Synthetic Methods

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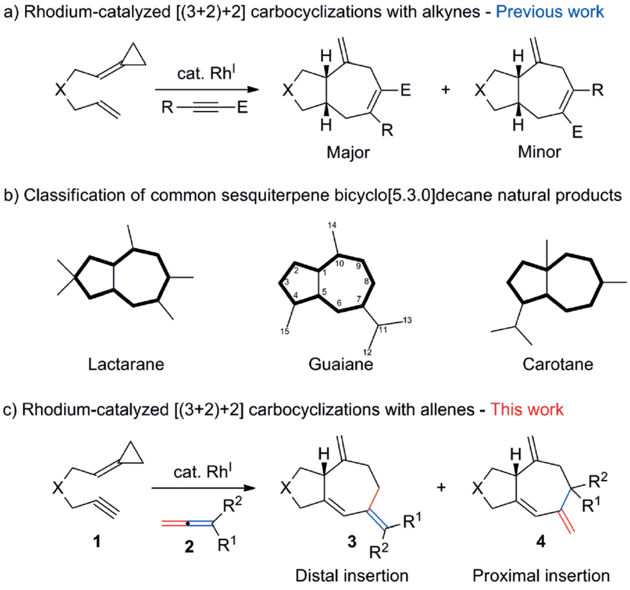
Rhodium-Catalyzed [(3+2)+2] Carbocyclization of Alkynylidenecyclopropanes with Substituted Allenes: Stereoselective Construction of Tri- and Tetrasubstituted Exocyclic Olefins**

P. Andrew Evans, Daniela E. Negru, and Deju Shang*

Dedicated to Dr. Alfred R. Bader on the occasion of his 90th birthday

Abstract: *The development of the stereoselective rhodium-catalyzed [(3+2)+2] carbocyclization of alkynylidenecyclopropanes (ACPs) with substituted allenes is described. This work demonstrates that activated and unactivated allenes preferentially undergo carbometalation at the distal terminus to generate tri- and tetrasubstituted exocyclic olefins with a neutral rhodium catalyst. In addition, this method provides a strategy for the total synthesis of the guaiane family of sesquiterpenes, which are not directly accessible using alkynes as exogenous π-components. Finally, the preparation of the bicyclo[5.4.0]undecane ring system using a homologated ACP tether serves to further illustrate the versatility of this approach.*


a) Rhodium-catalyzed [(3+2)+2] carbocyclizations with alkynes - Previous work

b) Classification of common sesquiterpene bicyclo[5.3.0]decane natural products

c) Rhodium-catalyzed [(3+2)+2] carbocyclizations with allenes - This work

Scheme 1. Rationale for the development of the rhodium-catalyzed [(3+2)+2] carbocyclization of ACPs with allenes.

The development of new strategies for the atom-economical assembly of architecturally challenging pharmacophores present in bioactive agents remains an important goal for modern synthetic organic chemistry. To this end, metal-catalyzed higher-order cycloaddition reactions provide a powerful and versatile approach for the construction of carbo- and heterocyclic systems through the combination of relatively simple building blocks, namely alkynes and alkenes.[1,2] Indeed, since Reppe reported the first cyclotrimerization of alkynes in 1948 there has been considerable emphasis on the development of new variants using novel π-components to extend the scope of this important class of reactions.[3] In this regard, we recently reported the rhodium-catalyzed [(3+2)+2] carbocyclization reaction of alkenylidenecyclopropanes with activated alkynes for the construction of *cis*-fused bicyclo[5.3.0]decanes (Scheme 1 a). Although this process provides an expeditious approach to the lactarane skeleton, as exemplified in the total synthesis of pyrovellerolactone, the reliance on activated alkynes and the inability to reverse the regioselectivity limits the application of this process to the synthesis of the guaianes (Scheme 1 b).[4–7] Hence, we envisioned the metal-catalyzed [(3+2)+2] carbocyclization reaction of an alkynylidenecyclopropane (ACP) with a substituted allene as a way to access the guaiane skeleton through the distal insertion of a 1,1-disubstituted allene (Scheme 1 c).[8,9] Nevertheless, rhodium-catalyzed higher-order carbocyclizations with exogenous allenes have a number of inherent challenges. For instance, conjugated allenes are generally required since unactivated allenes are either unreactive or provide mixtures of constitutional isomers. Moreover, the products from distal insertion are formed with poor geometrical control irrespective of the type of substituent on the allene. In addition, monosubstituted allenes are either unreactive or provide proximal insertion, thereby making this a challenging problem.[10–13] Herein, we describe the first regio- and stereoselective rhodium-catalyzed [(3+2)+2] carbocyclization of carbon- and heteroatom tethered ACPs (**1**) with activated and unactivated exogenous allenes (**2**) to afford the bicycloheptatrienes **3** with tri- and tetrasubstituted

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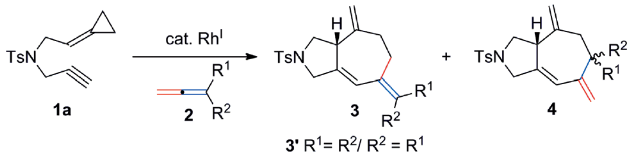
exocyclic olefins (Scheme 1c). Additionally, this process provides a rare example of a highly selective distal carbometalation of a mono- or 1,1-disubstituted allene in a metal-catalyzed cycloaddition reaction.

Table 1 outlines the optimization and preliminary substrate scope for the rhodium-catalyzed [(3+2)+2] carbocyclization reaction with substituted allenes. Treatment of the ACP **1a**[14] with the activated allene **2** ($R^1 = CO_2Et$, $R^2 = H$) using [{Rh(cod)Cl}$_2$], modified with triphenylphosphite in *p*-xylene at 100 °C, furnished the bicycloheptatriene **3a** as the exclusive constitutional and stereoisomer in 62% yield favoring the *E*-configuration (entry 1).[15–17] Interestingly, the analogous process with cationic complexes also provided **3a** as the major adduct, albeit in significantly lower yield (entries 2 and 3). Hence, the nature of the catalyst does not appear to be an underlying factor for controlling the chemoselective distal insertion.[10,12] Further optimization of the amount of ligand and temperature led to the optimal reaction conditions to afford **3a** in 90% yield (entries 4 and 5). Interestingly, the 1,1-disubstituted allene **2** ($R^1 = CO_2Et$, $R^2 = Me$) provided analogous results (entry 6), which illustrates the remarkable tolerance to substitution. In an attempt to further understand the origin of selectivity, we elected to examine other activated and unactivated allenes, wherein the latter are generally more challenging substrates. To this end, the phenyl-substituted allene **2** ($R^1 = Ph$, $R^2 = H$) afforded analogous selectivity (entry 7 versus 5), whereas the 1,1-disubstituted derivative ($R^1 = Ph$, $R^2 = Me$) led to a slight reduction in geometrical control (entry 7 versus 8). This trend was further highlighted with the unactivated allene **2** ($R^1 = CH_2OBn$, $R^2 = H$), which furnished the constitutional isomers **3/4** in excellent yield as a 1.5:1 mixture (entry 9), albeit the former was produced with ≥ 19:1 selectivity for the *E*-isomer. In contrast, the 1,1-disubstituted allene **2** ($R^1 = CH_2OBn$, $R^2 = CH_3$), provided both a mixture of constitutional and geometrical isomers, due to the similarity in the size of the substituents (entry 10).[18] Overall, this study outlines the factors that control selectivity in this process, albeit a more detailed theoretical analysis is required to provide further insight into the origin of selectivity.

Table 1: Optimization and preliminary scope for the rhodium-catalyzed [(3+2)+2] carbocyclization of the ACP **1a** with activated and unactivated allenes (**2**).[a]

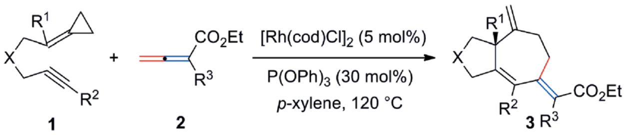


Entry	Allene **2** R^1	R^2	$P(OPh)_3$ (mol%)	*T* [°C]	**3**/**3'**[b]	(**3**+**3'**)/**4**[b]	Yield [%][c]
1	CO_2Et	H	20	100	≥19:1	≥19:1	62
2[d]	CO_2Et	H	20	100	≥19:1	≥19:1	24
3[e]	CO_2Et	H	20	100	≥19:1	≥19:1	31
4	CO_2Et	H	30	100	≥19:1	≥19:1	71
5	CO_2Et	H	30	120	≥19:1	≥19:1	90
6	CO_2Et	Me	30	120	≥19:1	≥19:1	86
7	Ph	H	30	120	≥19:1	≥19:1	73
8	Ph	Me	30	120	10:1	≥19:1	71
9	CH_2OBn	H	30	120	≥19:1	1.5:1	81
10	CH_2OBn	Me	30	120	2:1	0.7:1	89

[a] All reactions were performed on a 0.1 mmol reaction scale using 5 mol% [{Rh(cod)Cl}$_2$] modified with $P(OPh)_3$ (30 mol%) and the allene **2** (3 equiv) in *p*-xylene (0.05 M) at 120 °C. [b] The ratios of geometrical isomers **3**/**3'**, constitutional isomers **3**/**4**, and the diastereoisomers **4** (1:1) were determined by 500 MHz ^{1}H NMR analysis of the crude reaction mixture. The stereochemistry of the *E*-isomer for **3** was established using nOe studies. [c] Yields of the isolated products. [d] [Rh(cod)$_2$]OTf (10 mol%) was used. [e] [Rh(cod)$_2$]SbF$_6$ (10 mol%) was used. cod = 1,5-cyclooctadiene, Ts = 4-toluenesulfonyl.

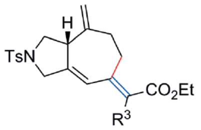
Table 2 outlines the application of the optimized reaction conditions (Table 1, entry 5) to a range of substituted carbon- and heteroatom-tethered ACPs with activated mono- and 1,1-disubstituted allenes.[19] In each case, the reaction proceeded with excellent selectivity to facilitate the construction of

Table 2: Scope of the rhodium-catalyzed [(3+2)+2] carbocyclization with activated allenes.[a]

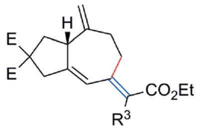


rs ≥19:1; *E/Z* ≥19:1[c,d]

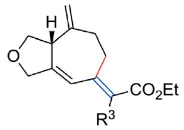
E = CO_2Me



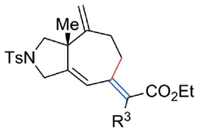
3a R^3 = H 90%
3b R^3 = Me 86%



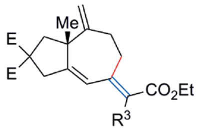
3c R^3 = H 89%
3d R^3 = Me 99%



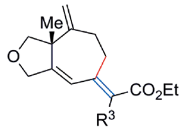
3e R^3 = H 62%
3f R^3 = Me 66%



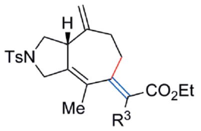
3g R^3 = H 97%
3h R^3 = Me 97%



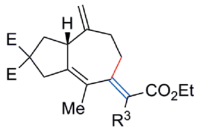
3i R^3 = H 90%
3j R^3 = Me 99%



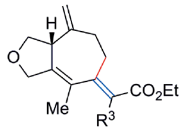
3k R^3 = H 66%
3l R^3 = Me 72%



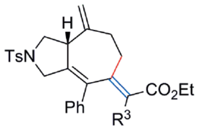
3m R^3 = H 95%
3n R^3 = Me 95%



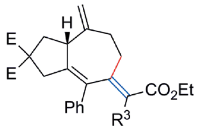
3o R^3 = H 83%
3p R^3 = Me 99%



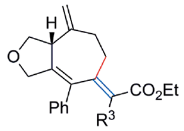
3q R^3 = H 60%
3r R^3 = Me 57%



3s R^3 = H 82%
3t R^3 = Me 81%



3u R^3 = H 90%
3v R^3 = Me 96%



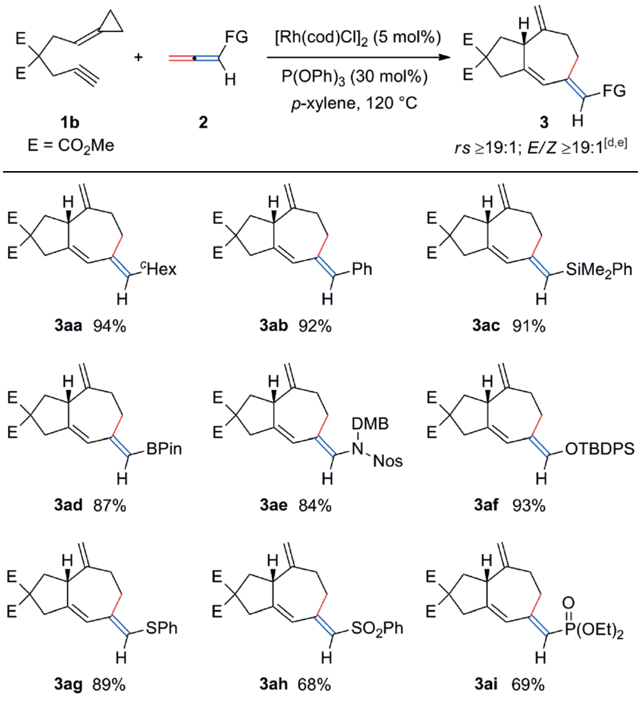
3w R^3 = H 69%
3x R^3 = Me 67%

[a] All reactions were performed on a 0.1 mmol reaction scale using 5 mol% [{Rh(cod)Cl}$_2$] modified with $P(OPh)_3$ (30 mol%) and the allene **2** (3 equiv) in *p*-xylene (0.05 M) at 120 °C. [b] Yields of isolated products. [c] Ratio of the constitutional isomers **3**/**4** was determined by 500 MHz ^{1}H NMR analysis of the crude reaction mixture. [d] Only the *E*-isomer was observed for **3**, and was established using nOe studies.

a single constitutional and geometrical isomer (≥19:1 by NMR). Moreover, the nature of the tether is inconsequential in this reaction, albeit the ether tethers tend to be slightly less efficient.[4,20] Additionally, the carbocyclization with the malonate tether provides the basis for constructing the carbon skeleton of the guaianes with the requisite unsaturation for further functionalization (Table 2, **3c**,**d**). Another key feature with this process is the scope of the reaction, which permits the introduction of angular methyl groups (**3g**–**l**) and tolerates internal alkynes (**3m**–**x**). For instance, the methyl- and phenyl-substituted alkyne derivative undergo the selective formation of hexasubstituted heteroannular dienes (**3m**–**x**). Overall, the efficiency and selectivity is quite striking for a metal-catalyzed cycloaddition with mono- and 1,1-disubstituted allenes.

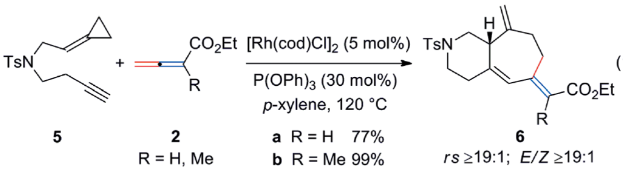
Table 3 details the examination of activated and unactivated allenes to further illustrate the scope and provide insight into the factors which govern selectivity. Although these allenes proved more demanding substrates owing to their propensity to decompose and/or polymerize under the reaction conditions, the slow addition of the allene by using a syringe-pump circumvented this problem. Hence, a number of challenging allenes participate in the cycloaddition to provide a new paradigm for the types of functional groups that can employed as substituents within the exogenous π-component. For instance, branched alkyl and aryl substituents afforded a single stereoisomer in excellent yield (**3aa**,**ab**), which contrasts the efficiency and selectivity obtained with the phenyl and linear alkyl substituents, respectively (Table 1, entries 7 and 9). Additionally, the vinyl silane **3ac** (Table 3) and vinyl borane **3ad** provide important motifs that enable further functionalization through cross-coupling reactions, whereas the enamine **3ae** and the silyl enol ether **3af** represent important carbon nucleophiles. Moreover, the phenyl allenyl sulfide also underwent the cycloaddition, despite the propensity for sulfur poisoning of the metal center (**3ag**).[21] Finally, extension of the repertoire of electron-withdrawing groups permitted the preparation of the vinyl sulfone **3ah** and vinyl phosphonate **3ai**. Overall, this study provides additional examples of the highly selective cycloaddition, which clearly demonstrates the versatility and tolerance to a variety of useful functional groups in the allene.

Table 3: Scope of the rhodium-catalyzed [(3+2)+2] carbocyclization with functionalized substituted allenes.[a]



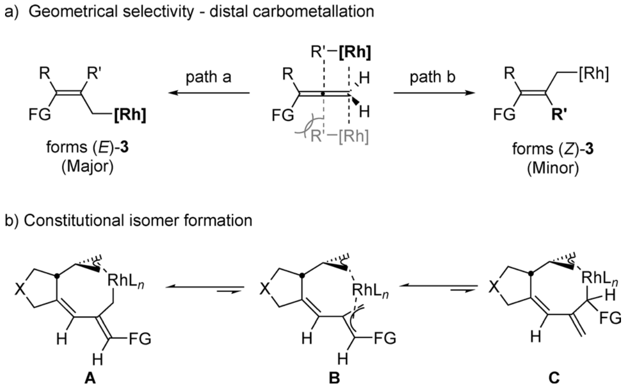
[a] All reactions were performed on a 0.1 mmol reaction scale using 5 mol% [{Rh(cod)Cl}$_2$] modified with P(OPh)$_3$ (30 mol%) and allene **2** (3 equiv) in *p*-xylene (0.05 M) at 120°C. [b] Yields of isolated products. [c] The allene **2** was added dropwise over ca. 2 h. [d] Ratio of the constitutional isomers **3**/**4** was determined by 500 MHz ^{1}H NMR analysis of the crude reaction mixture. [e] Only the *E*-isomer was observed for **3**, and was established using nOe studies. DMB = 2,4-dimethoxybenzyl, Nos = 4-nitrobenzenesulfonyl, FG = functional group, TBDPS = *tert*-butyldiphenylsilyl.

Additional studies probed the ability to increase the length of the tether in the ACP, which is generally challenging for related reactions.[6e,g,22] Gratifyingly, treatment of the ACP **5** with the substituted allenes **2** (R = H and Me) under the standard reaction conditions, afforded the 6,7-bicyclic derivatives **6a** (77%) and **6b** (99%), respectively [Eq. 1]. Hence, the ability to readily access the bicyclo[5.4.0]undecane ring system, which is also present in a number of important bioactive natural products, significantly expands the synthetic utility of this process.[23]



(1)

Scheme 2 outlines a plausible explanation for the geometrical control and the formation of the minor constitutional isomer in this process. In accord with our previous studies, the ligands in the key metallacycle intermediate are primarily responsible for efficiency of the insertion.[16] Hence, the



Scheme 2. Proposed rationale for chemo- and stereoselectivity in the rhodium-catalyzed [(3+2)+2] carbocyclization of ACPs with substituted allenes.

geometrical selectivity is ascribed to the nature of the groups on the allene, which is consistent with distal carbometalation (Scheme 2a; path a) opposite to the functional group (FG). Interestingly, 1,1-disubstituted allenes afford similar selectivity, provided the groups are stereoelectronically orthogonal to disfavor the formation of the opposite geometrical isomer (Scheme 2a, path b). Scheme 2b outlines the proposed rationale for the formation of the constitutional isomer **4**. We envision that the η^1-allyl metallacycle **A** could equilibrate via the bis(η^3-allyl) intermediate **B** to furnish **C** en route to **4**, provided the rate of the isomerization is faster than reductive elimination.[24] Alternatively, proximal carbometalation of the allene can also afford **4**, in which intermediate **C** would be subject to the analogous equilibration process.

In conclusion, we have developed the intermolecular rhodium-catalyzed [(3+2)+2] carbocyclization reaction of carbon- and heteroatom-tethered ACPs with activated and unactivated substituted allenes for the construction of bicycloheptatrienes. This study suggests that the stereoelectronic nature of the substituent on the allene controls distal ligation of mono- and 1,1-disubstituted allenes to permit the construction of tri- and tetrasubstituted exocyclic olefins, which provides a new strategy for the construction of the guaiane family of sesquiterpenes. The process is tolerant to ACP substitution and an array of functional groups on the allene, which expands the scope of functional groups in the exogenous π-component for these types of cycloaddition reactions. In addition, the reaction permits the efficient formation of 6,7-bicyclic structures, which tend to be particularly challenging in related carbocyclization reactions. Overall, this work provides a rare example of the highly selective distal carbometalation of a substituted exogenous allene.

Keywords: allenes · cyclizations · olefins · rhodium · synthetic methods

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[16] For the isolation and characterization of the rhodacycle involved in these higher-order carbocyclizations, see: P. A. Inglesby, J. Basca, D. E. Negru, P. A. Evans, *Angew. Chem. Int. Ed.* **2014**, *53*, 3952–3956; *Angew. Chem.* **2014**, *126*, 4033–4037.

[17] Although we have demonstrated the stoichiometric variant with an *alkenyl*idenecyclopropane, the catalytic version provides an inseparable mixture of at least six products.

[18] Interestingly, the octyl-substituted allene **2** ($R^1 = C_8H_{17}$, $R^2 = H$) provides the constitutional isomers **3**/**4** with 2.5:1 selectivity, thereby illustrating that the lower selectivity with the benzyloxymethyl group is not due to the Lewis basic nature of the benzyl ether group.

[19] Interestingly, the cycloaddition does not require the Thorpe–Ingold effect; for example, the methylene tethered ACP **1** (Table 2, $X = CH_2$, $R^1/R^3 = H$, $R^2 = Ph$) provides the cycloadduct **3** in 76% yield with $\geq 19{:}1$ selectivity for the *E*-isomer.

[20] The lower efficiency with the ethereal tethers is consistent with previous studies, see: a) S. Mazumder, D. Shang, D. E. Negru,

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[22] For a recent example which illustrates the challenges with longer tethers in a rhodium-catalyzed [(3+2)+1] carbocyclization, see: S. Kim, Y. K. Chung, *Org. Lett.* **2014**, *16*, 4352–4355.

[23] A. K. Miller, C. C. Hughes, J. J. Kennedy-Smith, S. N. Gradl, D. Trauner, *J. Am. Chem. Soc.* **2006**, *128*, 17057–17062, and references therein.

[24] For examples of allene insertion in a carbometalation as a result of C–H activation, see: a) H. Wang, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 7318–7322; *Angew. Chem.* **2012**, *124*, 7430–7434; b) D. N. Tran, N. Cramer, *Angew. Chem. Int. Ed.* **2013**, *52*, 10630–10634; *Angew. Chem.* **2013**, *125*, 10824–10828.

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