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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
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Rhodium-Catalyzed Intra- and Intermolecular [5 + 2] Cycloaddition of 3-Acyloxy-1,4-enyne and Alkyne with Concomitant 1,2-Acyloxy Migration

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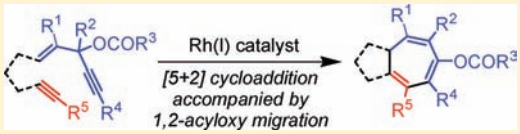
Supporting Information

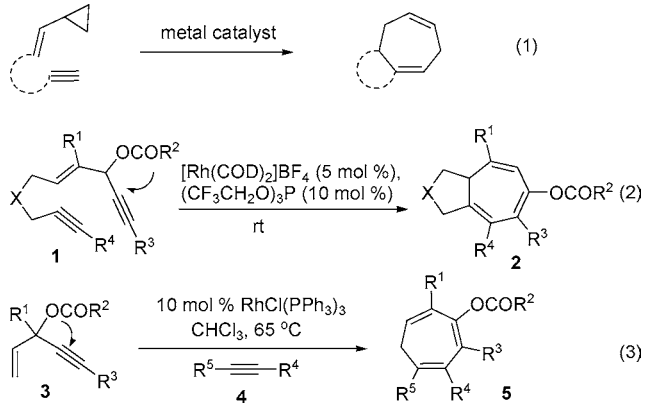
ABSTRACT: A new type of rhodium-catalyzed [5 + 2] cycloaddition was developed for the synthesis of seven-membered rings with diverse functionalities. The ring formation was accompanied by a 1,2-acyloxy migration event. The five- and two-carbon components of the cycloaddition are 3-acyloxy-1,4-enynes (ACEs) and alkynes, respectively. Cationic rhodium(I) catalysts worked most efficiently for the intramolecular cycloaddition, while only neutral rhodium(I) complexes could facilitate the intermolecular reaction. In both cases, electron-poor phosphite or phosphine ligands often improved the efficiency of the cycloadditions. The scope of ACEs and alkynes was investigated in both the intra- and intermolecular reactions. The resulting seven-membered-ring products have three double bonds that could be selectively functionalized.



1. INTRODUCTION

The Diels−Alder reaction is one of the most powerful tools for the construction of substituted six-membered rings. In contrast, it is difficult to find a cycloaddition method for the synthesis of seven-membered rings that can fully match the scope and impact of the Diels−Alder reaction, in spite of the prevalence of cycloheptanes in natural products and pharmaceutical agents.[1] Efficient synthesis of seven-membered rings with diverse functionalities continues to stimulate the development of novel cycloaddition reactions. Three types of two-component cycloadditions exist for the synthesis of seven-membered rings: [4 + 3],[2] [5 + 2],[3] and [6 + 1][4] cycloadditions. The first two methods are more general, since diverse two-carbon (2C) and four-carbon synthons are readily available. The discovery of new three-carbon and five-carbon (5C) synthons would therefore be highly desirable for the development of novel cycloaddition reactions that can lead to functionalized seven-membered rings.

Transition-metal catalysts often facilitate reactions that are difficult or impossible under thermal conditions, and they have proven to be particularly valuable in cycloaddition reactions.[5] The [5 + 2] cycloaddition of vinylcyclopropanes (VCPs) and alkynes (eq 1), a remarkable homo-Diels−Alder reaction, has been realized using different transition-metal catalysts developed in the research groups of Wender,[6−8] Trost,[9] Louie,[10] Fürstner,[11] Yu,[12] and Murai.[13,14] The significance of the intramolecular [5 + 2] cycloaddition of VCPs and alkynes has been highlighted in the synthesis of several natural products.[15] The mechanism of this novel cycloaddition was extensively investigated by Houk, Wender, and Yu.[16] A few other 5C synthons for [5 + 2] cycloadditions were also



discovered by Stryker[17] and Tanino[18] when employing stoichiometric amount of cobalt.

In comparison with other transition-metal-catalyzed [*m* + *n*] cycloadditions, the [5 + 2] cycloaddition is still underdeveloped, especially with respect to the intermolecular version. Although various catalysts for the intramolecular [5 + 2] cycloaddition of VCPs and alkynes have been discovered,[6,9−13] only a few examples of intermolecular counterparts are known because of challenging chemo- and regioselectivity issues.[7] The first Rh-catalyzed intermolecular [5 + 2] cycloaddition, which utilizes an activated vinylcyclopropane, was developed by Wender's group.[7a] Subsequently, the scope of the 5C synthon was expanded to unactivated systems.[7b,c] The significance of the intermolecular reaction is substantial in the preparation of

Received: November 20, 2011
Published: February 26, 2012

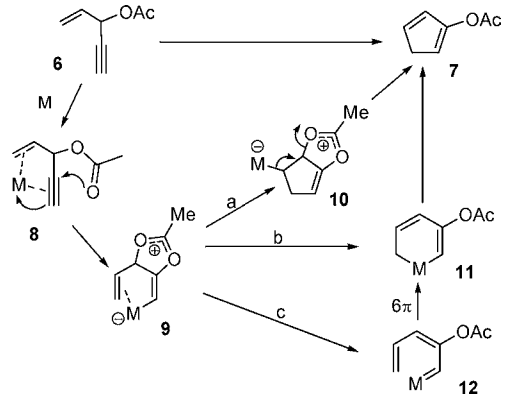
   dx.doi.org/10.1021/ja2109097 | J. Am. Chem. Soc. 2012, 134, 5211−5221

libraries of cycloheptenes from diverse commercially available alkynes.[8]

We have reported a Rh(I)-catalyzed cycloisomerization of 3-acyloxy-4-ene-1,9-diyne **1** to form bicyclo[5.3.0]decatriene **2** (eq 2).[19] One can view this transformation as an intramolecular [5 + 2] cycloaddition of a 3-acyloxy-1,4-enyne (ACE) and a tethered alkyne accompanied by a 1,2-acyloxy migration of the propargyl ester. In all previous examples, R^3 was limited to hydrogen for ene−diyne **1**. In this article, we present the details of the development of this intramolecular [5 + 2] cycloaddition and the expansion of its scope to include ACEs bearing an internal alkyne (R^3 = ester, ketone, Br; eq 2). We also disclose our study of the intermolecular reaction of ACE **3** with alkyne **4** for the first time (eq 3). These two new [5 + 2] cycloadditions provide easy access to seven-membered rings with substituents and functionalities that are complementary to those accessible with existing methods.

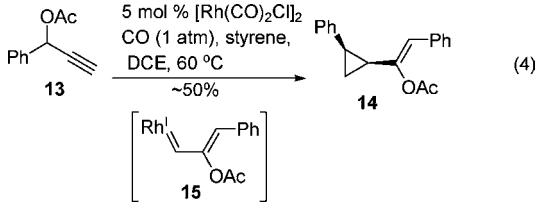
As 5C synthons, ACEs have been used for the synthesis of five- and six-membered rings in transition-metal-catalyzed reactions. Rautenstrauch first reported that ACE **6** could undergo cycloisomerization to form cyclopentadiene **7** in the presence of a palladium catalyst (Scheme 1).[20] The cascade reaction was initiated by a Pd(II)-promoted 1,2-acyloxy migration of the propargyl ester in complex **8** to form intermediate **9**. Three pathways for the conversion of this intermediate to cyclopentadiene **7** were proposed by Rautenstrauch. In pathway a, insertion of an olefin into the carbon−metal bond would give bicyclic intermediate **10**, which would undergo elimination to afford diene **7**. Alternatively, product **7** could be formed by reductive elimination of metallacyclohexadiene **11**, derived either from direct cyclization of metal complex **9** (pathway b) or through carbene intermediate **12** via a 6π electrocyclization (pathway c). The scope of this rearrangement was later expanded using gold[21] and platinum[22] catalysts for the synthesis of functionalized five-membered rings.[23] ACEs were recently also employed as 5C synthons in a novel Rh(I)-catalyzed [5 + 1] cycloaddition with CO for the synthesis of highly substituted phenols.[24]

Scheme 1. Mechanism Proposed by Rautenstrauch for the Rearrangement of ACE 6 to Cyclopentadiene 7



2. RESULTS AND DISCUSSION

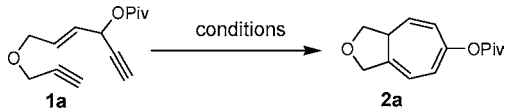
During the search for alternative ways to generate cyclopropyl metal carbenes for cycloadditions,[25] we found that $[Rh(CO)_2Cl]_2$ is able to catalyze 1,3-acyloxy migration of propargyl esters to form allenes,[26] which had previously been realized by π-acidic metals such as gold, platinum, and silver.[27] We then decided to examine the possibility of Rh(I)-catalyzed 1,2-acyloxy migration of simple propargyl esters for the formation of vinyl Rh(I) carbenes.



(4)

Treatment of ester **13** with the $[Rh(CO)_2Cl]_2$ catalyst in the presence of styrene indeed provided the known cyclopropane **14**[28] diastereoselectively (eq 4), demonstrating that Rh(I) carbene **15** could be generated by a 1,2-acyloxy migration of a propargyl ester. We did not further optimize this reaction, since

Table 1. Screening of Catalysts and Conditions for the Cycloisomerization of Enyne 1a



entry	conditions	yield
1	$[Rh(CO)_2Cl]_2$ (5 mol %), toluene, 90 °C, 8 h	19%[a]
2	$[Rh(CO)_2Cl]_2$ (5 mol %), DCE, 90 °C, 8 h	48%[a]
3	$[Rh(CO)_2Cl]_2$ (5 mol %), TCE,[b] 90 °C, 1.5 h	43%[a]
4	$[Rh(COD)Cl]_2$ (5 mol %), TCE, 90 °C, 8 h	21%[a]
5	$Rh(PPh_3)_3Cl$ (5 mol %), TCE, 90 °C, 8 h	77%[a]
6	$[Rh(COD)_2]BF_4$ (5 mol %), DCE, rt, 8 h	70%[a]
7	$[Rh(COD)_2]BF_4$ (5 mol %), toluene, rt, 8 h	NR[c]
8	$[Rh(COD)_2]BF_4$ (5 mol %), dioxane, rt, 8 h	NR
9	$[Rh(COD)_2]BF_4$ (5 mol %), TCE, 50 °C, 20 h	81%[a]
10	$[Rh(COD)_2]BF_4$ (5 mol %), CH_2Cl_2, rt, 8 h	83%[a]
11	$[Rh(COD)_2]BF_4$ (3 mol %), CH_2Cl_2, rt, 16 h	85%[d]
12	$AuCl(PPh_3)$ (5 mol %), AgOTf (5 mol %), MeCN, rt, 20 h	0%
13	$PtCl_2$, (10 mol %), DCE, 80 °C, 20 h	0%
14	$HNTf_2$ (10 mol %), CH_2Cl_2, rt, 20 h	0%

[a]Yields were calculated by ^1H NMR analysis using an internal standard. [b]TCE = tetrachloroethane. [c]NR = no reaction. [d]Isolated yield.

dx.doi.org/10.1021/ja2109097 | J. Am. Chem. Soc. 2012, 134, 5211−5221

it was already well-documented. This type of cyclopropanation was first reported in a $PtCl_2$-catalyzed intramolecular enyne cycloisomerization.[29] The intermolecular version was then extensively investigated using $[RuCl_2(CO)_3]_2$ and other metal catalysts.[28,30] The enantioselective inter- and intramolecular cyclopropanations mediated by chiral gold complexes were subsequently developed.[31] The atom-economical[32] formation of metal carbenes from propargyl esters via 1,2-acyloxy migration has been applied in many other transformations catalyzed by gold,[33−36] platinum,[34,35,37] copper,[35] and rhodium.[38]

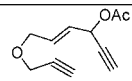
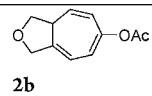
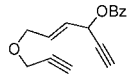
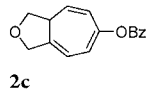
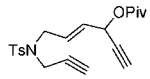
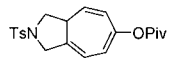
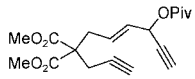
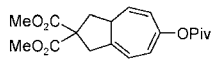
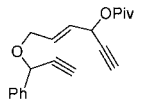
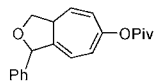
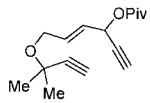
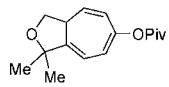
We envisioned that the combination of the novel reactivity of the Rh(I) catalyst in facilitating 1,2-acyloxy migration and its well-known capability to catalyze cycloadditions might offer myriad opportunities for the design of new reactions. For example, if metal complex **11** could be formed in the presence of a Rh(I) catalyst and intercepted by an alkyne, a conceptually new [5 + 2] cycloaddition could then be realized. Inspired by Rautenstrauch's pioneering work on the rearrangement of ACEs to cyclopentadienes, we proposed that the ACE moiety in substrate **1a** might be a suitable 5C synthon for a Rh-catalyzed intramolecular [5 + 2] cycloaddition with concomitant 1,2-acyloxy migration to afford bicyclic product **2a** (Table 1). There are a number of challenges, however, for this transformation. The 1,6-enyne in substrate **1a** might undergo cycloisomerization prior to 1,2-acyloxy migration. If a carbene intermediate similar to **12** is generated, it might undergo cyclopropanation or cyclopropenation with alkenes or alkynes, respectively, that are present in the system. Rautenstrauch rearrangement to form cyclopentadiene would be another potential competing pathway.

Substrate **1a** was easily prepared from commercially available *cis*-2-butene-1,4-diol in just four operations.[39] To our delight, when compound **1a** was treated with a catalytic amount of $[Rh(CO)_2Cl]_2$, product **2a** was obtained in yields of 19 and 48% in toluene and dichloroethane (DCE), respectively (Table 1, entries 1 and 2). A number of other rhodium catalysts also worked for this cycloisomerization (entries 4−6). The cationic Rh(I) complex could catalyze the reaction even at room temperature (entry 6). The solvent dependence was also investigated (entries 7−11). Bicyclic product **2a** with a cycloheptatriene moiety was thus prepared efficiently from readily available linear substrate **1a** under mild conditions (entry 11) using a Rh(I) catalyst. On the other hand, typical π-acidic metals such as Au(I) and Pt(II) or a Brønsted acid did not promote the desired transformation (entries 12−14).

We then investigated the scope of this cycloisomerization (Table 2). The reaction worked well when the ester was changed from pivalate to acetate or benzoate (entries 1 and 2). Substrates with nitrogen and *gem*-diester linkers smoothly yielded bicyclic compounds **2d** and **2e**, respectively (entries 3 and 4). The structure of the cycloisomerization product was unambiguously assigned by the X-ray analysis of product **2d** [Cambridge Crystallographic Data Centre (CCDC) entry 823148].[19] The reaction also tolerated mono- or geminal substitution at the propargylic position of the tether (entries 5 and 6).

Only a trace amount of product, however, was observed for substrate **1h**, which has an internal alkyne for the 2C component (Table 3, entry 1). This significantly limited the scope of the cycloisomerization. We therefore optimized the conditions for this substrate by examining the effect of ligands with the cationic $[Rh(COD)_2]BF_4$ complex. Mono- and

Table 2. Scope of the Cationic Rh(I)-Catalyzed Cycloisomerization of Enyne 1[a]

entry	substrate	product	yield[b]
1	 **1b**	 **2b**	81%
2	 **1c**	 **2c**	83%
3	 **1d**	 **2d**	96%
4[c]	 **1e**	 **2e**	75%
5[d]	 **1f**	 **2f**	90%
6	 **1g**	 **2g**	90%

[a]Conditions: $[Rh(COD)_2]BF_4$ (3−5 mol %), CH_2Cl_2 (0.05 M), rt, 8−48 h. [b]Isolated yields. [c]50 °C. [d]The dr of the substrate was 1:1.

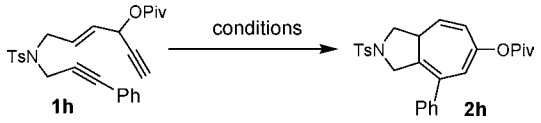
bidentate phosphine ligands such as PPh_3, $(i\text{-}Bu)_3P$, and dppe had no effect (entries 2−4). The yield of product **2h** was improved to 21% by the addition of a phosphite ligand (entry 5), and a similar improvement was also observed with an electron-poor phosphine ligand (entry 6). Most of the starting material was recovered in these two cases. We then combined the above two structural features by testing electron-poor phosphite ligands. Gratifyingly, substrate **1h** was completely consumed within 8 h using $(CF_3CH_2O)_3P$ ligand, and product **2h** was isolated in 88% yield (entry 7). The more sterically demanding electron-poor phosphite ligand $[(CF_3)_2CHO]_3P$ decreased the efficiency of this reaction (entry 8).

Dramatic improvements were also observed for other substrates with internal alkynes using the combination of $[Rh(COD)_2]BF_4$ and $(CF_3CH_2O)_3P$ (Table 4, entries 1−3). For substrates **1i−k**, no reaction or only trace amounts of the desired products were observed using just the cationic Rh(I) catalyst. Moderate yields (40−50%) were obtained for substrate **1l** with 3−10 mol % $[Rh(COD)_2]BF_4$ complex alone. The addition of $(CF_3CH_2O)_3P$ ligand again increased the yield of product **2l** (entry 4).

When we examined the effect of substitution in the tether region of the 1,6-enyne, we found that substituents adjacent to the alkyne had no apparent effect and that the cycloisomerization worked well using the cationic Rh(I) catalyst alone (Table 2, entries 5 and 6). Substituents adjacent to the alkene, however, slowed the reaction significantly. The addition of the $(CF_3CH_2O)_3P$ ligand was necessary to obtain good yields for substrates **1m** and **1n** (Table 4, entries 5 and 6). Substrate **1o** with a trisubstituted olefin also worked well,

dx.doi.org/10.1021/ja2109097 | J. Am. Chem. Soc. 2012, 134, 5211−5221

Table 3. Screening of Ligands for the Cycloisomerization of Substrate 1h Bearing an Internal Alkyne[a]



entry	ligand	yield
1	no ligand	trace
2	PPh_3	NR[c]
3	$(i\text{-Bu})_3P$	NR
4	dppe	NR
5	$(EtO)_3P$	21%[b]
6	$(p\text{-}CF_3C_6H_4)_3P$	12%[b]
7	$(CF_3CH_2O)_3P$	88%[d]
8	$[(CF_3)_2CHO]_3P$	14%[b]

[a]Conditions: $[Rh(COD)_2]BF_4$ (5 mol %), ligand (10 mol %), CH_2Cl_2, 50 °C, 8−16 h. [b]Yields were calculated by ^1H NMR analysis using an internal standard. [c]NR = no reaction. [d]Isolated yield.

affording product **2o** (entry 7). As shown in Table 4, this new catalyst composed of cationic Rh(I) and the electron-poor phosphite ligand appeared to be more general than the previous catalytic system involving just cationic $[Rh(COD)_2]BF_4$.

A complex mixture was observed for substrate **1p** bearing a tertiary propargyl ester (entry 8). Under the standard conditions in Table 4, no reaction was observed for substrates in which the ACE was tethered to an alkyne by six atoms (**1q**) or tethered with an alkene (**1r**) (entries 9 and 10).

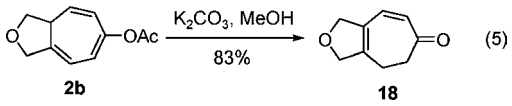
Propargyl esters with an internal alkyne tend to undergo 1,3-acyloxy migration in the presence of π-acidic transition-metal catalysts.[27k] When we treated substrate **1s** with the cationic Rh(I) catalyst, only a trace amount of product **2s** was observed, and most of the starting material was recovered (Scheme 2). We previously found that $[Rh(CO)_2Cl]_2$ is an efficient catalyst for promoting 1,3-acyloxy migration of propargyl esters.[26] Indeed, our preliminary study showed that product **2s** could be isolated in 30−40% yield using $[Rh(CO)_2Cl]_2$ as the catalyst. Benzene derivative **2s** was presumably derived from a cascade reaction involving 1,3-acyloxy migration of the propargyl ester to form vinylallene **16**, Diels−Alder cycloaddition to form isotoluene **17**, and aromatization. This tandem process could be mediated efficiently by $PtCl_2$ catalyst.[40] Our results suggested that 1,2- and 1,3-acyloxy migrations of propargyl esters depend on the substitution pattern of the substrate and the nature of the Rh(I) catalyst, which is consistent with observations using other transition metals.[27k]

It has been reported that electron-withdrawing esters may facilitate the 1,2-acyloxy migration of propargyl esters.[38] Indeed, ACE **1t** with an ester group at the terminal position of the alkyne smoothly underwent cycloisomerization with the tethered alkyne and led to the formation of bicyclic product **2t** upon treatment with the cationic Rh(I) catalyst (Table 5, entry 1). ACEs with different alkyl- or aryl-substituted ketones also participated in the cycloisomerization efficiently (entries 2−4). The sulfonamide tether could be replaced by an ether for this type of substrate (entries 5 and 6). For substrate **1z**, only a 47% yield of the desired cycloisomerization product was isolated using the cationic catalyst alone. The addition of $(CF_3CH_2O)_3P$ ligand increased the yield to 64% (entry 7). This was consistent with results obtained for substrate **1l** (Table 4, entry 4).

It was recently reported that propargyl esters with a haloalkyne undergo gold-catalyzed 1,2-acyloxy migration.[36] We thus prepared substrate **1aa** containing a 1-bromo-3-acyloxy-1,4-enyne fragment (Table 5, entry 8). However, a complex mixture was obtained for the cycloisomerization of substrate **1aa** using cationic Rh(I) alone. We were pleased to find that a 69% yield of the cycloisomerization product **2aa** could be isolated in the presence of the $[Rh(CO)_2Cl]_2$ catalyst. The same catalyst also worked for substrate **1ab**, which had internal alkynes for both the 5C and 2C components (entry 9).

In our previous communication concerning the Rh-catalyzed cycloisomerization of enediyne **1**, the ACEs were limited to terminal alkynes. Inspired by recent developments in the area of transition-metal-catalyzed 1,2-acyloxy migrations of propargyl esters, we have now expanded the scope of the ACEs to include internal alkynes with various electron-withdrawing groups, including ester, ketone, and bromine.

The enol olefin in triene **2** is a masked ketone. Direct hydrolysis of product **2b** under basic conditions released the ketone functionality. Isomerization also occurred under these conditions, leading to the formation of conjugated cycloheptadienone **18** (eq 5).

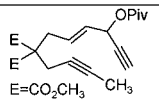
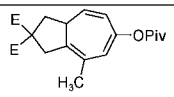
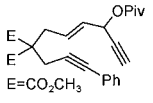
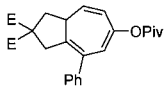
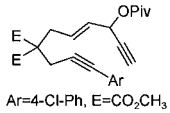
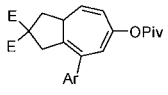
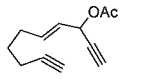
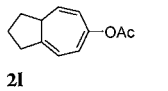
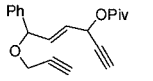
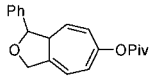
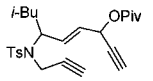
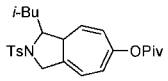
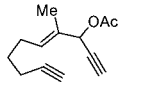
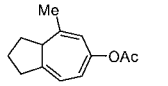
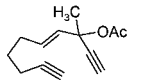
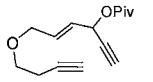
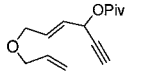


After the successful development of the intramolecular [5 + 2] cycloaddition with concomitant 1,2-acyloxy migration involving ACEs with tethered alkynes, we then turned our attention to the more challenging intermolecular reaction. Under the optimized conditions described in Tables 2 and 4, we did not observe any cycloaddition product derived from ACE **3a** and alkyne **4a** (Table 6, entries 1 and 2). We were pleased to find that neutral rhodium(I) complexes catalyze the intermolecular cycloaddition (entries 3−5). Cycloheptatriene **5a** could be isolated in 80% yield using Wilkinson's catalyst (entry 6).

We also studied the effect of ligands using the $[Rh(COD)Cl]_2$ catalyst (Table 6, entries 7−11). Surprisingly, no desired product was observed after the addition of the electron-poor phosphite ligand $(CF_3CH_2O)_3P$ (entry 7). Phosphine ligands generally promoted the intermolecular cycloaddition (entries 8−11). We found that the ligand $(4\text{-}CF_3C_6H_4)_3P$ provided a yield comparable to that for Wilkinson's catalyst (entry 11). The amount of alkyne **4a** could be reduced to 2.0 equiv without significantly changing the yield (entries 6, 12, and 13).

dx.doi.org/10.1021/ja2109097 | J. Am. Chem. Soc. 2012, 134, 5211−5221

Table 4. Scope of $[Rh(COD)_2]BF_4/(CF_3CH_2O)_3P$-Catalyzed Cycloisomerization of Enyne 1[a]

entry	substrate	product	yield[b]
1	 **1i**	 **2i**	82%
2	 **1j**	 **2j**	70%
3	 **1k**	 **2k**	60%
4	 **1l**	 **2l**	76%
5[c]	 **1m**	 **2m**	76%
6[c]	 **1n**	 **2n**	80%
7	 **1o**	 **2o**	80%
8	 **1p**	–	complex mixture
9	 **1q**	–	0%
10	 **1r**	–	0%

[a]Conditions: $[Rh(COD)_2]BF_4$ (5–10 mol %), $(CF_3CH_2O)_3P$ (10–20 mol %), CH_2Cl_2 (0.025–0.05 M), 50 °C, 8–24 h. [b]Isolated yields. [c]The dr of the substrate was 1:1.

Scheme 2. Tandem 1,3-Acyloxy Migration/Diels–Alder Reaction for ACEs with an Internal Alkyne

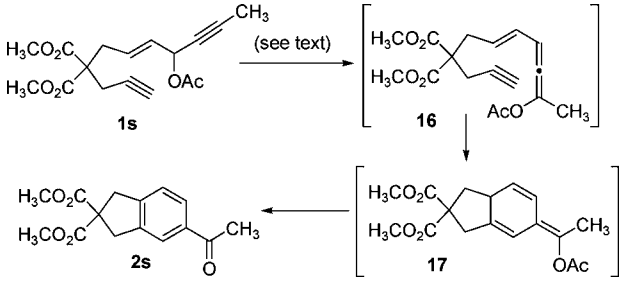
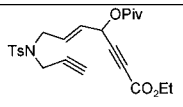
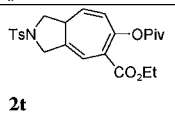
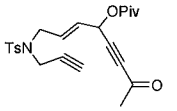
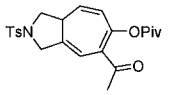
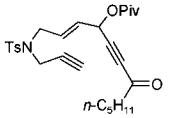
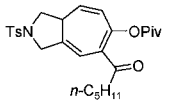
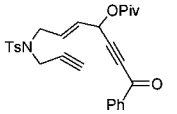
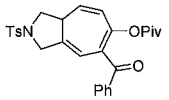
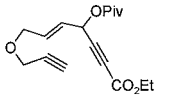
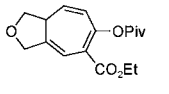
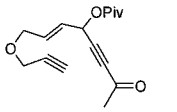
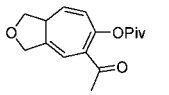
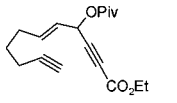
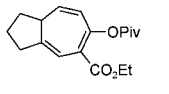
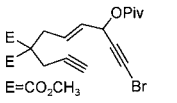
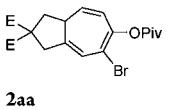
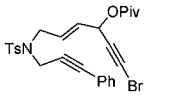
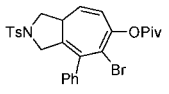


Table 5. Scope of Rh-Catalyzed Cycloisomerization of Enynes with an Electron-Withdrawing Substituent[a]

entry	substrate	product	yield[b]
1	 **1t**	 **2t**	83%
2	 **1u**	 **2u**	83%
3	 **1v**	 **2v**	81%
4	 **1w**	 **2w**	86%
5	 **1x**	 **2x**	72%
6	 **1y**	 **2y**	60%
7[c]	 **1z**	 **2z**	64%
8[d]	 **1aa**	 **2aa**	69%
9[d]	 **1ab**	 **2ab**	75%

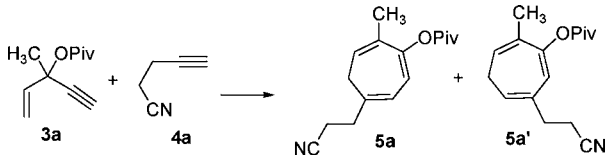
[a]Unless otherwise noted, the conditions in Table 2 were employed. [b]Isolated yields. [c]The conditions in Table 4 were employed. [d]$[Rh(CO)_2Cl]_2$ (5 mol %), DCE, 80 °C, 3–8 h.

Moreover, no cycloaddition product was observed in the presence of palladium, gold, or platinum catalysts (entries 14–17). ACE **3a** was prepared in one step by esterification of the corresponding commercially available alcohol.[39] Highly functionalized seven-membered ring **5a** could therefore be accessed regioselectively in just two steps.

With the optimized conditions in hand, we then studied the scope of terminal alkynes for the intermolecular [5 + 2] cycloaddition with concomitant 1,2-acyloxy migration (Table 7). The reaction between ACE **3a** and free propargyl alcohol (**4b**) proceeded smoothly in the presence of Wilkinson's catalyst to afford isomer **5b** exclusively. High regioselectivity

dx.doi.org/10.1021/ja2109097 | J. Am. Chem. Soc. 2012, 134, 5211–5221

Table 6. Screening of Catalysts and Conditions for the Intermolecular Reaction between ACE 3a and Alkyne 4a[a]



3a 4a 5a 5a'

entry	conditions	yield
1	$[Rh(COD)]BF_4$ (5 mol %), CH_2Cl_2, 50 °C	0
2	$[Rh(COD)]BF_4$ (5 mol %), $(CF_3CH_2O)_3P$ (10 mol %), CH_2Cl_2, 50 °C	0
3	$[Rh(CO)_2Cl]_2$ (5 mol %), DCE, 80 °C	27%
4	$[Rh(COD)Cl]_2$ (5 mol %), DCE, 80 °C	38%
5	$[Rh(PPh_3)_3Cl]$ (10 mol %), DCE, 80 °C	79%
6	$[Rh(PPh_3)_3Cl]$ (10 mol %), $CHCl_3$, 65 °C	89% (80%)[b]
7	$[Rh(COD)Cl]_2$ (5 mol %), $(CF_3CH_2O)_3P$ (30 mol %), $CHCl_3$, 65 °C	0
8	$[Rh(COD)Cl]_2$ (5 mol %), $(C_6F_5)_3P$ (30 mol %), $CHCl_3$, 65 °C	33%
9	$[Rh(COD)Cl]_2$ (5 mol %), $(2\text{-}CH_3C_6H_4)_3P$ (30 mol %), $CHCl_3$, 65 °C	25%
10	$[Rh(COD)Cl]_2$ (5 mol %), dppb (15 mol %), $CHCl_3$, 65 °C	67%
11	$[Rh(COD)Cl]_2$ (5 mol %), $(4\text{-}CF_3C_6H_4)_3P$ (30 mol %), $CHCl_3$, 65 °C	90% (84%)[b]
12	$[Rh(PPh_3)_3Cl]$ (10 mol %), $CHCl_3$, 65 °C, 1.2 equiv of **4a**	80%
13	$[Rh(PPh_3)_3Cl]$ (10 mol %), $CHCl_3$, 65 °C, 2.0 equiv of **4a**	90% (81%)[b]
14	$PdCl_2(CH_3CN)_2$ (10 mol %), CH_3CN, 80 °C	0
15	$PtCl_2$ (10 mol %), DCE, 80 °C	0
16	$Au(PPh_3)Cl$ (5 mol %), CH_2Cl_2, 50 °C	0
17	$Au(PPh_3)Cl$ (5 mol %), $AgSbF_6$ (5 mol %), CH_2Cl_2, rt	0

[a]Unless otherwise noted, 1.0 equiv of **3a** and 3.0 equiv of **4a** were employed and yields of **5a** were determined after 6 h by ^{1}H NMR analysis using an internal standard. For all entries, isomer **5a′** was not detected by ^{1}H NMR analysis of the crude product. [b]Isolated yields.

was also achieved with secondary and tertiary propargyl alcohols (**4c−e**). The olefin in 1,4-enyne **4e** did not interfere with the reaction. When propargyl ether **4f** was employed, regioisomer **5f′** became noticeable. Interestingly, higher regioisomeric ratios were observed for aryl propargyl ethers **4g** and **4h**. The formyl group in ether **4h** was tolerated under the reaction conditions. Regioisomeric ratios of >10:1 were generally obtained for propargyl amides and malonate derivatives (**4i−k**). For more complex alkynes **4h** and **4j**, an excess of ACE **3a** was used (conditions B).

We also examined the regioselectivity for nonfunctionalized aliphatic 1-heptyne (**4l**). A regioisomeric ratio of 6:1 was observed using Wilkinson's catalyst under conditions A. The selectivity could be improved to 10:1 using the combination of $[Rh(COD)Cl]_2$ and $(4\text{-}CF_3C_6H_4)_3P$ (conditions C). These conditions also improved the regioisomeric ratio from 5:1 to 10:1 for trimethylsilyl (TMS)-acetylene (**4m**). A moderate change of ratio (4:1 under conditions A and 5:1 under conditions C) was observed for substrate **4n**. However, similar yields and regioisomeric ratios were obtained for homopropargyl alcohol **4o** under conditions A and C. Alcohol **4p**, alkyl chloride **4q**, and conjugated enyne **4r** all participated in the cycloaddition. Good regioselectivity was achieved for most terminal aliphatic alkynes, except for ynoate **4s**. A similar electronic effect on the regioselectivity was also observed in Rh-catalyzed intermolecular [5 + 2] cycloadditions of VCPs and alkynes.[7c]

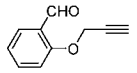
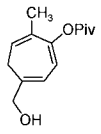
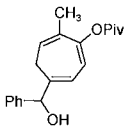
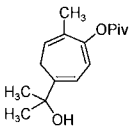
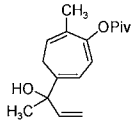
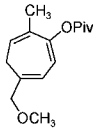
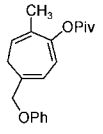
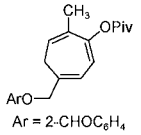
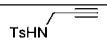
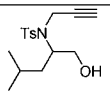
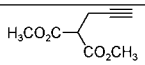
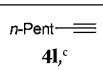
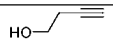
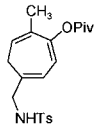
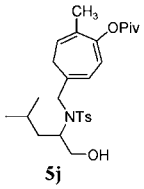
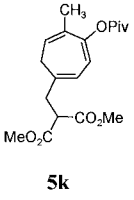
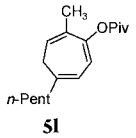
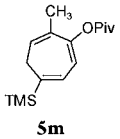
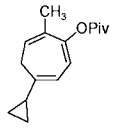
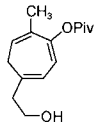
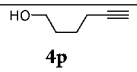
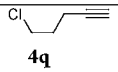
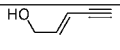
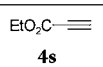
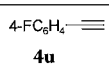
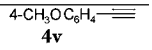
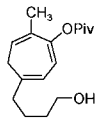
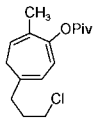
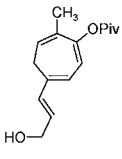
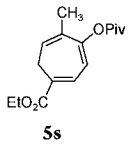
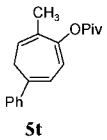
The two regioisomeric cycloheptatrienes **5t** and **5t′** derived from phenylacetylene (**4t**) were isolated in yields of 58 and 17%, respectively. The ratio of these two isomers was 4:1 when the reaction was conducted under conditions A. However, the regioselectivity dropped to 2:1 under conditions C. We then studied the electronic and steric effects of the substituents on the benzene ring under conditions A. An electron-withdrawing group improved the **5**/**5′** ratio, while an electron-donating group had the opposite effect (**4u** vs **4v**). The regioselectivity became higher when the heteroatoms were moved from the para to the ortho position in alkynes **4w** and **4x**. For substrate **4y** with an *o*-methyl group, the yield of product dropped to 32%, and the ^{1}H NMR spectrum of the crude products was too complex for the potential minor regioisomer to be identified. Highly functionalized terminal alkynes such as ethynylestradiol **4z** and norethindrone **4aa** also underwent cycloaddition with ACE **3a** regioselectively. The free phenol and conjugated enone in these two substrates were compatible with the cycloaddition.

Having investigated the utility of ACE **3a** for [5 + 2] cycloaddition with a wide variety of terminal alkynes, we then studied the scope of the 5C synthon (Table 8). The pivalate group in **3a** could be replaced by acetate (**3b**) or benzoate (**3c**) without a noticeable change in the reaction rate (entries 1 and 2). ACEs with various alkyl or aryl groups at the 3-position could also participate in the intermolecular cycloaddition efficiently and regioselectively (entries 3−6).

The conversion for secondary ester **3h** dropped significantly (Table 8, entry 7) and was similar to that in gold-catalyzed reactions.[27k] Results for ACEs with internal alkynes (entries 8 and 9) were similar to those for the intramolecular reaction. No desired product was observed for ACE **3i** (entry 8). The halogen substituent in ACE **3j** facilitated the cycloaddition and provided tetrasubstituted cycloheptatriene **19j** as a single regioisomer in moderate yield (entry 9). ACE **3k** with a ketone group at the terminal position of the alkyne also underwent cycloaddition smoothly upon treatment with the Rh(I) catalyst, leading to the formation of **19k** and its regioisomer **19k′** in a 5:1 ratio (entry 10). Isomer **19k** was isolated in 52% yield. ACEs bearing substituents on the alkene (entries 11−14) did not participate in the cycloaddition reaction under the standard conditions A or C given in Table 7.

dx.doi.org/10.1021/ja2109097 | J. Am. Chem. Soc. 2012, 134, 5211−5221

Table 7. Scope of the Intermolecular Reaction between ACE 3a and Different Terminal Alkynes[a]

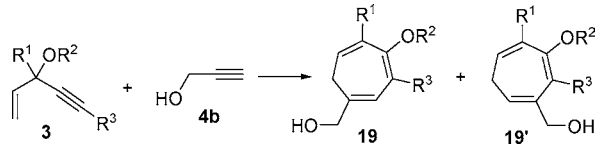
alkyne substrate	 **4b**	 **4c**	 **4d**	 **4e**	 **4f**	 **4g**	 **4h**,[b]
cycloaddition product	 **5b**	 **5c**	 **5d**	 **5e**	 **5f**	 **5g**	 **5h**
yield, (**5**/**5'**)	81%, (>20:1)	83%, (>20:1)	87%, (>20:1)	93%, (>20:1)	86%, (8:1)	89%, (17:1)	89%, (>20:1)
alkyne substrate	 **4i**	 **4j**,[b]	 **4k**	 **4l**,[c]	 **4m**,[c]	 **4n**,[c]	 **4o**
cycloaddition product	 **5i**	 **5j**	 **5k**	 **5l**	 **5m**	 **5n**	 **5o**
yield, (**5**/**5'**)	91%, (10:1)	80%, (>20:1)	85%, (14:1)	81%, (10:1)	53%, (10:1)	**5n**, 64%, **5n'**, 13%, (5:1)	80%, (10:1)
alkyne substrate	 **4p**	 **4q**	 **4r**	 **4s**	 **4t**	 **4u**	 **4v**
cycloaddition product	 **5p**	 **5q**	 **5r**	 **5s**	 **5t**	**5u**	**5v**
yield, (**5**/**5'**)	68%, (8:1)	77%, (8:1)	74%, (8:1)	82%, (1.4:1)	**5t**, 58%; **5t'**, 17%, (4:1)	83%, (6:1)	76%, (3.6:1)
alkyne substrate	**4w**	**4x**	**4y**	**4z**,[b]		**4aa**,[b]	
cycloaddition product	**5w**	**5x**	**5y**	**5z**		**5aa**	
yield, (**5**/**5'**)	80%, (11:1)	60%, (5:1)	32%	86%, (>20:1)		92%, (>20:1)	

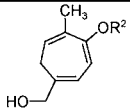
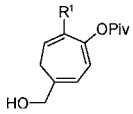
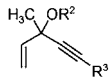
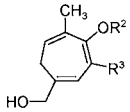
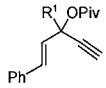
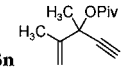
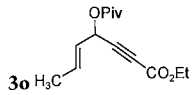
[a]Unless otherwise noted, conditions A were employed: 1.0 equiv of **3a**, 2.0 equiv of **4**, $Rh(PPh_3)_3Cl$ (10 mol %), $CHCl_3$, 65 °C, 4−12 h. Yields are isolated yields of combined **5** and **5'**. The structures of isomers **5'** are analogous to the structure of **5a'** in Table 6. Regioisomeric ratios of **5**/**5'** were determined by ^1H NMR analysis of the crude product. [b]Conditions B: The stoichiometry of the two reactants in conditions A was changed to 2.0 equiv of **3a** and 1.0 equiv of **4**. [c]Conditions C: The catalyst in conditions A was changed to $[Rh(COD)Cl]_2$ (5 mol %) and $(4\text{-}CF_3C_6H_4)_3P$ (30 mol %).

The reaction between ACE **3a** and internal alkyne **20a** was very sluggish, and only a 21% yield of product **21a** was isolated (Scheme 3). In contrast, the reaction between **3a** and 1,4-butynediol (**20b**) proceeded smoothly to yield cycloheptatriene **21b** in high yield under the identical conditions. The hydroxyl group at the propargylic position improved the reactivity of **20b** dramatically. For nonsymmetric internal alkyne **20c**, regioisomeric ratios of 3.3:1 and 5:1 were observed under conditions A and C, respectively. The reaction between ACE **3p** and internal alkyne **20b** afforded a moderate yield of bicyclic compound **23** after transesterification under conditions C. Product **23** was isolated in 71% yield simply by increasing the temperature to

dx.doi.org/10.1021/ja2109097 | J. Am. Chem. Soc. 2012, 134, 5211−5221

Table 8. Scope of the Intermolecular Reaction between Different ACEs and Propargyl Alcohol 4b[a]



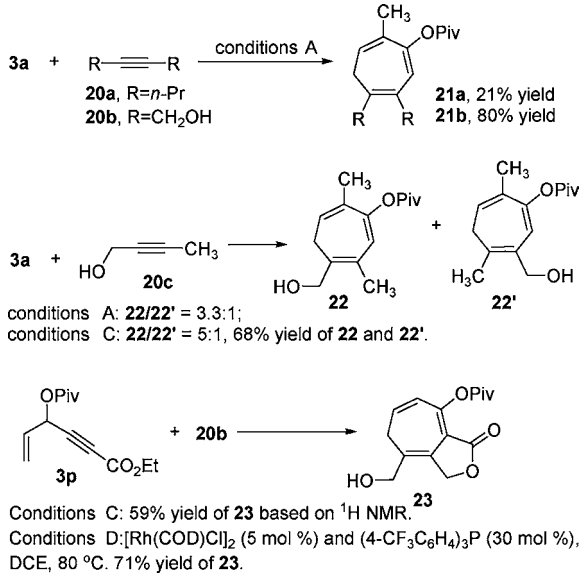
entry	ACE substrate	product	yield of **19**, (**19**/**19'**)[b]
			
1	**3b** (R^2=Ac)	**19b**	71%, (>20:1)
2	**3c** (R^2=Bz)	**19c**	58%, (>20:1)
			
3	**3d** (R^1=C_2H_5)	**19d**	87%, (>20:1)
4	**3e** (R^1=CH_2OTBS)	**19e**	92%, (>20:1)
5	**3f** (R^1=Ph)	**19f**	81%, (20:1)
6	**3g** (R^1=4-BrC_6H_4)	**19g**	76%, (>20:1)
7	**3h** (R^1=H)	**19h**	16%,[c] (>20:1)
			
8	**3i**, (R^2=Ac, R^3=CH_2CH_2Ph)	**19i**	0
9	**3j** (R^2=Piv, R^3=Br)	**19j**	34%, (>20:1)[e]
10	**3k** (R^2=Bz, R^3=COPh)	**19k**	52%,[d] (5:1)
		-	
11	**3l** (R^1=H)	-	0
12	**3m** (R^1= CH_3)	-	0
13	 **3n**	-	0
14	 **3o**	-	0

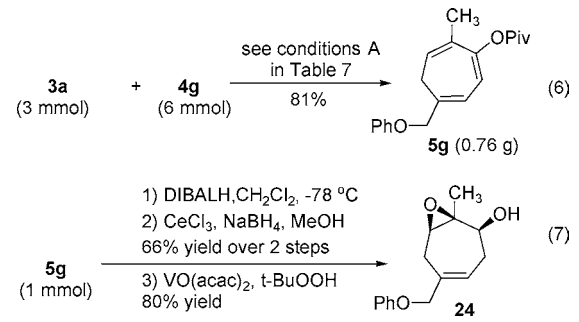
[a]See conditions A in Table 7. All yields are isolated yields. [b]The regioisomeric ratio of **19**/**19'** was determined by ^{1}H NMR analysis of the crude product. [c]ACE **3h** was recovered in 66% yield after 12 h. [d]Isolated yield of isomer **19k**. [e]The reaction was run at rt for 14 h.

80 °C and changing the solvent to DCE (conditions D; Scheme 3). ACEs bearing a secondary propargyl ester could therefore participate in the cycloaddition efficiently when the alkyne was substituted with an electron-withdrawing ester group.

The intermolecular [5 + 2] cycloaddition with concomitant 1,2-acyloxy migration could be scaled up, allowing the preparation of 0.76 g of product **5g** with a regioisomeric ratio of >20:1 (eq 6). The pivaloyl group in compound **5g** could be removed using DIBALH, as shown in eq 7. Further reduction[41]

Scheme 3. Intermolecular Reaction of ACE 3a and Internal Alkynes (See Table 7 for Conditions A and C)





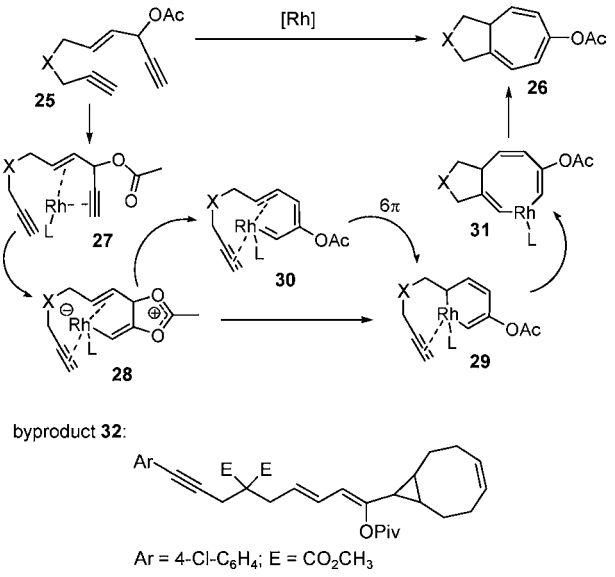
of the resulting cycloheptadienone followed by directed epoxidation[42] led to the isolation of highly functionalized cycloheptene **24**. This demonstrated that the three alkenes in cycloheptatriene **5g** could be further functionalized selectively. For the intermolecular cycloaddition, we could place substituents at only five of the seven possible positions on the cycloheptatriene skeleton, as shown in compounds **5**, **19**, and **21**–**23**. Through selective derivatization of the triene, however, more substituents and functionalities could be introduced on the seven-membered ring.

On the basis of the mechanism for the Rautenstrauch rearrangement (Scheme 1), we propose the mechanism shown in Scheme 4 for the Rh-catalyzed intramolecular [5 + 2] cycloaddition of ACEs and alkynes accompanied by a 1,2-acyloxy migration. It first involves a Rh-promoted 1,2-acyloxy migration of the propargyl ester in metal complex **27** to form intermediate **28**. Metallacyclohexadiene **29** could be derived either from direct cyclization of **28** or through carbene **30** via a 6π electrocyclization. Insertion of a tethered alkyne into metallacycle **29** followed by reductive elimination of metallacyclooctatriene **31** would then produce cycloheptatriene product **26**. In one of the intramolecular cycloadditions, we isolated a small amount of cyclopropane byproduct **32** (Scheme 4),[19] which was presumably derived from the reaction between Rh(I) carbene intermediate **30** and a cyclooctadiene present in the catalyst.

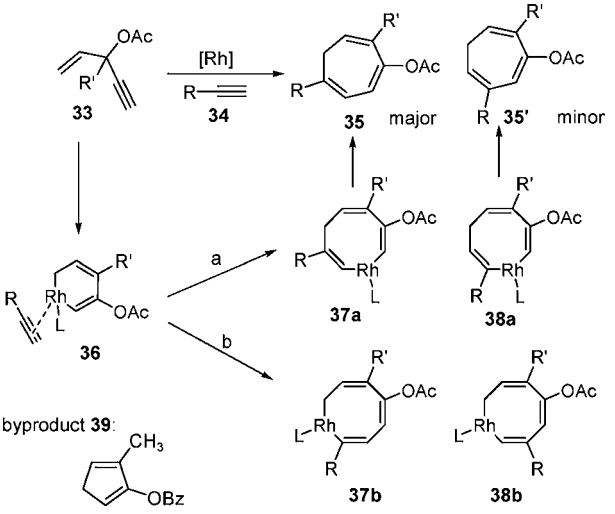
The mechanism of the Rh-catalyzed intermolecular [5 + 2] cycloaddition of ACEs and alkynes is shown in Scheme 5.

dx.doi.org/10.1021/ja2109097 | J. Am. Chem. Soc. 2012, 134, 5211–5221

Scheme 4. Proposed Mechanism for the Rh-Catalyzed Intramolecular [5 + 2] Cycloaddition of ACE and Alkyne with a Concomitant 1,2-Acyloxy Migration



Scheme 5. Proposed Mechanism for the Rh-Catalyzed Intermolecular [5 + 2] Cycloaddition of ACE and Alkyne with a Concomitant 1,2-Acyloxy Migration



Following the same 1,2-acyloxy migration and cyclization sequence, metal complex **36** would be formed from ACE **33** and alkyne **34**. The alkyne in intermediate **36** could insert into either the C(sp^3)−metal bond (pathway a) or the C(sp^2)−metal bond (pathway b). For terminal alkyne **34**, the R group could be either close (**37a** and **38b**) or distal (**37b** and **38a**) to the forming C−C bond. In all of our intermolecular [5 + 2] cycloadditions involving terminal alkynes, the major regioisomer we observed was product **35**, which was presumably derived from intermediate **37a** or **37b**. Previous computational studies of Rh-catalyzed reactions involving unsymmetrical alkynes showed that the bulkier alkyne substituent prefers to be distal to the forming C−C bond.[7c,43] The formation of product **35** via intermediate **37b** might also be the favored pathway in our intermolecular [5 + 2] cycloaddition. We often obtained slightly higher regioselectivity for alkynes with heteroatoms at the propargylic or homopropargylic position. Coordination of the heteroatom to the rhodium in metal complex **37b** might be responsible for the higher selectivity.

To gain a better understanding of the mechanism of the intermolecular cycloaddition, we also treated several of the ACEs in Table 8 with Wilkinson's catalyst (10 mol %) in the absence of any external alkyne. A complex mixture together with a significant amount of starting material was observed in all cases. After careful analysis, we were able to isolate a small amount of the Rautenstrauch rearrangement product **39** (~5% yield) from ACE **3c**. Presumably, cyclopentadiene **39** was derived from reductive elimination of the corresponding metal complex **36** prior to alkyne insertion. In the presence of external alkynes, we rarely observed the Rautenstrauch rearrangement product. The isolation of byproducts **32** and **39** is consistent with the mechanisms proposed in Schemes 4 and 5 based on intercepting Rautenstrauch intermediates with alkynes.

3. CONCLUSION

In summary, we have demonstrated for the first time that 3-acyloxy-1,4-enynes (ACEs) can serve as five-carbon synthons in Rh-catalyzed intra- and intermolecular [5 + 2] cycloadditions with alkynes. The ring formation was accompanied by a 1,2-acyloxy migration of propargyl ester. The two-carbon component could be either a terminal or internal alkyne. The ACE 5C component had a terminal alkyne in most cases. ACEs bearing internal alkynes could also participate in the cycloaddition when the terminal substituent was an electron-withdrawing halogen, ketone, or ester group. Various substituted mono- and bicyclic compounds with a seven-membered ring were prepared from readily available starting materials through inter- and intramolecular [5 + 2] cycloadditions, respectively. High regioselectivity was observed for most terminal alkynes in the intermolecular reaction. Applications of these new methods for the synthesis of natural products and pharmaceutical agents containing seven-membered rings are ongoing in this laboratory.

4. EXPERIMENTAL SECTION

4.1. General Information. Unless otherwise noted, all of the reactions in nonaqueous media were conducted under dry argon in glassware that had been oven-dried prior to use. Anhydrous solutions of reaction mixtures were transferred via an oven-dried syringe or cannula. All of the solvents were dried prior to use. Thin-layer chromatography (TLC) was performed using precoated silica gel 60 F254 plates (EMD Chemicals, Inc.). Flash column chromatography was performed with silica gel (Sillicycle, 40−63 μm). IR spectra were obtained as neat oils on a Bruker Equinox 55 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Unity-Inova 400 or 500 MHz NMR spectrometer and were recorded in parts per million (δ) downfield of tetramethylsilane (δ = 0) in $CDCl_3$. Signal splitting patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), or multiplet (m), with coupling constants (J) in hertz. High-resolution mass spectrometry (HRMS) was performed by the Analytical Instrument Center at the School of Pharmacy or the Department of Chemistry on an electrospray injection (ESI) mass spectrometer.

4.2. General Procedure for the Rh-Catalyzed Cycloisomerization of Enynes in Table 2. To a solution of $[Rh(COD)_2]BF_4$ (2.5 mg, 3 mol %) in CH_2Cl_2 (0.05 M) was

dx.doi.org/10.1021/ja2109097 | J. Am. Chem. Soc. 2012, 134, 5211−5221

added the propargylic ester (0.2 mmol). The solution was stirred at room temperature until the reaction was complete, as determined by TLC analysis. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel to afford the corresponding cycloheptatriene.

4.3. General Procedure for the Rh-Catalyzed Cycloisomerization of Enynes in Table 4. To a solution of $[Rh(COD)_2]BF_4$ (4.0 mg, 5 mol %) in CH_2Cl_2 (0.025−0.05 M) was added $(CF_3CH_2O)_3P$ (6.4 mg, 10 mol %), and the mixture was stirred at room temperature for 5 min. The propargylic ester (0.2 mmol) was then added, and the reaction mixture was allowed to stir at 50 °C until the reaction was complete, as determined by TLC analysis. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel to afford the corresponding cycloheptatriene.

4.4. General Procedure for the Rh-Catalyzed Cycloisomerization of Enynes 1aa and 1ab in Table 5. To a solution of $[Rh(CO)_2Cl]_2$ (3.9 mg, 5 mol %) in DCE (0.1 M) was added the propargylic ester (0.2 mmol). The reaction mixture was allowed to stir at 80 °C until the reaction was complete, as determined by TLC analysis. The solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel to afford the corresponding cycloheptatriene.

4.5. General Procedures for the Intermolecular Reaction between ACEs and Alkynes in Tables 7 and 8. *Conditions A.* To a solution of $Rh(PPh_3)_3Cl$ catalyst (18.5 mg, 10 mol %) in $CHCl_3$ (1 mL) were added the ACE (0.2 mmol) and alkyne (0.4 mmol). The reaction mixture was allowed to stir at 65 °C under argon until the reaction was complete, as determined by TLC analysis. After the solvent was removed under reduced pressure, the residue was purified by chromatography on silica gel to afford the corresponding product.

Conditions B. These conditions were identical to conditions A, except that the numbers of equivalents of the substrates were changed to the following: ACE, 0.4 mmol; alkyne, 0.2 mmol.

Conditions C. To a solution of $[Rh(COD)Cl]_2$ (5.2 mg, 5 mol %) in $CHCl_3$ (1 mL) was added $(4\text{-}CF_3Ph)_3P$ (28 mg, 30 mol %), and the mixture was stirred at rt for 5 min. The ACE (0.2 mmol) and alkyne (0.4 mmol) were then added, and the reaction mixture was allowed to stir at 65 °C under argon until the reaction was complete, as determined by TLC analysis. After the solvent was removed under reduced pressure, the residue was purified by chromatography on silica gel to afford the corresponding product.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization of new compounds (IR, ^1H NMR, ^{13}C NMR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the NIH (R01GM088285) and the University of Wisconsin for funding. W.T. is grateful for a Young Investigator Award from Amgen. S.H. was partially supported by a fellowship from the Chinese Scholarship Council.

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