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**Conference paper**

Casi M. Schienebeck, Xiaoxun Li, Xing-zhong Shu and Weiping Tang*

# 3-Acyloxy-1,4-enyne: A new five-carbon synthon for rhodium-catalyzed [5 + 2] cycloadditions[1]

**Abstract:** Seven-membered rings are ubiquitous in natural products and pharmaceutical agents, and their syntheses continue to stimulate the development of novel synthetic methods. The [5 + 2] cycloaddition is one of the most efficient ways to access seven-membered rings since the two-carbon components (alkenes, alkynes, or allenes) are readily available. Prior to our study, however, there was only one type of transition-metal-catalyzed [5 + 2] cycloaddition: the reaction between vinylcyclopropanes and alkenes, alkynes, or allenes. We recently developed a new type of transition-metal-catalyzed [5 + 2] cycloaddition, where the five-carbon building block is 3-acyloxy-1,4-enyne (ACE). Our recent progress on Rh-catalyzed intra- and intermolecular [5 + 2] cycloadditions of ACEs and alkynes is summarized in this article. Using chiral propargylic esters, bicyclic products were prepared in high optical purity by the intramolecular [5 + 2] cycloadditions. Monocyclic seven-membered rings were synthesized by intermolecular [5 + 2] cycloaddition of ACEs and alkynes. Kinetic studies indicated that the rate of this intermolecular cycloaddition was significantly accelerated when the acetate was replaced by dimethylaminobenzoate. DFT calculations suggested that novel metallacycles were generated by a Rh-promoted oxidative cycloaddition of 1,4-enynes accompanied by a 1,2-acyloxy migration of propargylic esters.

**Keywords:** carbenes; cycloadditions; OMCOS-17; rhodium catalysis.

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***Corresponding author: Weiping Tang,** School of Pharmacy and Department of Chemistry, University of Wisconsin, Madison, WI 53705, USA, e-mail: wtang@pharmacy.wisc.edu

**Casi M. Schienebeck, Xiaoxun Li and Xing-zhong Shu:** School of Pharmacy and Department of Chemistry, University of Wisconsin, Madison, WI 53705, USA

## Introduction

Formation of five- and six-membered rings via cycloaddition reactions has been well documented; however, the development of similar reactions for the formation of seven-membered rings lagged far behind [1]. This is not a result of the potential and utility of seven-membered rings; cycloheptanes and cyclopentenes are prevalent in many natural products and important biologically active molecules so, consequently, interest in these structures has been increasing recently [2]. For example, the five to seven fused bicyclic skeletons are present in at least seven families of sesquiterpenoids shown in Fig. 1 [3].

There are three different types of two-component cycloadditions that can produce seven-membered rings [4 + 3], [4] [5 + 2], [5] and [6 + 1] [6]. The first two cycloadditions are much more general because various two- and four-carbon synthons are readily available and the one-carbon synthons are limited to carbon monoxide. The discovery of new three- and five-carbon synthons are highly desirable and would lead to the development of a series of novel cycloaddition reactions for the synthesis of functionalized seven-membered rings. This is best illustrated by the transition-metal-catalyzed [5 + 2] cycloadditions of vinylcyclopropane (VCP) with alkynes, alkenes, and allenes (Scheme 1). In all thermal [5 + 2] cycloadditions, the five-carbon building blocks need to be locked in a six-membered ring (e.g., oxidopyrylium ion) [5]. Thermal [5 + 2] cycloadditions then

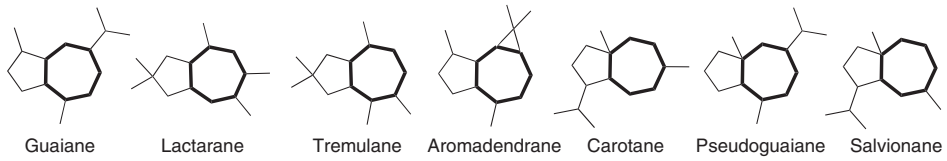
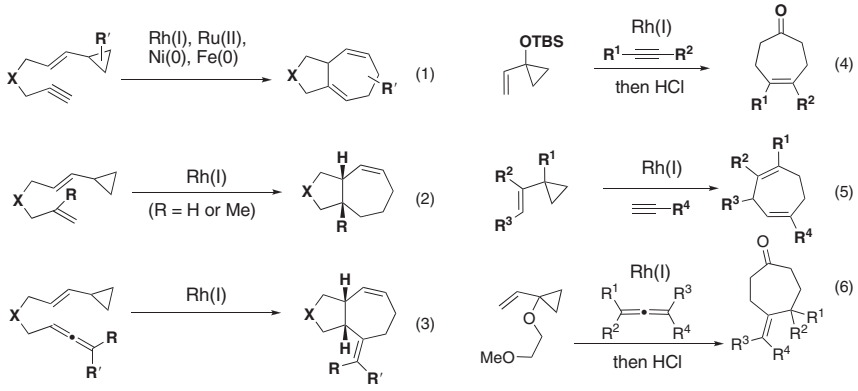



**Fig. 1** Selected sesquiterpenoid families with five to seven fused bicyclic skeletons.

lead to the formation of seven-membered rings with an extra bridge, which is often not necessary. Transition-metal-catalyzed [5 + 2] cycloadditions using VCP as the five-carbon synthon do not have this limitation. Prior to our study, however, VCP had been the only five-carbon synthon developed for transition-metal-catalyzed intra- and intermolecular [5 + 2] cycloadditions.

In 1995 Wender and his co-workers reported the first transition-metal-catalyzed [5 + 2] cycloaddition between VCP and a tethered alkyne as shown in eq. 1 (Scheme 1) [7]. The regio- and stereoselectivity were examined later with substituted cyclopropanes [8]. Shortly after, research groups of Trost [9], Louie [10], and Fürstner [11] discovered that Ru-, Ni-, and Fe-based catalysts could also promote this cycloaddition. The intramolecular [5 + 2] cycloaddition of VCP with alkenes shown in eq. 2 [12] is a much more challenging and also complex process since the alkene is less reactive than alkyne and diastereoselectivity also becomes an issue. It was found that *cis*-fused five to seven bicyclic compounds were observed as the only isomer. After the addition of CO, a two-component [5 + 2 + 1] was realized for the synthesis of five to eight fused bicyclic products [13]. The intramolecular [5 + 2] cycloaddition of VCP with an allene shown in eq. 3 [14] was also realized. The endo/exo selectivity and chirality transfer were examined for this reaction. Enantioselective intramolecular [5 + 2] cycloadditions of VCP and alkyne or alkene were realized using chiral BINAP [15] or phosphoramidite ligands [16].

It was generally much more difficult to realize intermolecular cycloadditions than the intramolecular counterparts because of potential reactivity, regio- and chemoselectivity issues after removing the tether between the two reactants. On the other hand, intermolecular cycloadditions are much more versatile as both reactants are easier to access. Rh-catalyzed intermolecular cycloadditions of activated VCP [17] and unactivated VCP [18] with alkynes were both developed as shown in eqs. 4 and 5, respectively. These two reactions provided easy access to diverse cycloheptenones and cycloheptadienes. By coupling with [4 + 2] cycloaddition [19] and Nazarov cyclization [20], more complex polycyclic products were prepared conveniently. Both three-component [5 + 2 + 1] [21] and four-component [5 + 1 + 2 + 1] [22] cycloadditions were also developed using VCP, alkyne, and CO as the starting materials. Intermolecular [5 + 2] cycloaddition of VCP with allene shown in eq. 6 was only realized with activated VCP [23].




**Scheme 1** Vinylcyclopropane (VCP) as the five-carbon component for [5 + 2] cycloadditions.

The synthetic utility of [5 + 2] cycloadditions of VCPs has been highlighted by their applications in natural product synthesis [24]. Extensive computational studies have also been conducted to understand the detailed mechanism of this type of cycloadditions [25].

Recently, Yu found that the position of the alkene and cyclopropane could be switched and either [5 + 2] or [3 + 2] cycloaddition could be realized depending on the structure of the substrates [26]. Murai extended the five-carbon component to allenylcyclopropanes for the preparation of 6-7 fused bicyclic compounds [27]. Hetero-[5 + 2] cycloadditions were also reported by Wender [28] and Zhang [29] using cyclopropyl imine and vinyl epoxide as the five-atom component, respectively.

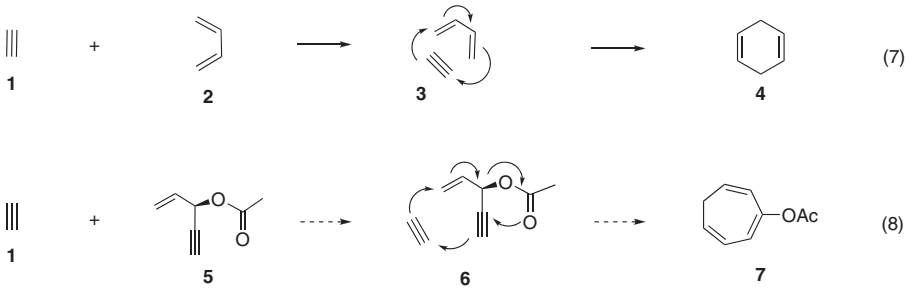
The initial discovery of VCP as a five-carbon component for [5 + 2] cycloadditions in 1995 has led to the development of many new metal catalysts and the realization of dozens of new reactions. In the next section, we will summarize our recent discovery on using 3-acyloxy-1,4-enyne (ACE) as the new five-carbon synthon for Rh-catalyzed intra- and intermolecular [5 + 2] cycloadditions. These new [5 + 2] cycloadditions complement existing methods for the synthesis of functionalized seven-membered rings. During our studies, a Rh-catalyzed [5 + 1] cycloaddition of ACE with CO was reported for the synthesis of substituted phenols [30].

## Results and discussion

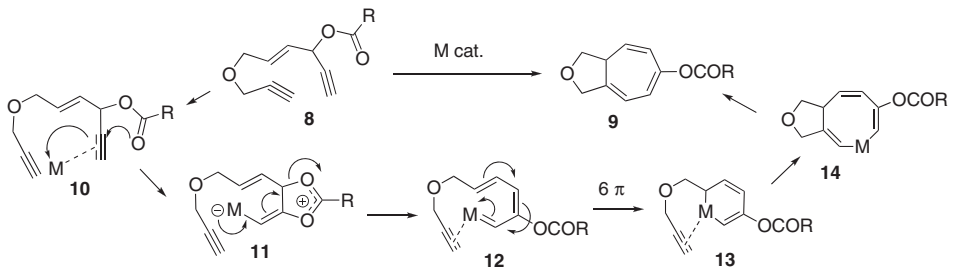
Based on the Diels–Alder [4 + 2] cycloaddition of alkyne **1** and diene **2** in eq. 7, we envisioned that a homo-Diels–Alder cycloaddition illustrated in eq. 8 might be possible (Scheme 2). The ester group between alkene and alkyne served as a mediator to link the unconjugated 1,4-enyne in ACE **5** through a 1,2-acyloxy migration for the [5 + 2] cycloaddition. Both reactions in eqs. 7 and 8 involve the cleavage of two C–C π-bonds and the formation of two C–C σ-bonds. The [5 + 2] cycloaddition in eq. 8 should be even more thermodynamically favored than Diels–Alder cycloaddition in eq. 7 because the former yields a conjugated triene while the latter involves the cleavage of a conjugated diene. Simply heating the mixtures of various alkynes and ACEs did not lead to any product. A catalyst such as transition metal is necessary for the proposed transformation.

### Intramolecular [5 + 2] cycloaddition of ACE and alkyne

In 1984, Rautenstrauch discovered that 3-acyloxy1,4-enynes underwent cycloisomerization to form cyclopentadienes in the presence of palladium or platinum catalysts [31]. A metal-mediated 1,2-acyloxy migration of propargylic ester was proposed. Various reactions involving 1,2-acyloxy migration of propargylic esters were developed recently using gold, platinum, and copper as the catalysts [32]. Inspired by these studies, we proposed a transition-metal-catalyzed [5 + 2] cycloaddition of ACE with a tethered alkyne as shown in Scheme 3 [33]. The first half of the mechanism (from intermediate **10** to **13**) was essentially the same as what Rautenstrauch proposed nearly 30 years ago [31]. Reductive elimination of **13** yielded the cyclopentadiene products




**Scheme 2** Diels–Alder [4 + 2] and homo-Diels–Alder [5 + 2] cycloadditions.



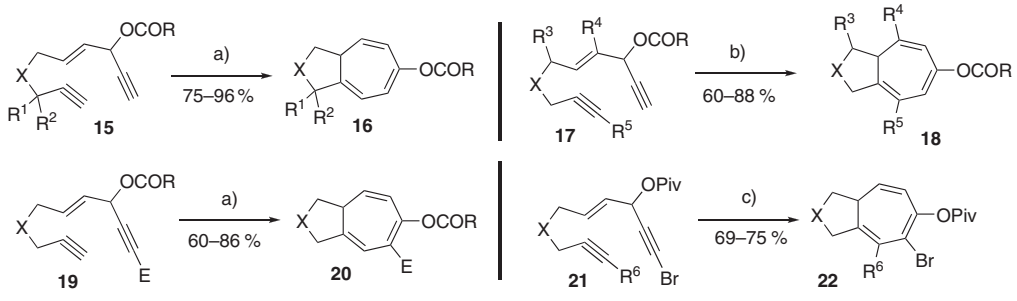

**Scheme 3** Proposed mechanism for a metal-catalyzed intramolecular [5 + 2] cycloaddition of ACE and alkyne.

observed by Rautenstrauch. We imagined that metallacyclohexadiene **13** could be trapped by the tethered alkyne to form metallacyclooctatriene **14**. Reductive elimination would then afford the [5 + 2] cycloaddition product **9** with a conjugated triene. This transformation doesn't come without potential challenges. Competing pathways could include, but are not limited to: 1) 1,6-enyne cycloisomerization prior to the 1,2 acyloxy migration, 2) cyclopropanations involving metal carbene **12**, and 3) Rautenstrauch rearrangement to form cyclopentadiene.

Substrate **8a** (R = *tert*-butyl group) was conveniently prepared from *cis*-2-butene-1,4-diol in four steps. We were delighted to find that enediyne **8a** was transformed to the cycloaddition product **9a** in the presence of most Rh(I) metal complexes [33]. In contrast, gold and platinum catalysts did not yield any seven-membered ring product. Cationic rhodium catalyst ($[Rh(COD)_2]BF_4$) afforded the highest isolated yield (85 %). This condition proved to be sufficient for a wide range of substrates (**15**, Scheme 4). Oxygen, nitrogen, or malonate linkers could be tolerated. Substrates with different ester groups on the ACE also worked well. Alkyl or aryl substituents could be introduced to the carbon adjacent to the tethered alkyne in **15**.

When the two-carbon component was an internal alkyne, only a trace amount of desired cycloaddition products was observed using cationic rhodium alone. The addition of an electron-poor phosphite ligand dramatically improved the yields for substrates with an internal tethered alkyne, all methylene carbon linkers, substitutions adjacent to the olefin, or trisubstituted olefins (**17**, Scheme 4). For tertiary esters, both conditions gave complex mixtures. Tethers of six atoms or longer gave no desired product under either condition a or b.

When an internal alkyne on the ACE was tested, we expected to see little of the desired product, since propargylic esters with an internal alkyne tend to undergo 1,3-acyloxy migration to generate a vinylallene intermediate [32]. Indeed, no seven-membered ring product was obtained after screening various metal catalysts [34]. The preference of the propargylic ester to undergo a 1,2 vs. 1,3 acyloxy migration is dependent on the nature of the substrate as well as the nature of the catalyst [32]. It is known that propargylic esters




a) $[Rh(COD)_2]BF_4$ (5 mol%); b) $[Rh(COD)_2]BF_4$ (5 mol%), $(CF_3CH_2O)_3P$ (10 mol%); c) $[Rh(CO)_2Cl]_2$ (5 mol%);
X = O, NTs, $C(CO_2Me)_2$, $CH_2$; R = Me, *t*Bu, Ph; $R^1$- $R^6$ = H, alkyl or aryl; E = ester or ketone

**Scheme 4** Scope and conditions for Rh-catalyzed intramolecular [5 + 2] cycloaddition of ACE and alkyne.

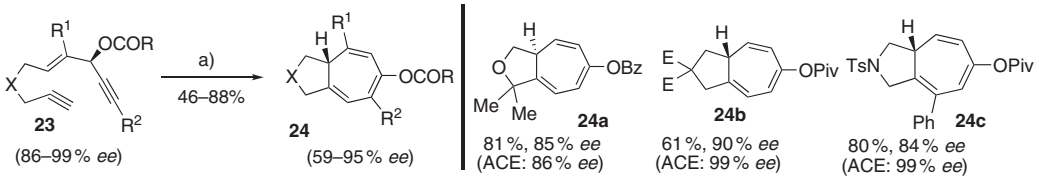
with an electron-deficient alkyne preferentially undergo 1,2-acyloxy migration in gold-catalyzed reactions [35]. Indeed, ACE **19** with an ester or ketone group at the terminal position of the alkyne underwent [5 + 2] cycloaddition with the tethered alkyne smoothly to yield bicyclic product **20** upon treatment of cationic Rh(I) catalyst.

Propargylic esters with a halo-alkyne also underwent 1,2-acyloxy migration in the presence of gold catalysts [36]. In the presence of the cationic Rh(I) catalyst (conditions a), however, a complex mixture was obtained for **21**. After screening different rhodium catalysts, we found that the desired cycloaddition product **22** was isolated in 69–75 % yields using $[Rh(CO)_2Cl]_2$ catalyst.

The Rh-catalyzed intramolecular [5 + 2] cycloaddition of ACE and alkyne is also enantiospecific (Scheme 5) [37]. Based on the absolute stereochemistry of the propargylic ester starting material and the bicyclic product, which was determined by X-ray diffraction, the Rh-catalyst should approach the ACE from the face opposite to the acyloxy group. The efficiency of the chirality transfer varies for different substrates. For example, the efficiency of the chirality transfer was nearly perfect for product **24a** and around 9–15 % *ee*s were lost for products **24b** and **24c**.

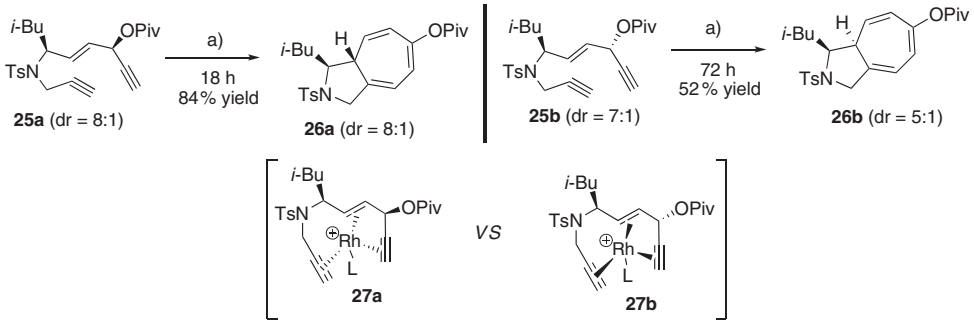
During our investigation, we also found that the efficiency of the chirality transfer was highly dependent on the ligand. Tris(pentafluorophenyl) phosphine ligand usually did not make any difference. Slightly lower *ees* were observed for triphenylphosphine ligands. Phosphite ligands decreased the efficiency of the chirality transfer significantly for most substrates. However, the addition of phosphite ligand was necessary for substrates bearing an internal alkyne as the two-carbon component [33]. We were pleased to find that a synthetically useful 84 % *ee* could be obtained for product **24c**, which required the phosphite ligand. Racemic products were also obtained for certain substrates after the addition of electron-poor phosphine ligands. This suggests that a dynamic kinetic asymmetric transformation of both enantiomers of substrate **23** to product **24** with high *ee* is possible with an appropriate chiral ligand.

A match-mismatched scenario is expected for substrates **25a** and **25b** with two stereogenic centers (Scheme 6) [37]. Indeed, the cycloaddition for **25a** was completed in 18 h with 84 % yield of the desired




a) $[Rh(COD)_2]BF_4$ (7 mol%); b) $Rh(COD)_2BF_4$ (7 mol%), $(CF_3CH_2O)_3P$ (14 mol%).
X = O, NTs, $C(CO_2Me)_2$, $CH_2$; R = Me, *t*Bu, Ph; $R^1$ = H , Me; $R^2$ = H, ester, ketone; E = $CO_2Me$

**Scheme 5** Transfer of chirality for Rh-catalyzed intramolecular [5 + 2] cycloaddition of ACE and alkyne.




Conditions: a) $[Rh(COD)_2]BF_4$ (5 mol%), $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (10 mol%), $CH_2Cl_2$, 50 °C.

**Scheme 6** Rh-catalyzed intramolecular [5 + 2] cycloaddition of ACEs with multiple stereogenic centers.

product without noticeable erosion of the diastereomeric ratio (dr). In contrast, the reaction for **25b** was sluggish and a 52 % yield was obtained after 72 h. The dr for product **26b** dropped to 5:1. These observations are consistent with the model of anti-coordination of Rh(I) complex to ACE. In **27a**, the Rh-metal is on the bottom face of the ACE and far away from the *i*-Bu group. The *i*-Bu group in **27b**, however, may have unfavorable steric interactions with the Rh–L complex on the top face of the ACE during the cycloaddition.

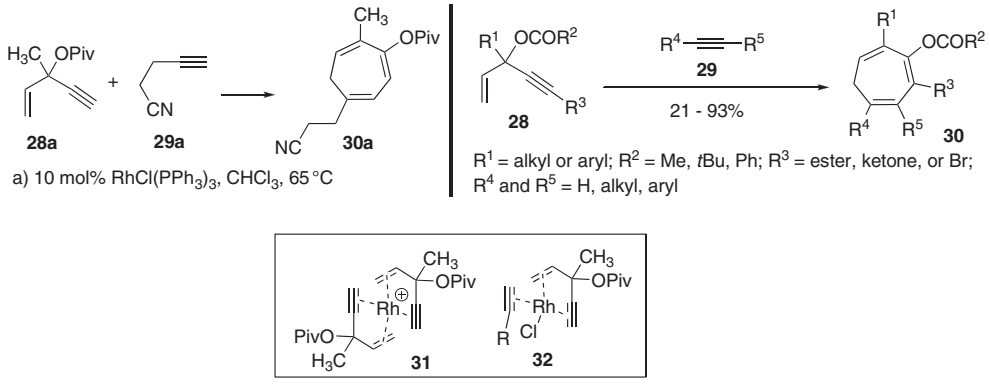
## Intermolecular [5 + 2] cycloaddition of ACE and alkyne

After successfully developing the intramolecular [5 + 2] cycloaddition of ACE and alkynes, we then investigated the more challenging intermolecular version of this reaction (Scheme 7). When we treated the mixture of ACE **28a** and alkyne **29a** with cationic catalyst ($[Rh(COD)_2]BF_4$) in the absence or presence of $(CF_3CH_2O)_3P$ ligand, no desired cycloaddition product **30a** was observed [34]. Two molecules of ACE might coordinate to the cationic rhodium as bidentate ligands to form complex **31**, and this would prevent the coordination of the two-carbon component alkyne. Using a rhodium complex with just three free coordination sites, the alkyne may compete effectively with ACE for coordination as shown in complex **32**. Indeed, when we applied the neutral Rh(I) catalysts to the reaction, we began to see the desired product **30a**. Wilkinson's catalyst gave a 81 % isolated yield. The combination of phosphine ligand $[(4\text{-}CF_3C_6H_4)_3P]$ with neutral catalyst $[Rh(COD)Cl]_2$ gave a yield (84 %), which is comparable to the result obtained with Wilkinson's catalyst. Other transition metals such as Pd, Au, and Pt resulted in no formation of desired product.

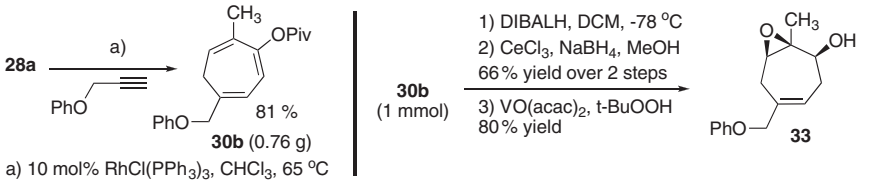
The Rh-catalyzed intermolecular [5 + 2] cycloaddition of ACE and alkyne is remarkably efficient, because it allows us to access highly functionalized seven-membered ring product **30a** in just two steps from commercially available materials. High regioselectivity was observed when the two-carbon component was a terminal alkyne. For internal alkynes, one or two activating groups are required (e.g., $R^4$ or $R^5 = CH_2OH$ or $CO_2Me$).

The Rh-catalyzed intermolecular [5 + 2] cycloaddition of ACE and alkyne could be scaled up to prepare 0.76 g of product **30b** with a more than 20:1 isomeric ratio (Scheme 8). The pivaloyl group in compound **30b** could be removed by DIBALH. Functionalized cycloheptene **33** could be obtained in a good yield by a sequence of reduction and oxidation, which demonstrated that the three alkenes in cycloheptatriene **30** could be selectively functionalized. The intermolecular cycloaddition allowed us to place substituents on five out of seven possible positions on the cycloheptatriene skeleton. Additional substituents and functionalities could be introduced to the seven-membered ring by further derivatization of the triene.

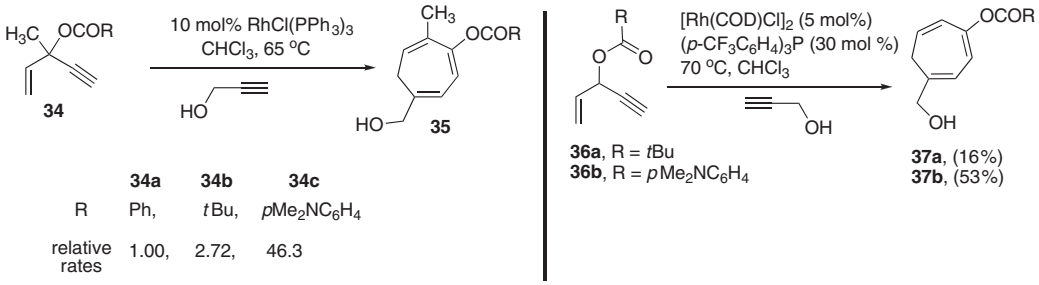
Our study on the effect of the ester indicated that the rate of the intermolecular cycloaddition was significantly accelerated when substrates with an electron-donating dimethylaminobenzoate were employed (Scheme 9) [38]. We could lower the catalyst loading down to 0.5 mol% for ACEs with a tertiary ester. We could also increase the yield of the cycloaddition product for ACEs with a secondary ester from 16 % for **37a** to 53 % for **37b**.




**Scheme 7** Scope and conditions for Rh-catalyzed intermolecular [5 + 2] cycloaddition of ACE and alkyne.




**Scheme 8** Selective functionalization of cycloheptatrienes.



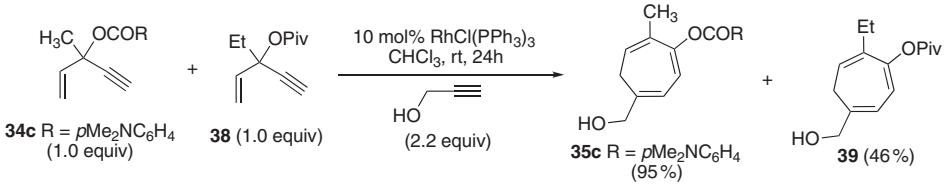

**Scheme 9** Effect of the ester for Rh-catalyzed intermolecular [5 + 2] cycloaddition of ACE and alkyne.

We also carried out the cross-over experiment for the cycloadditions between ACE **34c** and **38** with propargylic alcohol (Scheme 10). No cross-over product was observed. This suggested that the acyloxy group did not dissociate from the enyne.

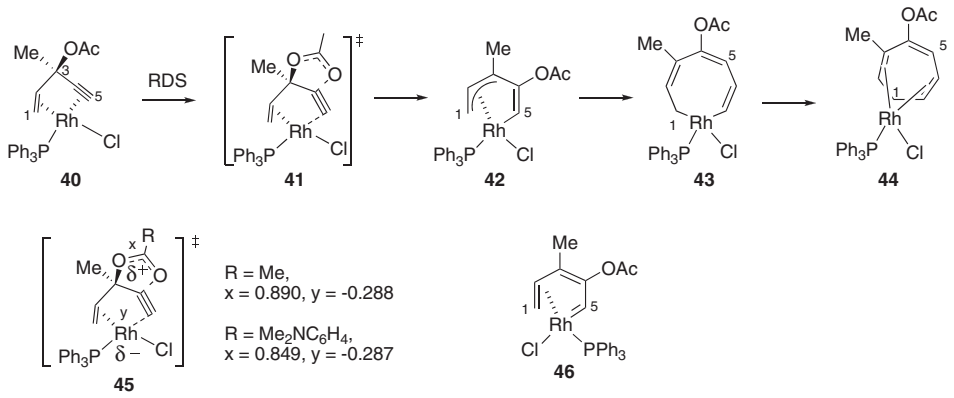
Based on DFT calculations [39], a concerted oxidative cycloaddition mechanism (Scheme 11) was preferred over a step-wise 1,2-migration of acyloxy group, which was proposed in gold-catalyzed reactions [32d,40]. Metallacyclohexadiene intermediate **42** was then generated directly from ACE **40** via transition state **41**, where the metal and the acyloxy group are located on the opposite faces. The anti-coordination model is consistent with our observations in Schemes 5 and 6. This 1,2-acyloxy migration step was also believed to be the rate-determining step (RDS).

Four metallacyclooctatriene intermediates could be proposed after the insertion of an alkyne to this metallacyclohexadiene intermediate. The alkyne could insert into either the allyl-carbon(C1)–metal bond or vinyl-carbon(C5)–metal bond. For a terminal alkyne, the R group could be either close or distal to the forming C–C bond. Computational studies suggested that the insertion of alkyne to C5–metal bond and having the bulkier alkyne substituent distal to the forming C–C bond were favored.

DFT calculation also predicted that positive charges would build up on the carbonyl carbon, which could be stabilized by the electron-donating group as shown in structure **45**. This is consistent with the effect of ester observed experimentally in Scheme 9. For the intramolecular cycloaddition, we were able to isolate a cyclopropane byproduct derived from cyclopropanation of cyclooctadiene, which supported the involvement of Rh(I) carbenes [34]. Computational studies predicted that when the Cl-ligand was placed on the transposition, the Rh–carbon bond had more carbene character as shown in **46**.




**Scheme 10** Cross-over experiments.




**Scheme 11** Mechanism of Rh-catalyzed intermolecular [5 + 2] cycloaddition of ACE and alkyne.

## Conclusion and outlook

In conclusion, we have demonstrated for the first time that ACE can serve as a five-carbon synthon in Rh-catalyzed intra- and intermolecular [5 + 2] cycloadditions with alkynes. This cycloaddition was accompanied by a 1,2-acyloxy migration of propargylic ester. The two-carbon component could be either terminal or internal alkynes for the intramolecular [5 + 2] cycloaddition. For the intermolecular [5 + 2] cycloaddition, all terminal alkynes and some activated internal alkynes worked well. The alkyne moiety in the ACE five-carbon component had to be either a terminal alkyne or internal alkynes bearing an electron-withdrawing halogen, ketone, or ester groups. Chirality could be transferred efficiently from the chiral propargylic esters to bicyclic products in intramolecular [5 + 2] cycloadditions. High regioselectivity and interesting ester effect were observed for the intermolecular reactions. Finally, DFT calculations provided a mechanism that could explain the regioselectivity observed for the intermolecular reaction and the stereospecificity observed in the intramolecular reaction.

The obvious next step is the development of [5 + 2] cycloadditions of ACEs with alkenes and allenes using an appropriate metal catalyst. The diastereoselectivity and stereospecificity can be examined in these cases if the cycloadditions can be realized. We also expect the successful developments of three- or four-component cycloadditions and cascade reactions involving [5 + 2] cycloaddition of ACEs. All of these new methods should complement reactions involving VCPs. The [5 + 2] cycloadditions involving ACEs will also undoubtedly find applications in the synthesis of natural products and pharmaceutical agents containing seven-membered rings.

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