Metallacycles

DOI: 10.1002/ange.201310232

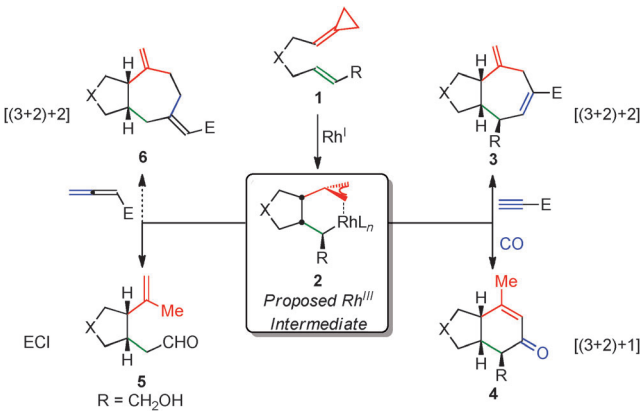
The Isolation and Characterization of a Rhodacycle Intermediate Implicated in Metal-Catalyzed Reactions of Alkylidenecyclopropanes**

*Phillip A. Inglesby, John Bacsa, Daniela E. Negru, and P. Andrew Evans**

Dedicated to Professor Philip D. Magnus on the occasion of his 70th birthday

Abstract: *The isolation and characterization of a rhodacycle intermediate implicated in rhodium-catalyzed reactions of alkylidenecyclopropanes (ACPs) is described. The structure of the metallacycle was unambiguously determined by X-ray crystallography and is catalytically competent in the rhodium-catalyzed carbocyclization and ene-cycloisomerization reactions of ACPs. This work represents a rare example of the isolation of a metallacycle in a metal-catalyzed higher-order carbocyclization reaction and thereby provides important insight into the ligand requirements for the insertion of π-components. Furthermore, it serves as a convenient synthon for the development of challenging higher-order carbocyclization reactions, as exemplified by the reaction with an activated allene.*

Transition-metal-catalyzed higher-order carbocyclization reactions provide unparalleled versatility for the step- and atom-economical construction of functionalized hetero- and carbocyclic ring systems using relatively simple π-components.[1] Indeed, since the initial discovery of the cyclotrimerization of alkynes by Reppe in 1948,[2] there has been considerable focus on the development of chemo-, regio-, and stereoselective variants, along with the introduction of novel π-components to increase the scope of these reactions. To this end, alkylidenecyclopropanes (ACPs) and methylenecyclopropanes (MCPs) have proven versatile three-carbon synthons for an array of metal-catalyzed annulation reactions.[3] The inherent utility of these intermediates can be attributed to their ability to undergo facile ring-opening with metals and provide constitutional isomers by tailoring distal versus proximal ring-opening.[4] In a program directed towards the development of higher-order reactions, we recently reported the stereoselective rhodium-catalyzed [(3+2)+2] and [(3+2)+1] carbocyclization reactions of ACPs **1** with alkynes and carbon monoxide for the synthesis of 5,7- and 5,6-bicyclic scaffolds **3** and **4**, respectively (Scheme 1).[5] In contrast, the omission of the exogenous π-component, namely the alkyne or carbon monoxide, facilitates the ene-cycloisomerization (ECI) reaction to furnish **5** ($R = CH_2OH$).[6,7] Interestingly, each of these reactions are proposed to proceed through the rhodium(III) metallacycle **2**.



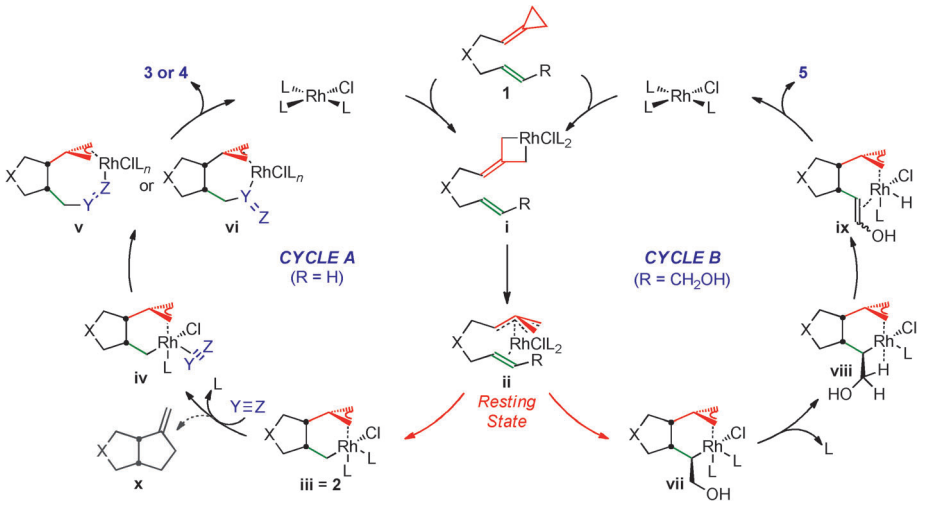
Scheme 1. Stereoselective rhodium-catalyzed $[(m+n)+o]$ carbocyclizations and ene-cycloisomerizations (ECI) of ACPs.

We envisioned that the ability to isolate and structurally characterize the metallacycle **2** would provide an opportunity to garner insight into the reaction mechanism. Additionally, it should also provide an important synthon for screening of new π-components to streamline the development of novel $[(m+n)+o]$ reactions. Nevertheless, there has been limited success in providing evidence of key organometallic intermediates involved in metal-catalyzed higher-order carbocyclization reactions, and the development of new reactions that involve the introduction of different π-components typically require lengthy optimization studies. Herein, we provide structural evidence for the π-allyl rhodacycle **2** and demonstrate its relevance to the aforementioned higher-order rhodium-catalyzed reactions of ACPs. Furthermore, we also describe a formal [(3+2)+2] carbocyclization reaction of the metallacycle **2** with an activated allene to produce **6**.

[*] Dr. P. A. Inglesby, Dr. J. Bacsa
Department of Chemistry, University of Liverpool
Crown Street, L69 7ZD (UK)
D. E. Negru, Prof. P. A. Evans
Department of Chemistry, Queen's University
90 Bader Lane, Kingston, ON K7L 3N6 (Canada)
E-mail: andrew.evans@chem.queensu.ca
Homepage: http://www.chem.queensu.ca/people/faculty/evans/pae.htm

[**] We sincerely thank the EPSRC (EP/G010250) for generous financial support and the Royal Society for a Wolfson Research Merit Award (P.A.E.). We also acknowledge NSERC for a Discovery Grant and a Tier 1 Canada Research Chair (P.A.E.).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201310232.



Scheme 2. Proposed mechanisms for the rhodium-catalyzed [(*m* + *n*) + *o*] carbocyclizations and ene-cycloisomerization reactions of tethered ACPs.

Scheme 2 outlines the proposed catalytic cycles for the higher-order carbocyclization and ene-cycloisomerization reactions. Oxidative addition of the low-valent rhodium complex into the ACP in **1** provides the metallacyclobutene **i** en route to the trimethylenemethane (TMM) complex **ii**.[5b] The TMM complex is the proposed resting state for this process, and undergoes rate-limiting carbometalation to afford the π-allyl metallacycle intermediates **iii**/**vii**, which are responsible for the carbocyclization and ene-cycloisomerization reactions. For example, in cycle A the coordination and insertion of the alkyne or carbon monoxide results in intermediates **v** and **vi**, which undergo facile $C(sp^2)$–$C(sp^2)$ reductive elimination to afford **3** and **4**, respectively. In contrast, the corresponding palladium(II) version of metallacycle **iii** readily undergoes facile $C(sp^2)$–$C(sp^3)$ reductive elimination to furnish the 5,5-bicyclic scaffold **x**, thereby making the isolation of the palladacycle challenging.[8] Interestingly, the π-allyl rhodium-alkyl intermediate **iii** (or **iv**) would require forcing conditions to induce $C(sp^2)$–$C(sp^3)$ reductive elimination to provide **x**.[9,10] Alternatively, cycle B outlines the ene-cycloisomerization in which rhodacycle **vii** leads to **viii** to facilitate β-hydride elimination and reductive elimination to afford **5**. We reasoned that although metallacycle **vii** undergoes rapid *exo*-β-hydride elimination, intermediate **iii** should be stable to *endo*-elimination owing to the poor alignment of the bridgehead proton with the rhodium atom. Thus, despite the challenges associated with the isolation of these types of metallacycle intermediates, we envisioned that these features would permit the isolation of the rhodium(III) intermediate **iii**.

Preliminary studies focused on the feasibility of isolating the key metallacycle intermediate **iii** by initially following the reaction by ^{1}H NMR in the absence of an exogenous π-component (Figure 1). Treatment of stoichiometric [{Rh(cod)Cl}$_2$] and triphenylphosphine (**A** and **B**) with the ACP **1a** at 100 °C (**C** and **D**) furnished the π-allyl rhodacycle intermediate **2a** (**E**) in 87 % yield as an air-stable pale yellow solid. Similarly, the corresponding triphenylphosphite complex was prepared in an analogous manner, affording **2b** in 82 % yield as an air-stable white solid, which illustrates the ability to vary the ligand in this process. The rhodacycles **2a** and **2b** were fully characterized by ^{1}H and ^{31}P NMR spectroscopy (d.r. ≥ 19:1 by ^{1}H NMR) in [D]chloroform. The ^{1}H NMR of **2a** clearly identified the rhodacycle as a π-allyl species with four allyl signals at 3.85, 3.40, 3.29, and 3.21 ppm. The two protons at 3.85 and 3.29 ppm show distinct $^3J_{H\text{-}P}$ couplings of 8.2 and 8.6 Hz, respectively, whereas the two protons at 3.40 and 3.21 ppm appear as broad singlets. The ^{1}H NMR of the phosphite complex **2b** also confirmed the η^3-hapacity of the allyl group, although the signals are more shielded than the phosphine complex with signals at 3.50, 3.13, 2.65, and 2.62 ppm. The ^{31}P NMR spectrum of **2a** shows two doublets at 27.9 and 19.4 ppm, which are consistent with $^1J_{P-Rh}$ couplings of 147.5 and 134.4 Hz, respectively, with no significant $^2J_{P\text{-}P}$ coupling observed. In contrast, complex **2b** shows two apparent double-double-quartets at 117.9 and 116.3 ppm, with coupling constants of 248.7 ($^1J_{P\text{-}Rh}$), 62.5 ($^2J_{P\text{-}P}$), 12.2 Hz ($^3J_{P\text{-}H}$), and 236.2 ($^1J_{P\text{-}Rh}$), 62.8 ($^2J_{P\text{-}P}$), 11.6 Hz ($^3J_{P\text{-}H}$), respectively. Hence, the metallacycle intermediates **2a** and **2b** contain distinctive η^3-allyl rather than a η^1-allyl, albeit

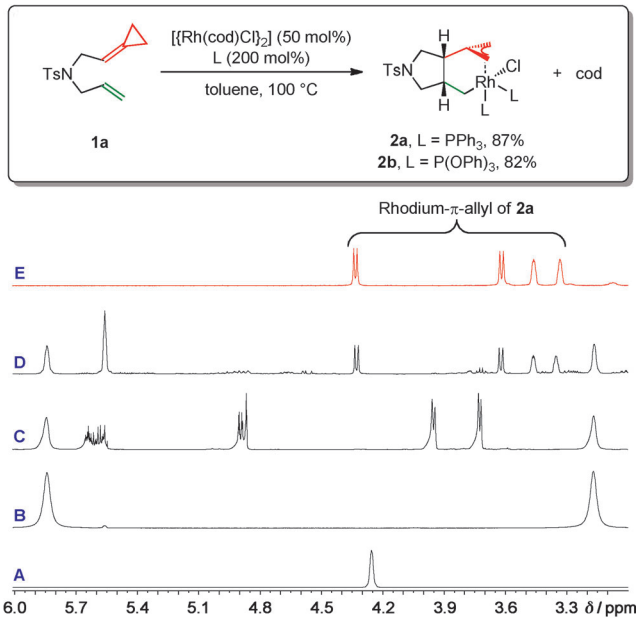


Figure 1. Isolation of rhodacycles **2a** and **2b**, and ^{1}H NMR spectroscopic study for **2a** in [D$_8$]toluene. **A**) [{Rh(cod)Cl}$_2$], RT. **B**) [{Rh(cod)Cl}$_2$], PPh_3, RT. **C**) **1a**, [{Rh(cod)Cl}$_2$], PPh_3, RT. **D**) **1a**, [{Rh(cod)Cl}$_2$], PPh_3, 100 °C, 120 min. **E**) **1a**, [{Rh(cod)Cl}$_2$], PPh_3, 100 °C, 120 min, then diluted with hexane and filtered. cod = 1,5-cyclooctadiene.

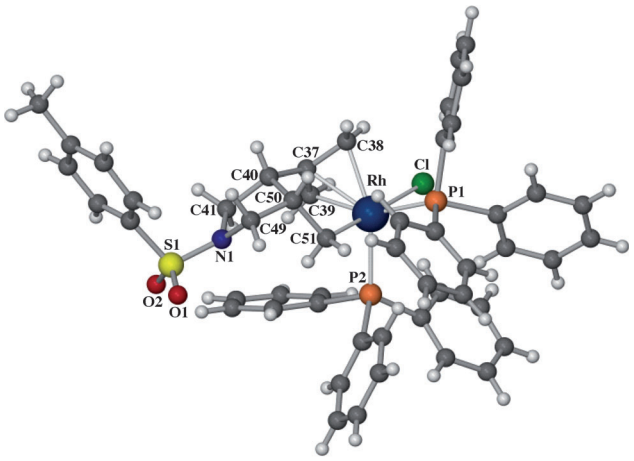
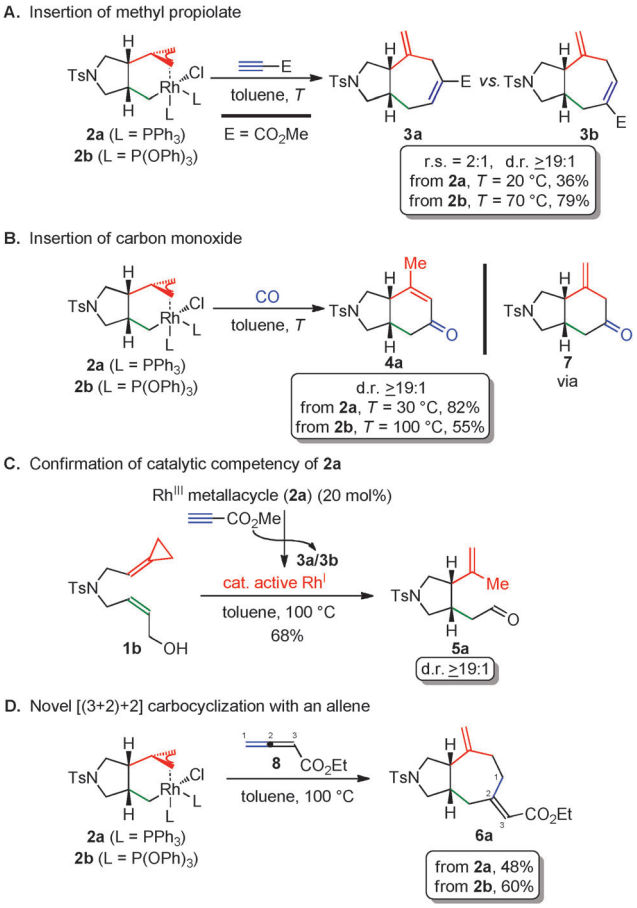


Figure 2. X-ray structure of rhodacycle **2a**.[11]

both types of bonding have been proposed for the corresponding palladacycle intermediates in related transformations.[8]

Recrystallization of **2a** from benzene/hexane afforded pale yellow crystals that were suitable for X-ray crystallographic analysis (Figure 2). The following describes the most significant data collected for **2a**, which co-crystallized with two molecules of benzene. The structure is a six-coordinate 18-electron rhodium species with a distorted monocapped octahedral geometry, which has two inequivalent triphenylphosphine groups, an η^3-allyl tethered to a methylene, and a chlorine atom. The unsymmetrical η^3-allyl moiety has Rh–C bond distances of 2.210(3), 2.181(3), and 2.253(3) Å for C37, C38, and C39, respectively. The Rh–P bond distances are 2.359(1) and 2.413(1) Å for P1 and P2, respectively, with the Rh–Cl bond being 2.516(1) Å. The equatorial sites have the two triphenylphosphine ligands and the two termini of the η^3-allyl, in which the latter is *endo* relative to the apical chlorine atom. The rhodium atom, two phosphorus atoms (P1/P2) and the two termini carbons of the η^3-allyl (C38/C39) are nearly planar, while the third carbon atom (C37) is slightly out of plane. The apical plane illustrates the chlorine atom is *anti* to the methylene with a Rh–C51 bond length of 2.091(3) Å. Furthermore, the C51–Rh–Cl angle is 179.00(9)°, thereby showing only a small degree of distortion. It is noteworthy that the dihedral angle between the rhodium atom and H50 is 71.66°, which rationalizes the absence of *endo*-β-hydride elimination at the ring junction (see above). Interestingly, this intermediate represents a rare example of a rhodacycle that contains C(sp^3) chirality, which makes it a structurally intriguing species.

The isolation of the π-allyl rhodacycle **2a** provided an important opportunity to probe the effect of the ligands on the insertion/reductive elimination, which occur after the rate-determining carbometalation step (Scheme 2).[5b] We envisioned that although the formation of **2a** requires high temperature (ca. 100 °C), the alkyne insertion and subsequent reductive elimination should occur at a lower temperature. In accord with our hypothesis, treatment of **2a** with methyl propiolate at 20 °C afforded the bicycloheptadienes **3a/3b** with identical regio- and diastereoselectivity to the catalytic



Scheme 3. Synthetic utility of rhodacycles **2a**/**2b** and their reactivity with π-components. A) Insertion of methyl propiolate in formal [(3+2)+2] carbocyclization reactions. B) Insertion of carbon monoxide in formal [(3+2)+1] carbocyclization reactions. C) Catalytic competency of **2a**. D) Development of a novel [(3+2)+2] carbocyclization by the insertion of an allene.

reaction with triphenylphosphite, albeit in low yield (Scheme 3 A). Interestingly, the phosphite-containing rhodacycle **2b**, which is the presumed intermediate for the catalytic process, furnished **3a/3b** with analogous efficiency and selectivity. Although a higher temperature is required for the insertion/reductive elimination (ca. 70 °C) in the latter case, it remains lower than the temperature to prepare the metallacycle **2b**.[12–14] The difference in the temperature required for these steps was tentatively attributed to the difference in the rate of ligand dissociation for $P(OPh)_3$ relative to PPh_3, which is presumably due to the increased π-acceptor capability of the former.

The insertion of carbon monoxide also provided an opportunity to determine the role of the ligand in the rhodium-catalyzed [(3 + 2) + 1] carbocyclization. Carbon monoxide undergoes insertion/reductive elimination at a slightly higher temperature for both **2a** and **2b** relative to the insertion of methyl propiolate (Scheme 3 B). However, the triphenylphosphine-containing metallacycle **2a** provides the optimal result, which mirrors the conditions for the catalytic process.[12–14] Interestingly, the analysis of the crude

reaction mixtures revealed that **2a** provides exclusively the exocyclic alkene **7**, whereas **2b** affords a mixture *exo* (**7**) and *endo* (**4a**) products. Nevertheless, both reactions furnish the *endo* product **4a** upon flash chromatography on silica gel. Although we had previously reported the importance of the nature of the ligand in the corresponding catalytic transformations, these studies did not delineate which part of the catalytic cycle the ligand is actually critical. Thus, it is now evident that the ligand directly impacts the temperature and efficiency of the insertion and/or reductive elimination of the π-component (**2** to **3**/**4**) and not the formation of the metallacycle (**1** to **2**).

Although the stoichiometric π-allyl rhodacycles **2a**/**2b** react with methyl propiolate and carbon monoxide, we sought to determine whether these intermediates are catalytically relevant (Scheme 3C). Treatment of a catalytic amount of **2a** with methyl propiolate furnished an active rhodium(I) catalyst to promote the related ene-cycloisomerization of ACP **1b** to the aldehyde **5a**, which is envisioned to proceed via a similar metallacycle intermediate (Scheme 2; **vii**). Thus, this clearly demonstrates that the metallacycle is catalytically relevant in these reactions.[15]

The realization that **2a** and **2b** can undergo rhodium-catalyzed $[(m+n)+o]$ carbocyclization reactions provided the impetus to employ previously unchallenged π-components. For example, we postulated that allene insertion into **2a**/**2b** would constitute a novel [(3+2)+2] carbocyclization reaction (Scheme 3D). Treatment of metallacycle **2a** with allene **8** at 100 °C afforded **6a** in 48 % yield along with several unidentified products. For example, in this reaction there is the potential to form eight stereoisomers, excluding enantiomers, that are due to 1,2- versus 2,3-chemoselectivity, which result in regio-, stereo-, and geometrical isomers. Interestingly, the treatment of metallacycle **2b** with allene **8** at 100 °C afforded **6a** as a single constitutional and stereoisomer in 60 % yield.[16] This study further highlights the impact of the ligand on $[(m+n)+o]$ carbocyclization reactions involving ACPs. It is noteworthy that the selectivity in this transformation complements that of alkyne insertion (cf. Scheme 3A), by providing access to the carbon framework of the *guaiane* family of sesquiterpenes. Furthermore, this reaction represents a rare example of a metal-catalyzed $[m+n+o]$ carbocyclization reaction that employs only alkenes and allenes as the reactive π-component.[17]

In conclusion, the novel π-allyl rhodacycles **2a**/**2b** implicated in the rhodium-catalyzed higher-order carbocyclization and ene-cycloisomerization reactions with ACPs were isolated and structurally characterized. Although related transition-metal-catalyzed transformations also postulate similar intermediates, this study provides unequivocal evidence for their existence with rhodium. This work also offers insight into ligand requirement for the insertion/reductive elimination of various π-components and demonstrates that the metallacycle is catalytically competent. We have also expanded the repertoire of π-components pertinent in this type of carbocyclization by demonstrating that allenes now provide excellent two-carbon synthons. Finally, the ability to employ rhodacycles **2a**/**2b** as formal [(3+2)] synthons with novel π-components, with a view of developing catalytic reactions, provides exciting opportunities for streamlining new developments in this field.

Received: November 25, 2013
Published online: March 11, 2014

Keywords: carbocyclization · ene-cycloisomerization · π-allyl ligands · reactive intermediates · rhodium

[1] For selected reviews on transition-metal-catalyzed $[m+n+o]$ carbocyclization reactions, see: a) P. A. Inglesby, P. A. Evans, *Chem. Soc. Rev.* **2010**, *39*, 2791 – 2805; b) C. Aubert, M. Malacria, C. Ollivier in *Science of Synthesis*, *Vol. 3* (Eds.: J. G. de Vries, G. A. Molander, P. A. Evans), Thieme, Stuttgart, **2011**, pp. 145 – 242, and pertinent references therein.

[2] W. Reppe, W. J. Schweckendiek, *Justus Liebigs Ann. Chem.* **1948**, *560*, 104 – 116.

[3] a) M. Rubin, M. Rubina, V. Gevorgyan, *Chem. Rev.* **2007**, *107*, 3117 – 3179; b) H. Pellissier, *Tetrahedron* **2010**, *66*, 8341 – 8375.

[4] a) A. Masarwa, I. Marek, *Chem. Eur. J.* **2010**, *16*, 9712 – 9721; b) C. Aïssa, *Synthesis* **2011**, 3389 – 3407.

[5] a) P. A. Evans, P. A. Inglesby, *J. Am. Chem. Soc.* **2008**, *130*, 12838 – 12839; b) S. Mazumder, D. Shang, D. E. Negru, M.-H. Baik, P. A. Evans, *J. Am. Chem. Soc.* **2012**, *134*, 20569 – 20572; For a highlight on the combination of computational studies with experimental results, see: I. Thiel, M. Hapke, *Angew. Chem.* **2013**, *125*, 6030 – 6032; *Angew. Chem. Int. Ed.* **2013**, *52*, 5916 – 5918.

[6] P. A. Evans, P. A. Inglesby, *J. Am. Chem. Soc.* **2012**, *134*, 3635 – 3638.

[7] For a recent review on transition-metal-catalyzed ene-cycloisomerization reactions, see: I. D. G. Watson, F. D. Toste in *Science of Synthesis*, *Vol. 3* (Eds.: J. G. de Vries, G. A. Molander, P. A. Evans), Thieme, Stuttgart, **2011**, pp. 243 – 307, and pertinent references therein.

[8] For selected examples of reactions that propose palladacycles similar to **2**, see: a) P. Binger, U. Schuchardt, *Angew. Chem.* **1977**, *89*, 254 – 255; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 249 – 250; b) B. M. Trost, M. L. Miller, *J. Am. Chem. Soc.* **1988**, *110*, 3687 – 3689; c) M. Lautens, Y. Ren, *J. Am. Chem. Soc.* **1996**, *118*, 10668 – 10669; d) M. Gulías, R. García, A. Delgado, L. Castedo, J. L. Mascareñas, *J. Am. Chem. Soc.* **2006**, *128*, 384 – 385.

[9] For an example of the consequence of σ- vs. π-character on reductive elimination, see: Y. Wang, J. Wang, J. Su, F. Huang, L. Jiao, Y. Liang, D. Yang, S. Zhang, P. A. Wender, Z.-X. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 10060 – 10061.

[10] For an example of an allyl-rhodium-alkyl species that does not readily undergo $C(sp^3)-C(sp^2)$ reductive elimination, see: S. Ikeda, Y. Maruyama, F. Ozawa, *Organometallics* **1998**, *17*, 3770 – 3774.

[11] CCDC 954061 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] The formation of **2a**/**2b** did not occur below 100 °C, which was also apparent for the formation of **3a**/**3b** in the corresponding catalytic reaction.[5a]

[13] The temperatures for insertion represent the point at which the reaction reaches full conversion (see the Supporting Information).

[14] The excellent yield for methyl propiolate insertion into **2b** (Scheme 3A) is consistent with our previous observation that phosphites are excellent ligands in the [(3+2)+2] carbocyclization reaction. Furthermore, complex **2a** is optimal in the formal [(3+2)+1] carbocyclization reaction (Scheme 3B), which again

mirrors the catalytic process wherein phosphines were optimal.[5a]

[15] Similarly, **2b** is catalytically competent for the conversion of **1a** with methyl propiolate to the carbocyclization adducts **3a/3b** (85% yield).

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

[17] For a recent example of this type of transformation, see: N. N. Noucti, E. J. Alexanian, *Angew. Chem.* **2013**, *125*, 8582 – 8585; *Angew. Chem. Int. Ed.* **2013**, *52*, 8424 – 8427.

