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Rhodium-Catalyzed [5+2] Cycloaddition of 3-Acyloxy-1,4-enyne with Alkene or Allene

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Abstract: We recently developed a completely new type of Rh-catalyzed [5+2] cycloaddition by using 3-acyloxy-1,4-enyne (ACE) as the 5-carbon building block. In this update, we show that ACE can undergo intramolecular [5+2] cycloaddition with either an alkene or an allene in the presence of an appropriate rhodium catalyst and ligands to afford bicyclic compounds with multiple stereogenic centers. In most cases, *cis*-fused bicyclo[5.3.0]decadienes are prepared highly diastereoselectively.

Keywords: allenes; catalysis; cycloaddition; enynes; rhodium

The bicyclo[5.3.0]decane carbon skeleton is present in numerous bioactive sesquiterpenes and diterpenes as shown in Figure 1.[1] The importance of this bicyclic structure continues to stimulate the development of novel and efficient stereoselective methods.[2] Cycloaddition is one of the most efficient ways to access ring systems by forming at least two bonds during the ring-forming event. Numerous cycloaddition reactions have been developed for the synthesis of four-, five-, and six-membered rings. For example, Diels–Alder cycloaddition is one of the most widely used methods for the stereoselective synthesis of six-membered rings with multiple stereogenic centers. In contrast, a cycloaddition that can match the scope and stereocontrol of Diels–Alder cycloaddition for the synthesis of seven-membered rings, the homolog of Diels–Alder cycloaddition, has yet to be discovered, although the seven-membered ring is as prevalent as five- and six-membered rings in natural products.

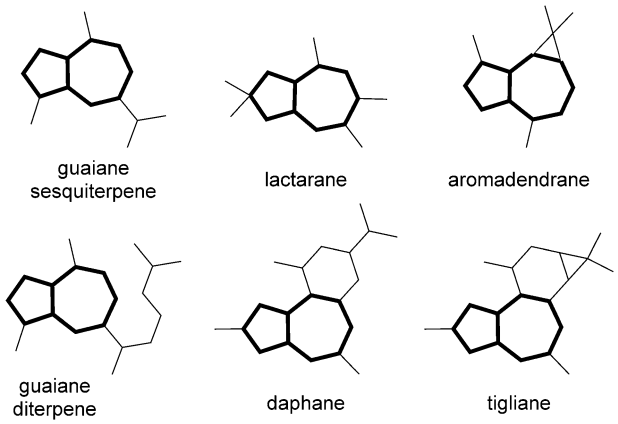
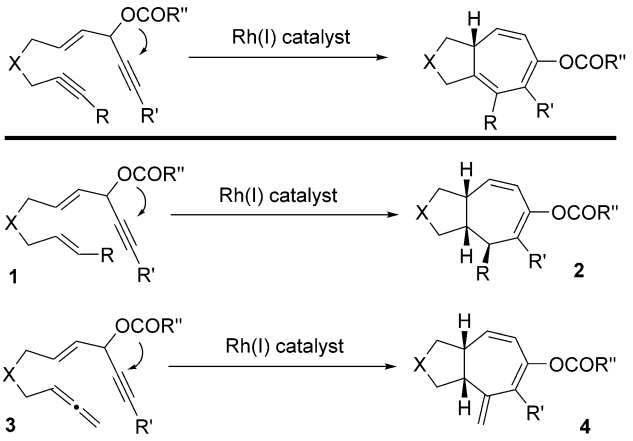


Figure 1. Carbon skeletons of selected terpene families.

Among the three types of two-component cycloadditions including [6+1], [5+2], and [4+3], the [5+2] cycloaddition is particularly attractive because a variety of two-carbon components are readily available, such as alkynes, alkenes, and allenes. The discovery of novel five-carbon building blocks is highly desirable and will lead to a plethora of new [5+2] cycloadditions. Most [5+2] cycloadditions reported to date used vinylcyclopropanes[3] or related species such as iminylcyclopropanes,[4] allenylcyclopropanes,[5] vinyl epoxides,[6] and vinylaziridines,[7] as the five-carbon component. In 2011, we first reported that 3-acyloxy-1,4-enyne (ACE) could serve as a novel 5-carbon component for Rh-catalyzed [5+2] cycloaddition with alkynes for the synthesis of cycloheptatrienes (Scheme 1).[8] Cycloadditions with less reactive alkenes are generally much more challenging than those with alkynes. Cycloaddition products derived from alkenes, however, are also more attractive because multiple stereogeneric centers can be generated in a single step. We found that alkene could participate in the Rh-catalyzed intramolecular [5+2] cycloaddition with ACE and communicated this result recently.[9] In this update, we further explored the scope of the Rh-catalyzed intramolecular [5+2] cycloaddition of ACE with alkenes and describe the intramolecular [5+2] cycloaddition of ACE with allenes for



Scheme 1. ACE as the 5-carbon building block for Rh-catalyzed [5+2] cycloadditions.

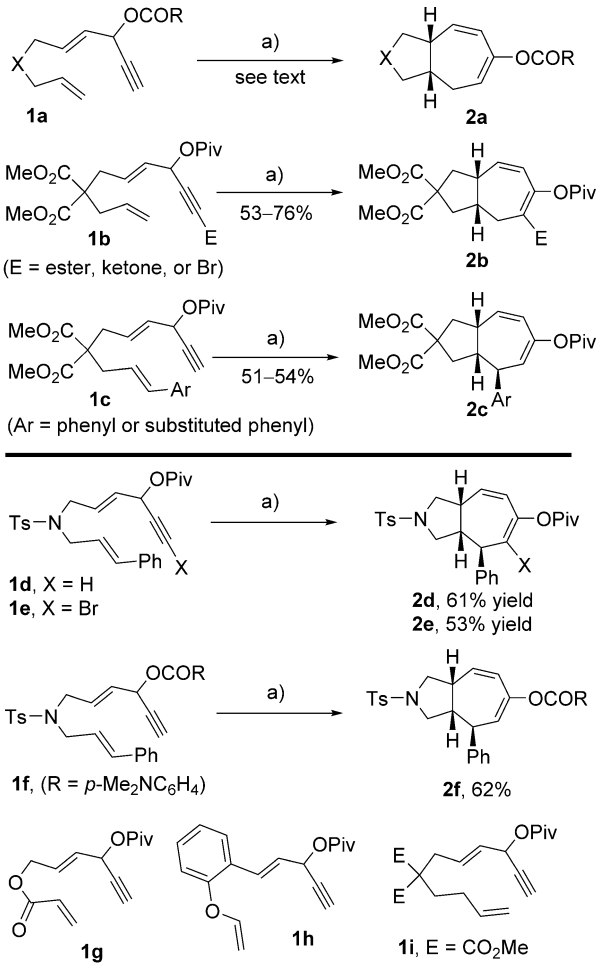
the first time.[10] In all [5+2] cycloadditions involving ACEs, a 1,2-acyloxy migration also occurred.

Various substrates **1a**[9] were prepared by adopting our previously established procedures (Scheme 2).[8] We found that the cationic rhodium catalyst did not provide any desired cycloaddition product, while a neutral rhodium catalyst with electron-deficient phosphine or phosphite ligands generally afforded **2a** in good yields.[9] The combination of $[Rh(coe)_2Cl]_2$ and $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ worked for various substrates with different linker X and ester R units.[9] The chirality in the substrates could be transferred to the products.

We have previously shown that ACEs with an internal alkyne tend to undergo 1,3-acyloxy migration to form allene intermediates.[8,11] For Rh-catalyzed [5+2] cycloaddition of ACEs with alkynes, electron-withdrawing groups including ester, ketone and bromine on the terminal position of alkyne can switch the regioselectivity back to 1,2-acyloxy migration and promote the formation of [5+2] cycloaddition products.[8] ACEs in substrates **1b** could also undergo Rh-catalyzed [5+2] cycloaddition with the tethered alkene to yield products **2b** successfully.[9]

In addition to monosubstituted alkene, we also investigated polysubstituted alkenes in the [5+2] cycloaddition of ACE with alkene. Alkyl groups could not be tolerated on either the internal or external position. Various aryl groups could be tolerated in substrates **1c** with a *gem*-diester linker.[9] We now demonstrate that substrate **1d** with a sulfonamide tether and substrate **1e** with a bromine substituent are also compatible with phenyl-substituted alkene to afford products **2d** and **2e**, respectively.

Previously, we found that the yields of [5+2] cycloaddition products could be slightly increased by around 5% when the pivalate was replaced by electron-rich *para*-dimethylaminobenzoate.[9] We did not



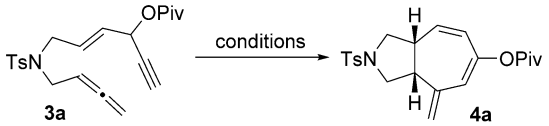
Scheme 2. Scope of Rh(I)-catalyzed intramolecular [5+2] cycloaddition of ACE with alkene.

observe an obvious difference between substrates **1d** and **1f**.

No desired product was obtained for substrate **1g** with an ester linkage. Efforts towards the synthesis of a tricyclic product were also not successful when an enol ether was employed as the 2-carbon component in **1h**. We also tried substrate **1i** with a six-carbon tether. Less than 20% yield of product was observed by NMR. Pure product could not be isolated under standard conditions.

We next prepared substrate **3a** to examine the possibility of Rh-catalyzed intramolecular [5+2] cycloaddition of ACE with allenes. No reaction occurred by using Wilkinson's catalyst (entry 1, Table 1). A complex mixture was observed when the catalyst was switched to $[Rh(cod)OH]_2$ (entry 2). A cationic catalyst afforded the desired cycloaddition product **4a**, albeit in low yield (entry 3). The addition of different

Table 1. Screening of catalysts and conditions for intramolecular [5+2] cycloaddition of ACE and allene.



Entry	Conditions	Yield[a]
1	$Rh(PPh_3)_3Cl$ (5 mol%), DCE, 80 °C	NR
2	$[Rh(cod)OH]_2$ (5 mol%), DCE, 8 h, 80 °C	complex
3	$[Rh(cod)_2]BF_4$ (5 mol%), DCE, 8 h, r.t. or 80 °C	30%
4	$[Rh(cod)_2]BF_4$ (5 mol%), DCE, 8 h, $[(CF_3)_2CHO]_3P$ (30 mol%), 80 °C	NR
5	$[Rh(cod)_2]BF_4$ (5 mol%), DCE, 8 h, $[CF_3CH_2O]_3P$ (30 mol%), 80 °C	complex
6	$[Rh(cod)_2]BF_4$ (5 mol%), DCE, 8 h, $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (30 mol%), 80 °C	33%
7	$[Rh(cod)Cl]_2$ (5 mol%), DCE, $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (30 mol%), 80 °C	41%
8	$[Rh(cod)Cl]_2$ (5 mol%), $CHCl_3$, $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (30 mol%), 60 °C	20%
9	$[Rh(cod)Cl]_2$ (5 mol%), CH_2Cl_2, $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (30 mol%), 40 °C	33%
10	$[Rh(coe)_2Cl]_2$ (5 mol%), DCE, $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (30 mol%), 80 °C	46%
11	$[Rh(coe)_2Cl]_2$ (5 mol%), DCE, $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (30 mol%), 90 °C	55% (52%)[b]
12	$[Rh(coe)_2Cl]_2$ (5 mol%), DCE, $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (30 mol%), 110 °C	34%
13	$[Rh(coe)_2Cl]_2$ (5 mol%), DCE, $(p\text{-}CF_3C_6H_4)_3P$ (30 mol%), 90 °C	25%
14	$[Rh(coe)_2Cl]_2$ (5 mol%), DCE, $[CF_3CH_2O]_3P$ (30 mol%), 90 °C	NR
15	$[Rh(coe)_2Cl]_2$ (5 mol%), DCE, $(C_6F_5)_3P$ (30 mol%), 90 °C	NR

[a] Yields were calculated based on ^1H NMR using internal standard.
[b] Isolated yield; NR = no reaction, DCE = dichloroethane, cod = cyclooctadiene, coe = cyclooctene.

electron-poor phosphite ligands led to either no reaction or a complex mixture (entries 4 and 5). The addition of an electron-poor phosphine ligand to the cationic rhodium catalyst led to a 33% yield of product **4a** (entry 6). The addition of the same ligand to $[Rh(cod)Cl]_2$ led to a slightly improved yield of **4a** (entry 7). No further improvement was observed by examining different solvents (entries 8 and 9). Replacement of the $[Rh(cod)Cl]_2$ catalyst by $[Rh(coe)_2Cl]_2$ further improved the yield to 46% (entry 10). A 52% isolated yield was obtained by raising the temperature to 90 °C (entry 11). A lower yield was obtained after further raising the temperature (entry 12). Other combinations of metal precursor and ligands did not improve the yield. One major by-product observed on the NMR of the crude product was the diene isomer derived from allene. This was unambiguously confirmed later by isolating the diene by-product derived from a substrate in Table 2.

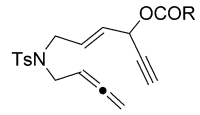
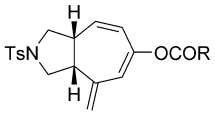
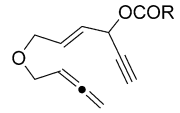
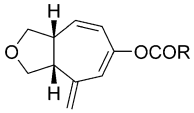
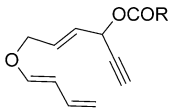
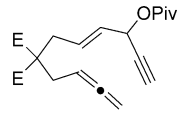
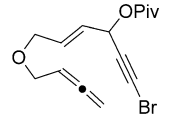
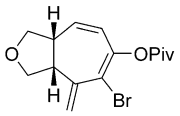
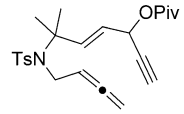
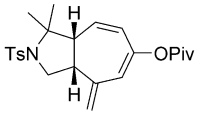
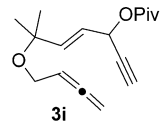
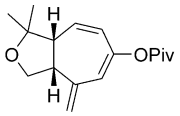
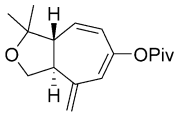
After extensive screening of different conditions, we were not able to improve the yield of the cycloaddition product further for allenes. We began to explore the scope of the substrates (Table 2). Substrate **3b** with an electron-rich dimethylaminobenzoate ester provided a slightly higher yield of the product than **3a** (entry 1). This was also true for substrates with an oxygen tether (entries 2 and 3). Interestingly, diene **4e′** was obtained as the major product when *para*-methoxybenzoate was employed as the ester (entry 4). Diene by-products were also observed in the NMR of the crude products in all other cases. But they were often the minor component in the crude products. It was not clear to us why diene **4e′** became the major product. The diene products were likely generated by allylic C–H activation to form Rh-π-allyl followed by β-hydride elimination.[12]

We were also surprised that substrate **3f** failed to afford the desired cycloaddition product and only a complex mixture was obtained (entry 5). An internal alkyne with a bromine substituent could be tolerated in the ACE moiety (entry 6).

We also introduced a *gem*-dimethyl group to the carbon adjacent to ACE in substrates **3h** and **3i**, with an oxygen and tosylamide linker, respectively (entries 7 and 8). While product **4h** with a *cis*-configuration was isolated in 56% yield, both *cis*- and *trans*-products **4i** and **4i′** were isolated. The major isomer **4i** had the *cis*-configuration, which was assigned based on nOe studies. The *gem*-dimethyl group in the linker region clearly influenced the conformation of the substrate during its coordination to the metal catalyst and led to the formation of *trans*-product.

Based on the mechanism previously proposed for Rh-catalyzed [5+2] cycloaddition of ACEs and alkynes,[8d] the mechanisms for the Rh-catalyzed intramolecular [5+2] cycloadditions with alkenes or allenes are proposed in Scheme 3. Oxidative cyclization of metal complexes **5** and **9** accompanied by 1,2-acyloxy migration yield metallacycles **6** and **10**, respectively. Insertion of the tethered alkene or allene to these two metallacycles affords intermediates **7** and **11**, respectively. Finally, products **8** and **12** are formed after

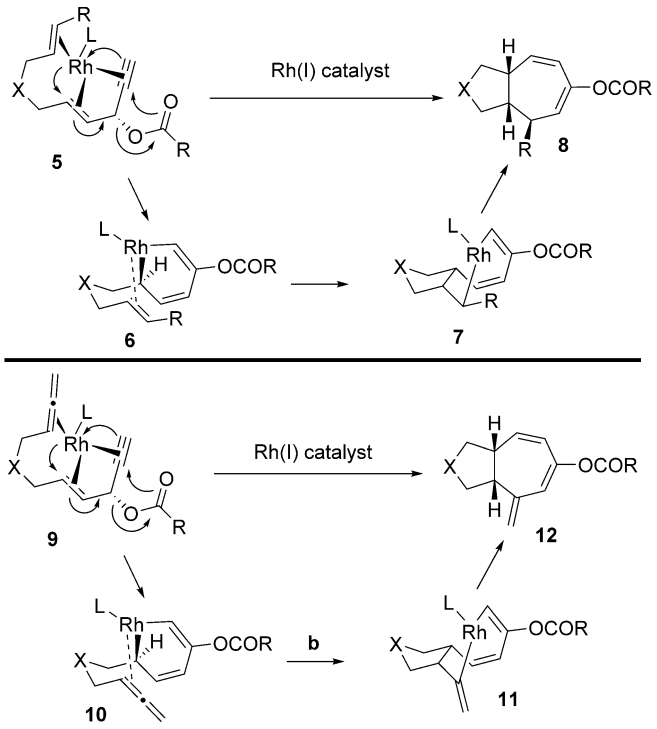
Table 2. Scope of Rh(I)-catalyzed intramolecular [5+2] cycloaddition of ACE with allene.[a]

Entry	Substrate	Product	Yield[b]
			
1	**3b** (R = *p*-$Me_2NC_6H_4$)	**4b**	58%
			
2	**3c** (R = *t*-Bu)	**4c**	45%
3	**3d** (R = *p*-$Me_2NC_6H_4$)	**4d**	55%
			
4	**3e** (R = *p*-$MeOC_6H_4$)	**4e'** (*E*/*Z* = 7:1)	58%
		–	
5	**3f** (E = CO_2Me)		complex
			
6	**3g**	**4g**	50%
			
7	**3h**	**4h**	56%
8	 **3i**	 **4i**	58%
		 **4i'**	10%

[a] *Conditions:* $[Rh(coe)_2Cl]_2$ (5 mol%), $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (30 mol%), DCE, 90 °C, 6–12 h.
[b] All yields were isolated yields.

reductive elimination of the two eight-membered metallacycles.

In conclusion, we have developed Rh-catalyzed [5+2] cycloadditions of ACEs with a tethered alkene or a tethered allene for the synthesis of highly functionalized bicyclic 5–7 fused ring systems. Products



Scheme 3. Proposed mechanism for Rh(I)-catalyzed intramolecular [5+2] cycloaddition of ACE and alkene or allene.

derived from these two new [5+2] cycloadditions have one or two more stereogenic centers compared to the previously reported [5+2] cycloaddition of ACE and alkynes. High diastereoselectivity could be achieved in most cases. For the intramolecular [5+2] cycloaddition of ACE and allene, the reaction occurred preferentially for the internal alkene.

Experimental Section

General Procedure for the [5+2] Cycloaddition of ACE with Alkene

To a solution of $[Rh(coe)_2Cl]_2$ (3.6 mg, 5 mol%) in 1,2-dichloroethane (1 mL) at room temperature was added tris[3,5-bis(trifluoromethyl)phenyl]phosphine (20 mg, 30 mol%) under an argon atmosphere. The reaction solution was stirred at room temperature for 10 min. The alkene substrate (0.1 mmol) was added. The reaction mixture was allowed to stir at 80 °C for 20 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the corresponding bicyclic product.

General Procedure for the [5+2] Cycloaddition of ACE with Allene

To a solution of $[Rh(coe)_2Cl]_2$ (3.6 mg, 5 mol%) in 1,2-dichloroethane (1 mL) at room temperature was added tris[3,5-bis(trifluoromethyl)phenyl]phosphine (20 mg,

30 mol%) under an argon atmosphere. The reaction solution was stirred at room temperature for 10 min. The allene substrate (0.1 mmol) was added. The reaction mixture was allowed to stir at 90 °C for 6–12 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel to afford the corresponding bicyclic product.

Acknowledgements

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