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Rhodium-Catalyzed Stereoselective Intramolecular [5 + 2] Cycloaddition of 3-Acyloxy 1,4-Enyne and Alkene

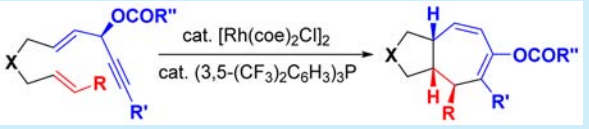
Xing-zhong Shu,[†] Casi M. Schienebeck,[†] Xiaoxun Li,[†] Xin Zhou,[†] Wangze Song,[†] Lianqing Chen,[†] Ilia A. Guzei,[‡] and Weiping Tang*[,†,‡]

[†]School of Pharmacy, University of Wisconsin—Madison, Madison, Wisconsin 53705, United States

[‡]Department of Chemistry, University of Wisconsin—Madison, Madison, Wisconsin 53706, United States

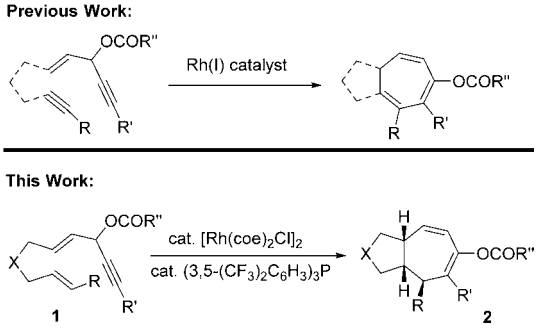
Supporting Information

ABSTRACT: The first rhodium-catalyzed intramolecular [5 + 2] cycloaddition of 3-acyloxy 1,4-enyne and alkene was developed. The cycloaddition is highly diastereoselective in most cases. Various *cis*-fused bicyclo[5.3.0]decadienes were prepared stereoselectively. The chirality in the propargylic ester starting materials could be transferred to the bicyclic products with high efficiency. Electron-deficient phosphine ligand greatly facilitated the cycloaddition. Up to three new stereogenic centers could be generated. The resulting diene in the products could be hydrolyzed to enones, which allowed the introduction of more functional groups to the seven-membered ring.



The importance of seven-membered ring in organic synthesis[1] continues to stimulate the development of novel and efficient stereoselective methods.[2] Cycloaddition is one of the most efficient means to achieve high atom- and step-economic efficiency.[3] An important breakthrough in this area is the [5 + 2] cycloaddition of vinylcyclopropane (VCP) with alkyne, which can be catalyzed by Rh,[4] Ru,[5] Ni,[6] or Fe[7] for the formation of cycloheptadienes.[8,9] The [5 + 2] cycloaddition of VCP with less reactive alkene may generate multiple new stereogenic centers. However, it proved to be a much more challenging process and has only been realized by the research groups of Wender[10] and Yu[11] using Rh catalysts.[12] We recently found that 3-acyloxy 1,4-enyne (ACE) could also serve as a five-carbon component for Rh-catalyzed [5 + 2] cycloaddition with alkynes for the synthesis of cycloheptatrienes (Scheme 1).[13] A 1,2-acyloxy migration was accompanied by this [5 + 2] cycloaddition.[14] We herein report the first Rh-catalyzed highly stereoselective intramolecular [5 + 2] cycloaddition of ACEs and alkene for the synthesis of bicyclo[5.3.0]decane carbon skeletons, which are present in numerous bioactive sesquiterpenes and diterpenes (Scheme 1).[1] This new reaction complements the existing methods for the preparation of highly functionalized seven-membered rings.

Scheme 1. Rh-Catalyzed [5 + 2] Cycloadditions of ACE



No desired cycloaddition product was observed when substrate **1a** was treated with cationic rhodium catalyst (entry 1, Table 1). The addition of various ligands did not result in any cycloaddition product. Gratifyingly, a 63% yield of [5 + 2] cycloaddition product **2a** was obtained in the presence of Wilkinson's catalyst at 80 °C (entry 2). Other neutral Rh(I) complexes such as $[Rh(cod)Cl]_2$ or $[Rh(CO)_2Cl]_2$ provided either no product or lower yield in the absence of any phosphine ligand (entries 3 and 4). We then examined the effect of phosphine ligands. While the addition of the $(C_6F_5)_3P$ ligand shut down the reaction (entry 5), the $(p\text{-}CF_3C_6H_4)_3P$ ligand was beneficial (entry 6). Finally, the combination of $[Rh(cod)Cl]_2$ and $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ ligand afforded the desired cycloaddition product in 80% isolated yield (entry 7). Lower yields were obtained in other solvents or by running the reaction at lower temperatures (entries 8 and 9). Switching the metal complex to $[Rh(coe)_2Cl]_2$ slightly improved the yield (entry 10).

Having the optimized conditions in hand, we next investigated the scope of this [5 + 2] cycloaddition with alkenes (Table 2). Cycloaddition product **2b** with an all-carbon linker was isolated in 82% yield. The diene moiety in product **2b** could be completely reduced to afford a mixture of two diastereomeric isomers in a 1:1 ratio as shown in eq 1. For *trans*-fused cycloaddition product **2b′**, only one stereoisomer would be expected after hydrogenation as shown in eq 2. The relative stereochemistry of bicyclic compound **2b** was therefore assigned as the *cis*-configuration.[10]

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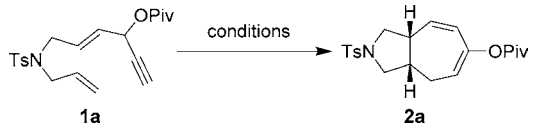
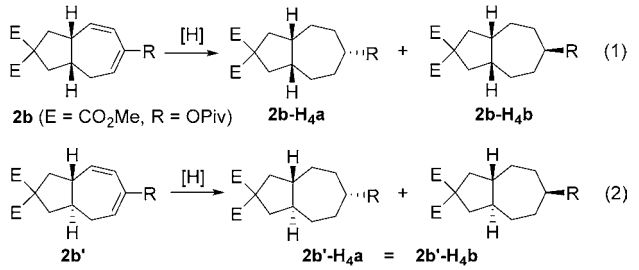
Table 1. Screening of Catalysts and Conditions for 1a



1a **2a**

entry	catalyst and ligands	conditions	yield[a] (%)
1	$[Rh(cod)_2]BF_4$ (10 mol %)	DCE, 8 h, rt or 80 °C	0
2	$Rh(PPh_3)_3Cl$ (10 mol %)	DCE, 10 h 80 °C,	63
3	$[Rh(cod)Cl]_2$ (5 mol %)	DCE, 8 h,80 °C,	0
4	$[Rh(CO)_2Cl]_2$ (5 mol %)	DCE, 8 h, 80 °C	32
5	$[Rh(cod)Cl]_2$ (5 mol %), $(C_6F_5)_3P$ (30 mol %)	DCE, 20 h, 80 °C	0
6	$[Rh(cod)Cl]_2$ (5 mol %), $(p\text{-}CF_3C_6H_4)_3P$ (30 mol %)	DCE, 20 h, 80 °C	50
7	$[Rh(cod)Cl]_2$ (5 mol %), $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (30 mol %)	DCE, 20 h, 80 °C	91 (80)[b]
8	$[Rh(cod)Cl]_2$ (5 mol %), $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (30 mol %)	$CHCl_3$, 20 h, 50 °C	34
9	$[Rh(cod)Cl]_2$ (5 mol %), $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (30 mol %)	CH_2Cl_2, 20 h, 50 °C	31
10	$[Rh(coe)_2Cl]_2$ (5 mol %), $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (30 mol %)	DCE, 20 h, 80 °C	(82)[b]

[a]Yields were calculated on the basis of ^1H NMR using internal standard. [b]Isolated yield.

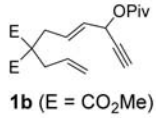
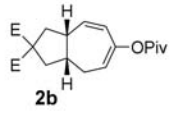
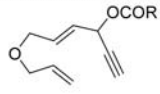
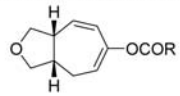
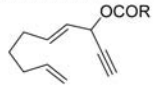
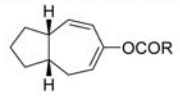
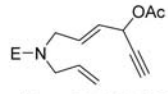
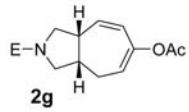
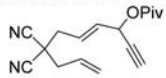
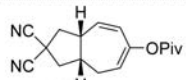
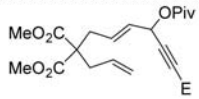
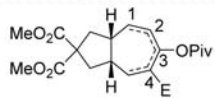
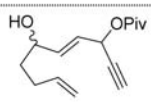
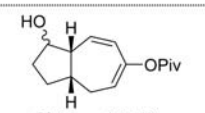


The yield of cycloaddition product was slightly increased when the pivalate in **1c** was changed to *p*-dimethylaminobenzoate in **1d** (entry 3).[15] Similarly, the yield of product **2f** was slightly higher than that of product **2e** (entries 4 and 5) but lower than **2b**, presumably due to the Thorpe−Ingold effect.[16] The yield of cycloaddition for acetate substrate **1g** with a sulfonamide tether (entry 6) was as good as the corresponding pivalate substrate **1a** in Table 1. Substrate **1h** with a bis-nitrile tether also worked well (entry 7).

Propargylic esters with an internal alkyne generally prefer to undergo 1,3-acyloxy migration to form allene intermediates in the presence of rhodium(I) catalysts.[17] An electron-withdrawing group such as ester, ketone, or halogen on the alkyne may switch the regioselectivity back to 1,2-acyloxy migration. This was demonstrated by the successful Rh-catalyzed [5 + 2] cycloadditions of this type of electron-deficient ACEs and alkynes.[13] We were pleased to find that ACEs in substrates **1i**, **1j**, and **1k** also underwent [5 + 2] cycloadditions with the tethered alkenes (entries 8−10). A small amount of isomeric diene products was observed in these cases. We also found that a free hydroxyl group could be tolerated in the tether region (entry 11).

Catalytic asymmetric [5 + 2] cycloaddition of vinylcyclopropanes with alkenes or alkynes is a very challenging reaction.[18] Highly enantioselective processes only appeared recently using chiral phosphine ligands.[10b,19] Inspired by Toste's work on Au-catalyzed Rautenstrauch rearrangement[20] of enantioenriched ACEs to cyclopentenones[21] through a center-to-helix-to-center chirality transfer mechanism,[22] we demonstrated that it was also possible to transfer the chirality from ACEs to bicyclic products in Rh-catalyzed intramolecular [5 + 2] cycloaddition of ACEs and alkynes.[13c] If a similar process can be realized for the cycloaddition between ACE and alkene, we will then be able to access highly valuable enantioenriched 5−7 bicyclic products with multiple stereogenic centers from readily available starting materials. Substrates **1b**, **1m**, and **1n** were easily prepared with high optical purity from the corresponding propargylic alcohols (Scheme 2). The chirality in these substrates could be

Table 2. Scope of Rh(I)-Catalyzed [5 + 2] Cycloaddition of ACE with Monosubstituted Alkene[a]

entry	substrate	product	yield[b]
1	 **1b** (E = CO_2Me)	 **2b**	82%
			
2	**1c** (R = *t*Bu)	**2c**	62%
3	**1d** (R = *p*-$Me_2NC_6H_4$)	**2d**	67%
			
4	**1e** (R = *t*Bu)	**2e**	56%
5	**1f** (R = *p*-$Me_2NC_6H_4$)	**2f**	61%
6	 **1g** (E = p-$BrC_6H_4SO_2$)	 **2g**	84%
7	 **1h**	 **2h**	83%
			
8	**1i** (E = CO_2Et)	**2i** (14:1)[c]	76%
9	**1j** (E = C(O)*n*C_4H_9)	**2j** (5:1)[c]	73%
10[d]	**1k** (E = Br)	**2k** (13:1)[c]	53%
11	 **1l** (dr = 1:1)	 **2l** (dr = 1.5:1)	71%

[a]Conditions: $[Rh(coe)_2Cl]_2$ (5 mol %), $[3,5\text{-}(CF_3)_2C_6H_3]_3P$ (30 mol %), DCE, 80 °C, 20 h. [b]All yields were isolated yields. dr > 20:1 unless noted otherwise. [c]The ratio of 1,3-diene and 2,4-diene. [d]$[Rh(cod)_2Cl]_2$ was employed as the catalyst.

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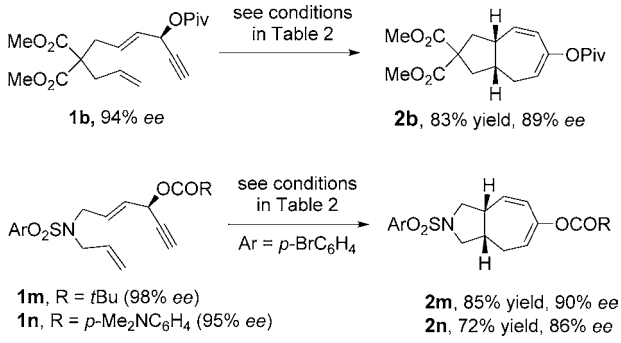
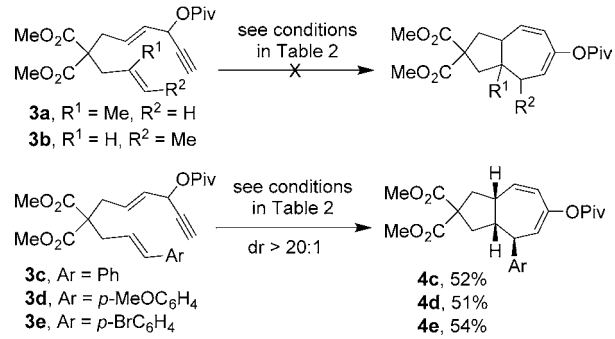
Scheme 2. Transfer of Chirality



transferred to the cycloaddition products efficiently. The ee's of bicyclic products **2b**, **2m**, and **2n** ranged from 86% to 90%. Only one diastereomer was observed in all three cases. The absolute and relative stereochemistry of product **2n** was confirmed by X-ray analysis (CCDC977964).

It has been shown that Rh-catalyzed [5 + 2] cycloaddition of VCPs and alkenes works with substrates bearing a 1,1-disubstituted olefin but not a 1,2-disubstituted olefin as the two-carbon component.[10a,18] In our case, no reaction occurred for substrate **3a**, while a complex mixture was observed for substrate **3b** (Scheme 3). Interestingly, substrates with a

Scheme 3. Cycloaddition of ACE with Substituted Alkene



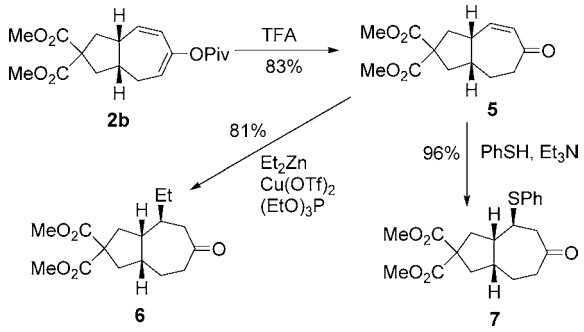
styrene moiety participated in the cycloaddition.[23] Bicyclic compounds with three new stereogenic centers were prepared diastereoselectively in all three cases (dr >20:1). The relative stereochemistry of the three stereogenic centers was assigned based on NOE analysis.

Although only styrene-type disubstituted alkenes participated in the cycloaddition reaction, the diene moiety in all products is essentially a masked enone, which may allow for the introduction of diverse functional groups and substituents to the seven-membered ring. Indeed, the pivalate group in cycloaddition product **2b** was hydrolyzed to afford enone **5**, which could undergo diastereoselective conjugate addition with carbon or sulfur nucleophiles to yield substituted bicyclo[5.3.0]decanes **6** and **7**, respectively (Scheme 4).

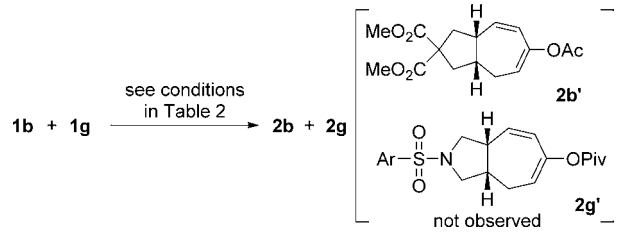
We also found that no crossover product **2b′** or **2g′** was formed under standard conditions when a mixture of compounds **1b** and **1g** was employed as the substrate in a ratio of 1:1 (Scheme 5). This suggests that the acyloxy group does not completely dissociate from the enyne substrate.

The mechanism for the Rh-catalyzed [5 + 2] cycloaddition of ACEs with alkenes is proposed in Scheme 6. Recent DFT calculations suggested that coordination of the Rh catalyst anti to the acyloxy group on the ACE was preferred as shown in

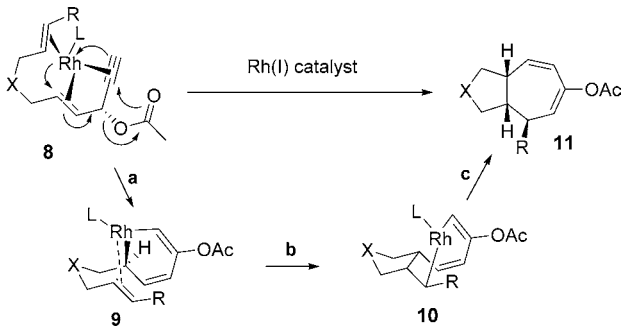
Scheme 4. Functionalization of Cycloaddition Product



Scheme 5. Crossover Experiment



Scheme 6. Proposed Mechanism



complex **8**.[24] The Rh catalyst can then promote 1,2-acyloxy migration and oxidative cyclization to form metallacyclohexadiene intermediate **9**. Insertion of the tethered alkene to this metallacycle may afford intermediate **10**. Reductive elimination of metallacyclooctadiene **10** can then produce cycloheptadiene product **11**. This mechanism is consistent with the observed absolute stereochemistry of propargylic ester **1n** and product **2n**, which was confirmed by its X-ray structure.

In summary, we have demonstrated for the first time that ACEs can serve as the five-carbon synthon in Rh-catalyzed intramolecular [5 + 2] cycloadditions with less reactive alkenes. The chirality transfer from readily available optically pure propargylic esters to cycloaddition products was also shown to be feasible for this new [5 + 2] cycloaddition. The two-carbon alkene component could be either a terminal or a 1,2-disubstituted alkene with an aryl substituent, which produced products with three new stereogenic centers.

■ ASSOCIATED CONTENT

Supporting Information

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Detailed experimental procedures, characterization data, and spectra (^{1}H, ^{13}C NMR, IR, HRMS, and X-ray) (PDF)
X-ray data for compound **2n** (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: weiping.tang@wisc.edu.

Notes

The authors declare no competing financial interest.

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