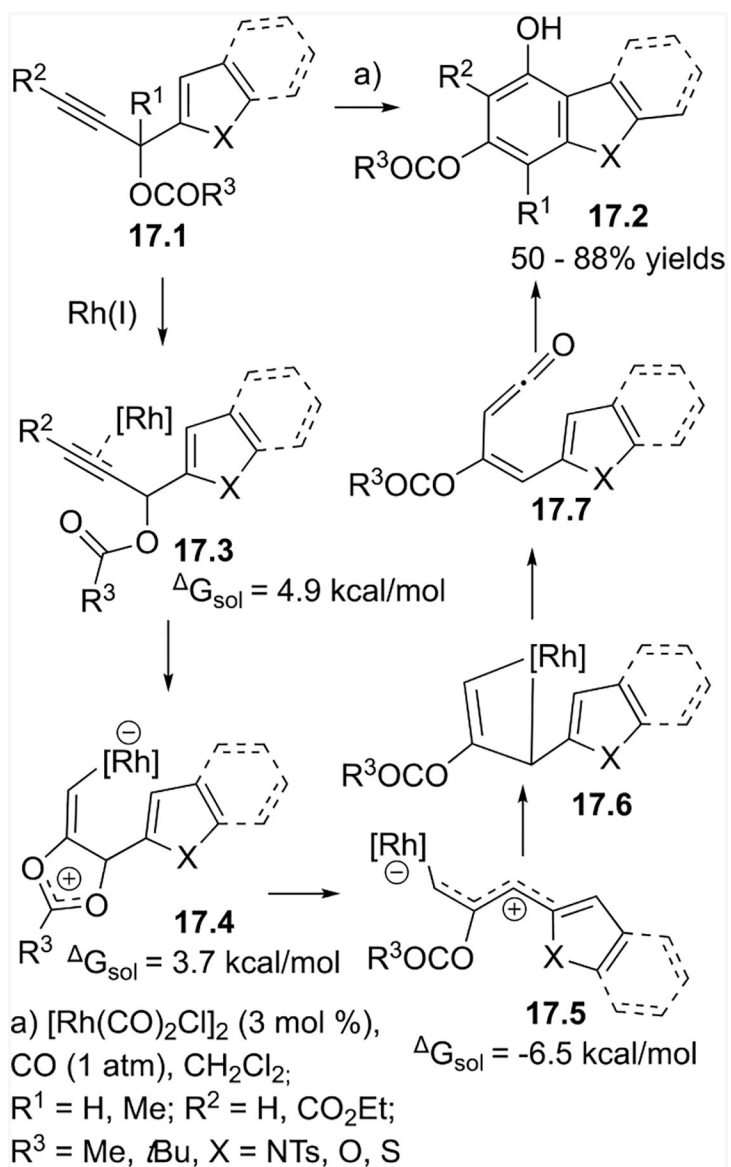
Scale-up and functionalization potential of intermolecular (5+2) cycloaddition product



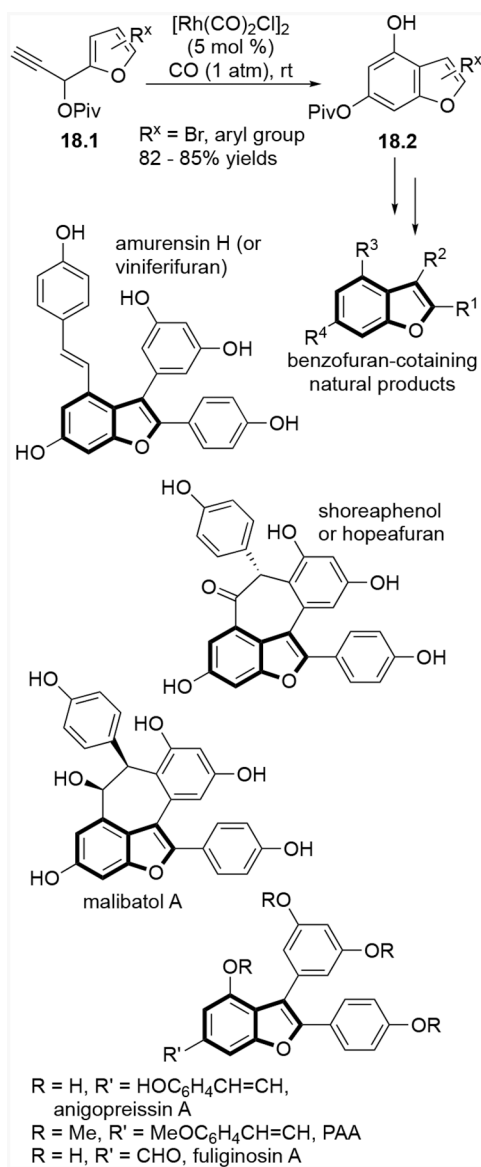
Scheme 15:
Mechanism of the intermolecular (5+2) cycloaddition



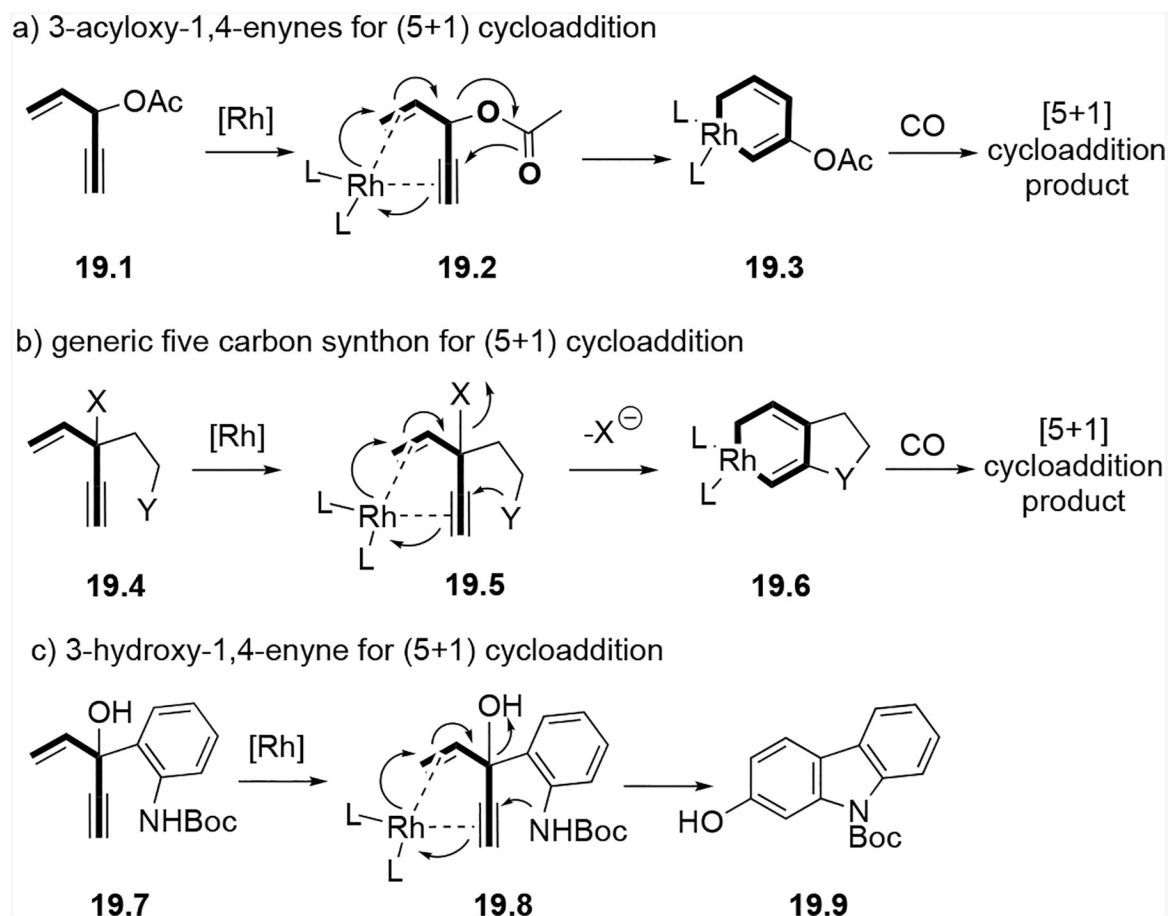
Scheme 16:
Effect of esters on the rate of Rh-catalyzed intermolecular (5+2) cycloadditions



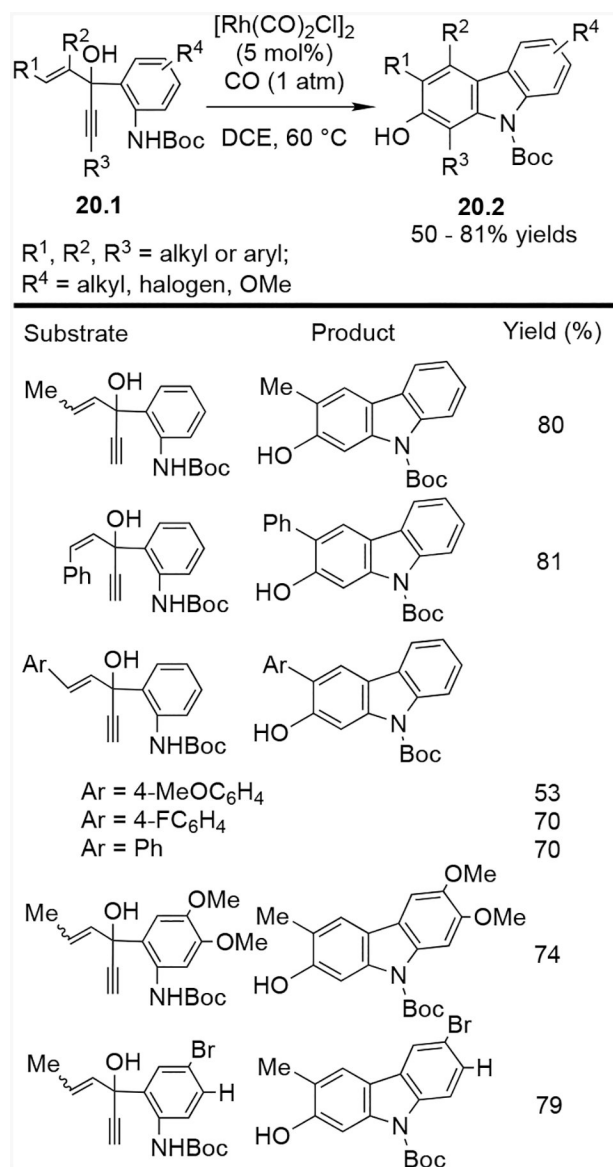
Scheme 17:
Benzannulation of propargylic esters and heteroaryl propargylic esters



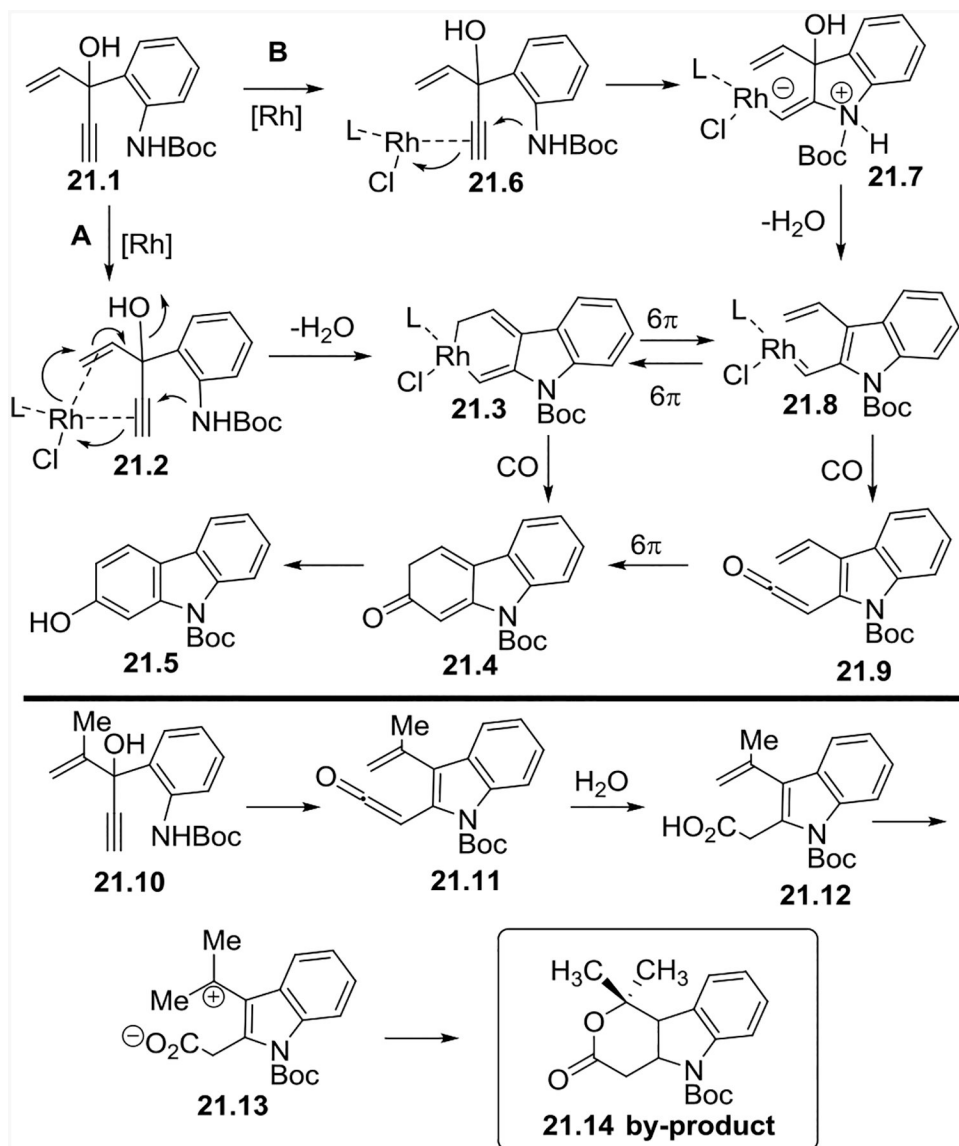
Scheme 18:
Selected benzofuran-containing natural products synthesized

**Scheme 19:**

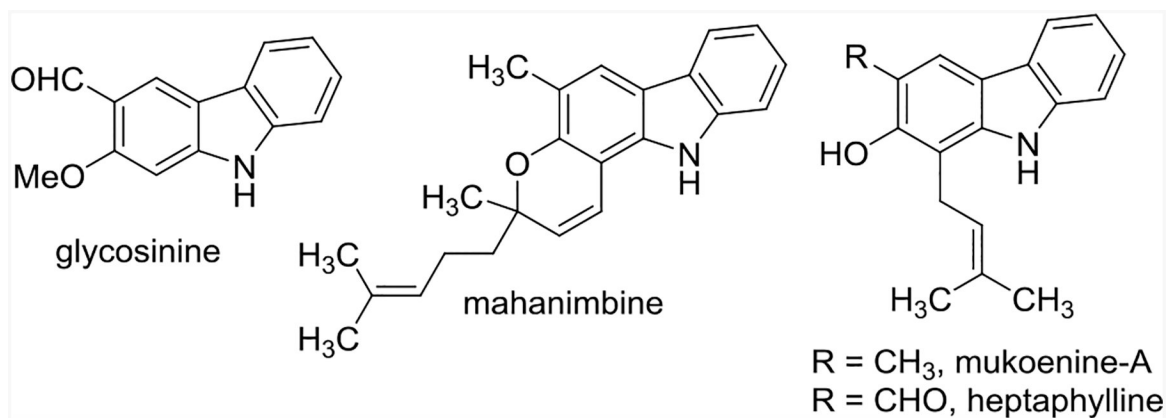
Comparison of five-carbon synthons developed for (5+1) cycloadditions



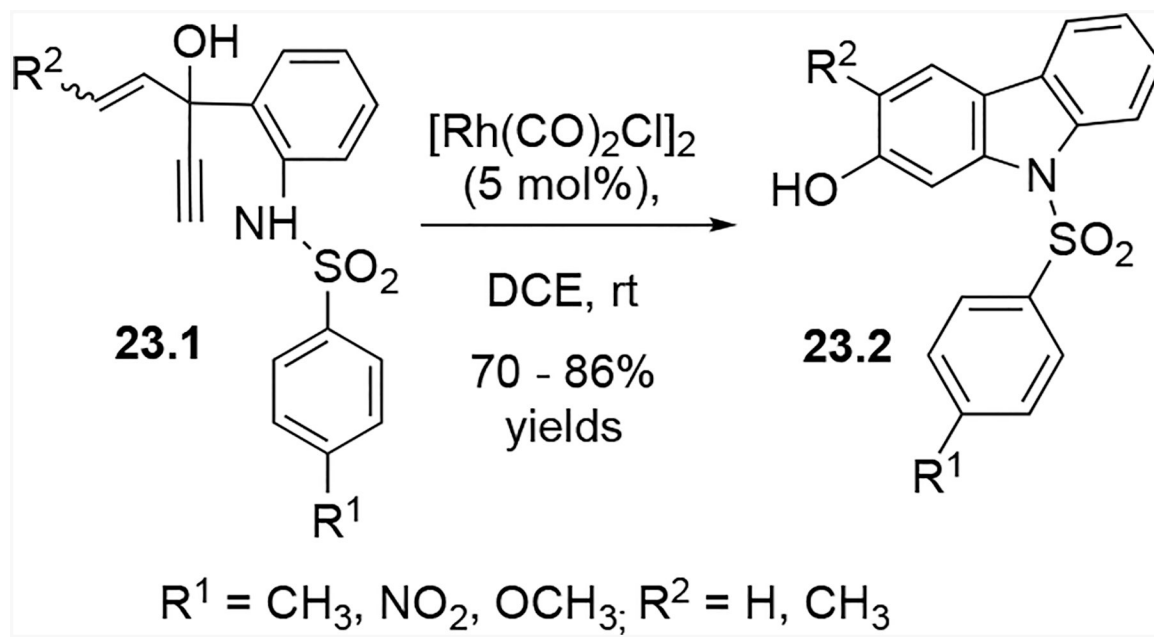
Scheme 20:
 Scope of 3-hydroxy-1,4-enynes (HYEs) for the synthesis of polycyclic ring systems



Scheme 21:
Proposed reaction mechanisms for the tandem annulation (5+1) cycloaddition with HYE and CO



Scheme 22:
Natural products with carbazole cores synthesized via tandem annulation (5+1)
cycloadditions



Scheme 23:
HYEs with sulfonamide nucleophiles

