# JOC Article

# Rhodium-Catalyzed Tandem Cyclization: Formation of 1H-Indenes and 1-Alkylideneindans from Arylboronate Esters in Aqueous Media

Mark Lautens* and Tzvetelina Marquardt

*Davenport Chemical Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario M5S 3H6, Canada*

*mlautens@chem.utoronto.ca*

Arylboronate esters bearing a pendant Michael-type acceptor olefin or acetylene linkage undergo transmetalation with a rhodium-based catalytic complex to generate a functionalized organorhodium intermediate which can cyclize onto nonterminal acetylenes in good to excellent yields. The catalytic system involves the use of electron-rich, sterically bulky ligands as tri-*tert*-butylphosphonium tetrafluoroborate stabilizing the organorhodium intermediates and reduces the incidence of protodeboronation in aqueous media.

## Introduction

In recent years, carbon−carbon bond formation using transition-metal catalysts in water has gained popularity as an attractive strategy in organic synthesis for the efficient construction of complex organic molecules.[1] As an alternative to the palladium-catalyzed cross-couplings, rhodium-catalyzed reactions of boronic acids with activated alkenes in aqueous media have been developed as very efficient methods for the formation of carbon−carbon bonds. Significant contributions include the seminal studies by Miyaura and Hayashi,[2] who demonstrated highly enantioselective conjugate addition of arylboronic acids to aldehydes and enones, respectively. An important aspect of these reactions was that water was necessary as a cosolvent (or additive) to promote the coupling process through the generation of a catalytically active hydroxorhodium(I) intermediate.[3]

Recently, we reported the rhodium-catalyzed reaction of various arylboronic acids to aromatic or heteroaromatic alkenes[4] or alkynes using the water-soluble ligands TPPDS **1**[5] or the pyridine-substituted ligand **2**[6] (Figure
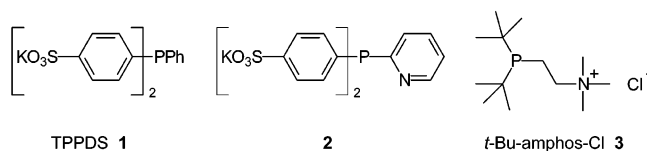


**FIGURE 1.**

1). As the study pointed to reactivity differences between rhodium and palladium in intermolecular couplings, it was of interest to determine how intramolecular processes would fare. The majority of methodologies reported using rhodium catalysis focus on intermolecular processes with the metal mediating the formation of only *one* carbon−carbon bond.

Recently, we demonstrated our first studies on the intramolecular tandem carbocyclization process with arylboronate esters bearing a pendant Michael-acceptor double bond and strained olefins as coupling partners, utilizing a water-soluble rhodium catalyst system with *t*-Bu-amphos-Cl **3** as a ligand (Figure 1).[7]

Inspired by the good results for obtaining the indan systems, our investigations were then focused on applications of alkynes as coupling partners as this would significantly broaden the general applicability of the rhodium-catalyzed tandem cyclization reaction and would generate products that could undergo further transformations providing access to biologically active compounds. For example, the products synthesized by the present coupling methodology might be easily subjected

(1) For rewiews of organic synthesis in water, see: (a) Grieco, P. A. *Organic Synthesis in Water*; Blackie Academic and Professional: London, 1998. (b) Cornils, B.; Herrmann, W. A. *Aqueous-Phase Organometallic Chemistry: Concepts and Applications*; Wiley-VCH: Weinheim, 1998. (c) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; Wiley-Interscience: New York, 1997. (d) Horváth, I. T.; Joó, F. *Aqueous Organometallic Chemistry and Catalysis*; Kluwer Academic: Dordrecht, The Niederlands, 1995. (e) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. (f) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *93*, 2023. (g) For a general review on rhodium-catalyzed carbon−carbon bond-forming reactions of organometallic compounds, see: Fagnou, K.; Lautens, M. *Chem Rev.* **2003**, *103*, 169.

(2) For addition to enones: (a) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (c) For a review, see: Hayashi, T. *Synlett* **2001**, 879.

(3) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

(4) (a) Lautens, M.; Roy, A.; Fukuoka, K.; Fagnou, K.; Martín-Matute, B. *J. Am. Chem. Soc.* **2001**, *123*, 5358.

(5) Other examples for reactions using TPPDS, see: (a) Thorpe, T.; Brown, S. M.; Crosby, J.; Fitzjohn, S.; Muxworthy, J. P.; Williams, J. M. J. *Tetrahedron Lett.* **2000**, *41*, 4503. (b) Chen, H.; Li, Y.; Chen, J.; Cheng, P.; Li, X. *Catal. Today* **2002**, *74*, 131.

(6) (a) Lautens, M.; Yoshida, M. *Org. Lett.* **2002**, *4*, 123. (b) Lautens, M.; Yoshida, M. *J. Org. Chem.* **2003**, *68*, 762. (c) Recently, Hayashi has reported a similar addition of alkynes: Hayashi, T.; Inoue, K.; Taniguchi, N.; Ogasawara, M. *J. Am. Chem. Soc.* **2001**, *123*, 9918.

(7) Lautens, M.; Mancuso, J. *Org. Lett.* **2002**, *4*, 2105.

**TABLE 1.   Optimization Using Pinacol Boronate Ester 1 and Activated Alkyne as Coupling Partner**
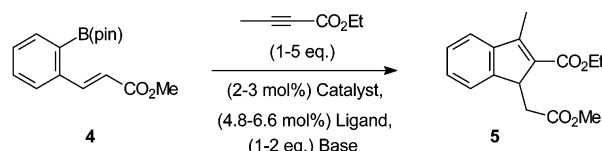


| entry | catalyst/ligand | solvent | $T$ (°C) | time (h) | yield$^a$ (%) |
|---|---|---|---|---|---|
| 1$^b$ | [Rh(cod)Cl]$_2$/$t$-Bu-amphos-Cl **3** | toluene/water (1:1) | 80 | 3 | 22 |
| 2$^c$ | [Rh(cod)Cl]$_2$/$t$-Bu$_3$PH$^+$·BF$_4^-$ | dioxane/water (10:1) | 80 | 3 | 99 |
| 3$^d$ | [Rh(cod)Cl]$_2$/$t$-Bu$_3$PH$^+$·BF$_4^-$ | dioxane/water (10:1) | 80 | 3 | 99 |
| 4$^d$ | [Rh(cod)Cl]$_2$/$t$-Bu$_3$PH$^+$·BF$_4^-$ | dioxane/water (10:1) | rt | 19 | 47 |

$^a$ Isolated yield by flash coloumn chromatography. $^b$ 1.2 equiv of the alkyne, 2 mol % catalyst, 4.8% ligand, 0.6 equiv of SDS, 1.0 equiv of Na$_2$CO$_3$. $^c$ 5.0 equiv of the alkyne, 3 mol % catalyst, 6.6 mol % ligand, 2.0 equiv of Na$_2$CO$_3$. $^d$ 1.3 equiv of the alkyne.

**SCHEME 1**
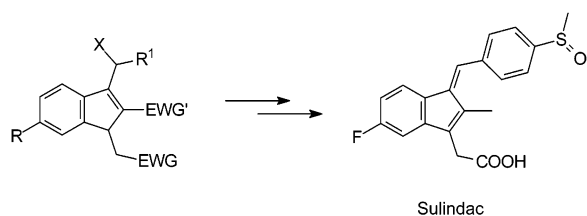


Sulindac
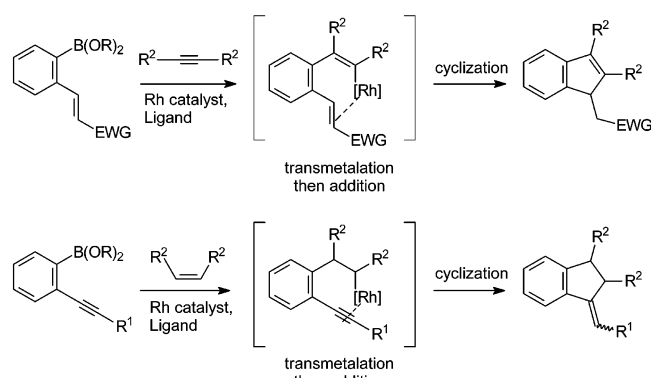
**SCHEME 2**



to post modifications involving an elimination step in order to obtain new analogues of the nonsteroidal anti-inflammatory drug sulindac[8] (Scheme 1). More recently, interest in this class of compounds has grown, due to the use of sulindac for cancer treatment and cancer prevention.[9]

Herein we report the successful utilization of a wide variety of activated alkynes in the rhodium-catalyzed carbocyclization reaction, which would allow access to cyclic systems with *exo*- or *endo*-cyclic double bonds on the newly formed five-membered ring (Scheme 2).

## Results and Disscusion

Our initial experiments were focused on finding a catalyst system that would promote the addition and intramolecular cyclization reactions. According to our previously reported protocol for addition to alkenes,[7] the reaction of ethyl-2-butynoate and the model substrate pinacol (pin) boronate ester **4** in the presence of 2 mol % of [Rh(cod)Cl]$_2$, 4.8 mol % of $t$-Bu-amphos-Cl **3**, 1 equiv of Na$_2$CO$_3$, and 0.6 equiv of sodium dodecyl sulfate (SDS) in toluene/water (1:1 mixture) at 80 °C for 3 h gave the corresponding cyclization product **5** in 22% yield (25% yield based on recovered starting material) (Table 1, entry 1). Because of the low yield and competing pro-todeboronation of the starting material, our attention turned to finding a new catalyst system that would avoid these unwanted processes. In analogy to the conditions reported by Hayashi and Miyaura,[2] a solvent mixture of dioxane/water (10:1) was applied and the reaction was performed with 3 mol % of [Rh(cod)Cl]$_2$ and 6.6 mol % of tri-$tert$-butylphosphonium tetrafluoroborate[10] as a ligand, which increased the yield to 99% (entry 2). The number of equivalents of alkyne appeared to be insignificant to the yield, whereas elevated temperature was essential for good conversion (entry 3 and 4).

A series of coupling partners bearing an alkyne moiety were then subjected to the modified reaction conditions to further define the reaction scope (Table 2). Reaction with the commercially available 1-phenylpropyne led to 95% yield of product **6** (Table 2, entry 1). When ethyl 4-methylpent-2-ynoate[11] was subjected to the reaction conditions, the corresponding product **7**, was obtained in good (77%) yield (entry 2). The same reaction applied to diphenylacetylene gave **8** in quantitative yield (entry 3). Further reduction in the electron density of the triple bond resulted in lower yield, which was shown when ethyl 3-phenylprop-2-ynoate reacted to afford product **9** (entry 4). In the case of diethyl acetylenedicarboxylate (entry 5), cyclotrimerization occurred and instead of the envisaged indan-type product the corresponding hexa-substituted benzene **10** was obtained in 72% yield.
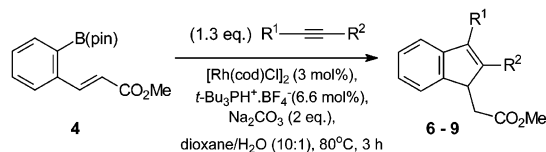
Encouraged by the excellent results obtained for alkynes featuring a phenyl residue as an electron-withdrawing group, several alkynes bearing electron-deficient heteroaromatic or nitrophenyl groups were screened in the reaction, and the results are summarized in Table 3. The starting materials were prepared according to our previously reported protocol.[6a] In contrast to the reactions of **11** and **13** (Table 3, entries 1 and 2), the reaction of **15**, which has the alkynyl group in the

(8) (a) Maguire, A. R.; Papot, S.; Ford, A.; Touhey, S.; O'Connor, R.; Clynes, M. *Synlett* **2001**, *1*, 41. (b) Karaguni, I.-M.; Herter, P.; Courzoulidou, E.; Carpintero, M.; Müller, O.; Waldmann, H. German Patent DE 101 63 426.9, 2003.

(9) Selected references: (a) Giardellio, R. M.; Hamilton, S. R.; Krush, A. J. N. *Engl. J. Med.* **1993**, *328*, 1313. (b) Heath, C. W.; Thun, M. J.; Greeberg, E. R.; Levin, B.; Marnett, L. J. *Cancer* **1994**, *74*, 2885. (c) Pepin, P.; Bouchard, L.; Nicole, P.; Castonguay, A. *Carcinogenesis* **1992**, *13*, 341. (d) Rao, C. V.; Rivenson, A.; Simi, B.; Zang, E.; Kelloff, G.; Steele, V.; Reddy, B. S. *Cancer Res.* **1995**, *55*, 1464. (e) Thompson, H. J.; Jiang, C.; Lu, J.; Menta, R. G.; Piazza, G. A.; Paranka, N. S.; Pamukcu, R.; Ahnen, D. J. *Cancer Res.* **1997**, *57*, 6.

(10) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *26*, 4295.

(11) Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron* **1989**, *45*, 363.
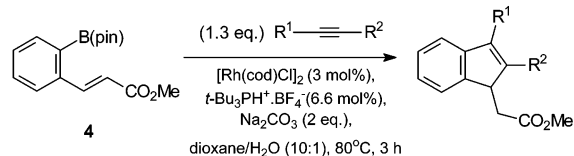
**TABLE 2.   Screening Alkynes with Activated Triple Bond as Coupling Partners[a]**



| entry | substrate | product | yield[b] |
|---|---|---|---|
| 1 | | 6 | 95% |
| 2 | | 7 | 77% |
| 3 | | 8 | quantitative |
| 4 | | 9 | 30% |
| 5[c] | | 10 | 72% |

[a] Reactions were carried out in the presence of 3 mol % of [Rh(cod)Cl]$_2$, 6.6 mol % of $t$-Bu$_3$PH$^+$·BF$_4^-$, 1.3 equiv of pinacol boronate ester **4**, and 2 equiv of Na$_2$CO$_3$ in dioxane/H$_2$O (10:1) at 80 °C, for 3 h. [b] Isolated yields by flash column chromatography. [c] The reaction was performed at 80 °C, 2 equiv of the alkyne, 2 mol % of [Rh(cod)Cl]$_2$, 4.8% $t$-Bu-amphos Cl **3**, 0.6 equiv of SDS, 1.0 equiv of Na$_2$CO$_3$.

**TABLE 3.   Screening Alkynes Containing Various Heteroaromatic Substituents[a]**



| entry | substrate | product | yield[b] |
|---|---|---|---|
| 1 | 11 | 12 | 98% |
| 2 | 13 | 14 | 60% |
| 3 | 15 | ----- | N.R. |
| 4 | 16 | ----- | N.R. |
| 5[c] | 17 | 18 | 76% |
| 6 | 19 | 20 | trace[c] |
| 7 | 21 | 22 | 92% |
| 8 | 23 | ----- | N.R. |

[a] Reactions were carried out in the presence of 3 mol % of [Rh(cod)Cl]$_2$, 6.6 mol % of $t$-Bu$_3$PH$^+$·BF$_4^-$, 1.3 equiv of pinacol boronate ester **4**, and 2 equiv Na$_2$CO$_3$ in dioxane/H$_2$O (10:1) at 80 °C, for 3 h. [b] Isolated yields by flash column chromatography. [c] A considerable amount of both starting materials remained.

2-position on the pyridine ring, failed to undergo the addition (entry 3). Similarly, no reaction was observed when bromo-2-pyridylalkyne **16** was used (entry 4). When alkyne **17**, bearing a pyrimidyl moiety, was subjected to the reaction conditions, the product **18** was obtained in 76% yield (entry 5). The quinolyl-substituted alkyne **19** (entry 6) resulted in a complex reaction mixture that contained the envisaged product **20** only in minute amounts. An excellent yield was obtained when alkyne **21**, bearing a *p*-nitrophenyl group, was reacted providing **22** (entry 7). In contrast, no reaction was observed for the isomeric alkyne **23** with a nitro moiety in the *ortho*-position, very possibly due to steric hindrance caused by the nitro group (entry 8).

The reactions of propargylic type substrates with an ethyl ester moiety attached to the triple bond were also examined (Table 4). Initially, alkynes **24** and **26** were subjected to the optimized reaction conditions for aryl and heteroaryl alkynes and the products. Adducts **25** and **27** were obtained respectively, both in 36% yields (Table

4, entries 1 and 2). Because of the stereocenter present in the THP group, the product **25** was obtained as a mixture of diastereomers. Substrate **26** which bears a Boc-protected amine function gave the desired product **27** as 5:1 mixture of two regioisomers which were

**TABLE 4.  Screening and Optimization of the Tandem Cyclization Using Substituted Propargylic Alkynes[a]**



| entry | alkyne | product | base | conditions | yield[b] | regioisomers ratio (I:II) |
|---|---|---|---|---|---|---|
| 1 | **24** | **25** | $Na_2CO_3$ | 80 °C, 3 h | 36% | diastereomeric mixture |
| 2 | **26** | **27** | $Na_2CO_3$ | 80 °C, 3 h | 35% | 5:1 |
| 3 | **26** | **27** | $Na_2CO_3$ | 80 °C, 17 h | 65% | 7:1 |
| 4 | **26** | **27** | $Na_2CO_3$ | r.t., 17 h | 71% | 6:1 |
| 5 | **26** | **27** | KF | r. t., 17 h | 78% | 6:1 |
| 6 | **28** | **29** | $Na_2CO_3$ | 80 °C, 24 h | traces | single regiosomer |
| 7 | **28** | **29** | KF | r. t., 17 h | 89% | single regiosomer |
| 8 | **30** | ----- | KF | r. t., 17 h | ---- | ---- |

[a] Reactions were carried out in the presence of 3 mol % of [Rh(cod)Cl]$_2$, 6.6 mol % of $t$-Bu$_3$PH$^+$·BF$_4^-$, 1.3 equiv of pinacol boronate ester **4**, and 2 equiv of Na$_2$CO$_3$ in dioxane/H$_2$O (10:1) at 80 °C, for 3 h. [b] Isolated yields by flash column chromatography.

separated by flash chromatography. The structure of the major product was found to be analogous to the structures of the other cyclization products, as confirmed by 2D-NMR experiments. Prolongation of the reaction time increased the yield and the regioisomeric ratio changes from 5:1 to 7:1 (entries 2 and 3). A decrease of the reaction temperature resulted in a slightly increased yield (entries 4), and the best result was obtained when 2 equiv of KF was used instead of Na$_2$CO$_3$ as a base (entry 5). However, no significant change was observed regarding the regioisomeric ratio.

To avoid the problems arising from the stereocenter in the THP-ether, we examined substrate **28** bearing a siloxyl group. Under the initially established conditions, only traces of the desired product **29** (entry 6) were obtained. When the same reaction was performed at room temperature overnight in the presence of 2 equiv of KF **29** was obtained in 89% yield as single regioisomer (entry 7). The corresponding substrate **30** with a free hydroxyl moiety was also tested but no product formation was observed and only deboranated starting material was isolated (entry 8).

A plausible explanation for the formation of two regioisomers in the case of substrate **26** is shown in Scheme 3. Electronic effects would favor the formation of the C−C bond by carborhodation in the $\beta$-position, and products corresponding to regioisomer-I are indeed formed exclusively. However, the coordinative features of the functional moieties neighboring the triple bond have also to be taken into account. Apparently, the ability of the NHBoc-group to interact with the rhodium can also favor the formation of regioisomer-II (see Scheme 3). In this case, both directing effects compete with each other and corespondingly a mixture of regioisomers was obtained whereby regioisomer-I was formed predominantly.

Next, we tried the reaction of ethyl-2-butynoate with aryl boronates bearing different pendant Michael acceptors or substituents (Table 5). Boronate ester **31** with a *tert*-butyl ester moiety adjacent to the double bond gave the corresponding product **32** in a moderate yield of 60% (Table 5, entry 1). In contrast, the reaction with aryl boronate **33**, featuring an acetyl residue as an electron withdrawing group, led to a quantitative yield of the desired product **34** (entry 2). Surprisingly, when sub-
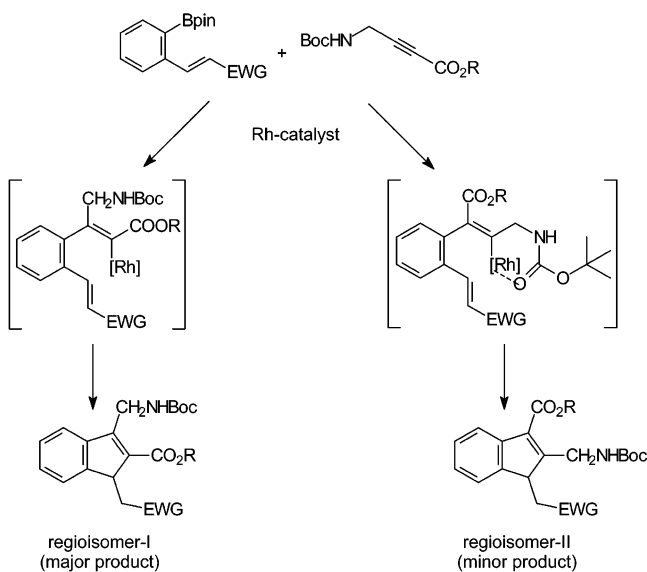
**SCHEME 3**



regioisomer-I
(major product)

regioisomer-II
(minor product)

**TABLE 5. Screening of Aryl Boronates Bearing Different Pendant Michael Acceptors or Substituents on the Aryl Residue**[a]



| entry | substrate | product | yield[b] |
|---|---|---|---|
| 1 | **31** | **32** | 60% |
| 2 | **33** | **34** | quantitative |
| 3 | **35** | **36** | trace[c] |
| 4 | **39** | **40** | quantitative |

[a] Reactions were carried out in the presence of 3 mol % of [Rh(cod)Cl]₂, 6.6 mol % of $t$-Bu$_3$PH$^+$·BF$_4^-$, 1.3 equiv of pinacol boronate ester, and 2 equiv of Na$_2$CO$_3$ in dioxane/H$_2$O (10:1) at 80 °C, for 3 h. [b] Isolated yields by flash column chromatography. [c] Mainly deboronated starting material was obtained.

strate **35**, bearing a tertiary amide group, was subjected to the reaction conditions, mainly deboronated starting material was obtained and only traces of product **36** were observed (entry 3).

**TABLE 6. Optimization of the Coupling Reaction of Boronate Ester 41 and *tert*-Butylacrylate**[a]

| entry | solvent | yield[b] (%) | product ratio (**42a**/**42b**) |
|---|---|---|---|
| 1 | dioxane/H$_2$O (10:1) | 82 | 1.3:1 |
| 2 | dioxane/H$_2$O (1:1) | 66 | 1:1 |
| 3 | dioxane | 36 | only **42b** |
| 4 | H$_2$O[c] | 85 | 0.4:1 |
| 5 | MeOH/H$_2$O (6:1) | 81 | only **42a** |
| 6 | H$_2$O/MeOH (6:1)[c] | 91 | 0.1:1 |

[a] Reactions were carried out in the presence of 3 mol % of [Rh(cod)Cl]₂, 6.6 mol % of $t$-Bu$_3$PH$^+$·BF$_4^-$, 2 equiv of Na$_2$CO$_3$, and 5.0 equiv of *tert*-butylacrylate, at 80 °C, for 3–5 h. [b] Isolated yields by flash column chromatography. [c] 0.6 equiv of SDS was added.

We then investigated the effect of a *p*-methoxy substituent on the aromatic ring of the pinacol boronate ester. Compound **39** was prepared as shown in Scheme 4. After bromination of 4-methoxybenzaldehyde and subsequent acetalization, **37** was obtained (70% yield over two steps).[12] Lithiation with *n*-BuLi at −100 °C, quenching with trimethyl borate, and subsequent hydrolysis of the resulting boronate[13] as well as cleavage of the acetal group with 3.0 M hydrochloric acid at 0 °C gave the desired boronic acids **38**.[14] Commonly, many boronic acids tend to cyclotrimerize to the corresponding boroxin on standing.[15] Consequently, the boronic acid functionality was protected with pinacol. Subsequent Wittig reaction with methyl(triphenylphosphoranylidene)-acetate led to **39** (52% isolated yield based on compound **37**).

Compound **39** was subjected to the reaction conditions with ethyl 2-butynoate and the desired cyclized product **40** was obtained in quantitative yield (see Table 5, entry 4).

In the course of our study of the rhodium-catalyzed tandem cyclization reaction with alkynes we have also tested arylboronic acid derivatives with a pendant triple bond as a Michael acceptor. Interestingly, we found that when substrate **41**[16] was reacted with *tert*-butylacrylate in the presence of [Rh(cod)Cl]₂ and tri-*tert*-butylphosphonium tetrafluoroborate a third carborhodation occurred (see Figure 2) and a mixture of two products **42a** and **42b** was obtained (Scheme 5). The saturated compound **42a** results from protodemetalation at the last step of the catalytic cycle, and the unsaturated Heck-type product **42b** is a result of $\beta$-hydride elimination. Both processes compete, and after optimization it was found that the ratio between the products depended mainly on the solvent mixture (Table 6). By changing the solvent system it was possible to favor the formation of one coupling product prior to the other. For example, when the reaction was conducted in dioxane and in the absence of water, the unsaturated product **42b** was formed in moderate yield of 36% (entry 3). In contrast, when the reaction was performed in mixture of methanol/water (6:1), only the saturated product **42a** was obtained in 81%

(12) Kaiser, F.; Schwink, L.; Valzer, J.; Schmalz, H.-G. *J. Org. Chem.* **2002**, *67*, 9248.

(13) Brown, H. C.; Cole, T. E. *Organometallics* **1983**, *2*, 1316.

(14) Kumar, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1018.

(15) Li, W.; Burgess, K. *Tetrahedron Lett.* **1999**, *40*, 6527.

(16) Compound **41** was synthesized by Sonogashira coupling of 2-bromoiodobenzene and phenylacetylene and further application of our standard protocol for obtaining the corresponding boronate ester derivative.

**SCHEME 4**



70% (over two steps)

52% (based on compound **37**)
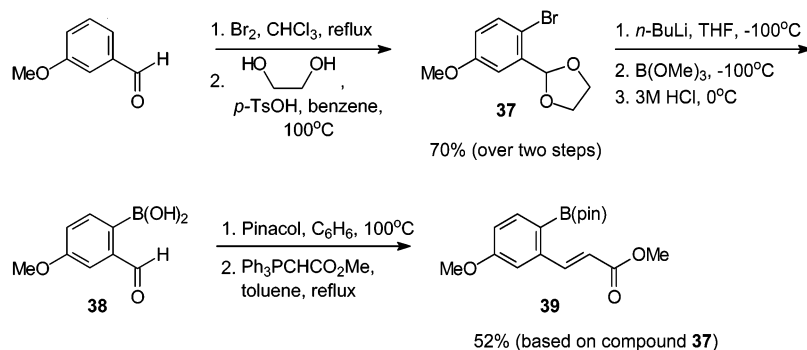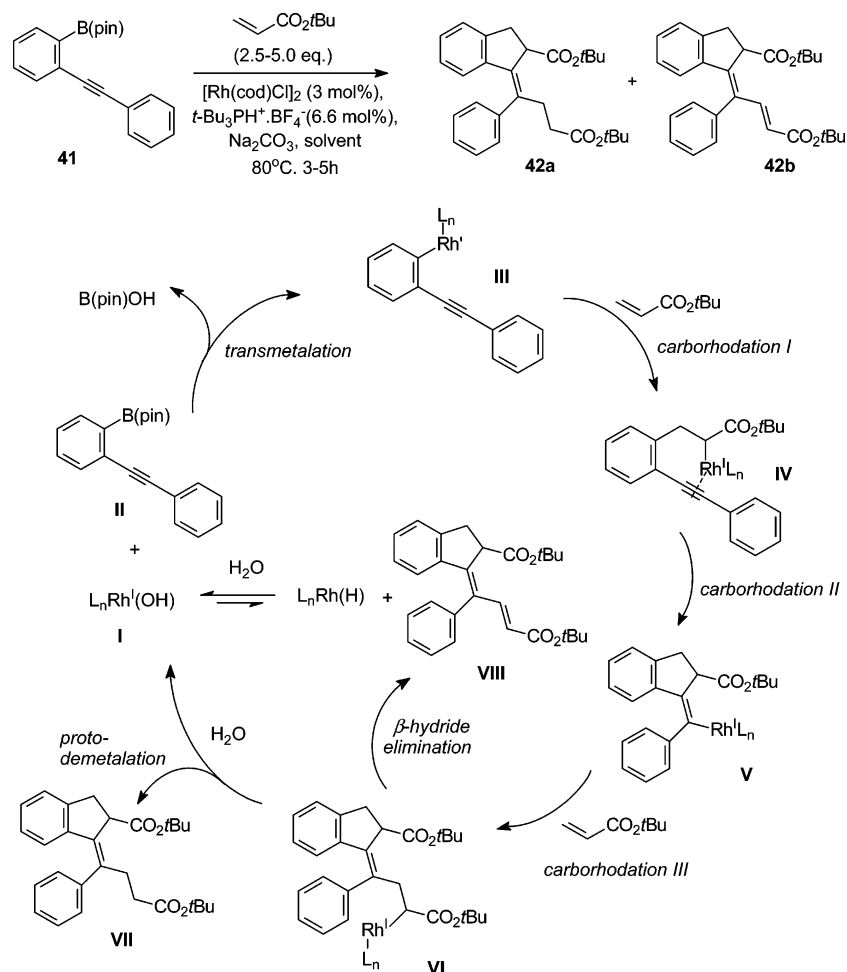
**SCHEME 5**



**FIGURE 2.**

yield (entry 5). X-ray crystallographic analysis confirmed the structure of **42b**.

The catalytic cycle of this rhodium-catalyzed tandem cyclization is believed to involve the presence of hydroxorhodium(I) intermediates. The rhodium(cyclooctadiene)-chloride dimer is known to hydrolyze at room temperature in basic aqueous solution to generate the corresponding hydroxorhodium(I) species.[17] Although the presence of a base such as sodium carbonate is needed to

generate a small quantity of hydroxide ion to produce the active rhodium catalyst and to render the boron center tetracoordinate, it was found that fluoride is also suitable, as has been previously observed for studies on the Suzuki coupling.[18] Two equivalents of fluoride are believed to promote the formation of an $Ar(BF_nOH_{3-n})^-$ species which transmetalates more readily.[19] Indeed, the reduced basicity of fluoride has proven beneficial in cases

(17) Joó, F.; Kovács, J.; Bényei, A. C.; Nádasdi, L.; Laurenczy, G. *Chem. Eur. J.* **2001**, *7*, 193.

(18) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.

(19) The addition of fluoride may also promote the formation of a catalytically active fluororhodium(I) intermediate.
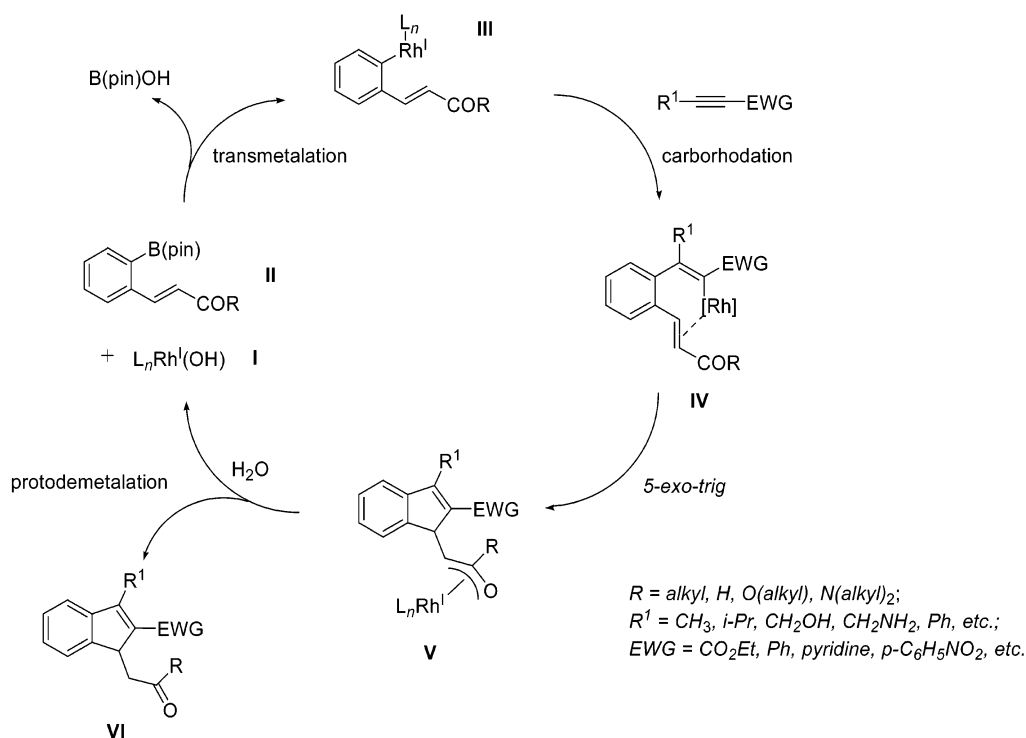
**FIGURE 3.**

where very acidic protons are present within the coupling partners, thus rendering the use of protecting groups unnecessary.

In the coupling reaction with activated alkynes, the catalytic cycle (Figure 3) is initiated by transmetalation of $L_nRh(OH)$ **I** with the arylboronate substrate **II** to generate the arylrhodium(I) species **III** and release B(pin)OH. Coordination of the alkyne followed by selective carborhodation gives **IV** in which the rhodium is presumably coordinated to the internal pendant olefin. The 5-*exo-trig* ring closure leads to the (oxa-$\pi$-allyl)-rhodium species **V**. This is rapidly protodemetalated by water which releases the product **VI** and regenerates the hydroxorhodium(I) species.[3]

## Conclusion

In conclusion, we have developed a rhodium-catalyzed tandem cyclization involving a variety of arylboronic esters with various activated alkynes as coupling partners, which gives access to highly functionalized polycyclic systems. The reaction was run in the presence of water, which is not only acting as a solvent, but is also required to provide a proton source to form the product and regenerate the catalyst.

We have demonstrated the use of activated alkynes for the synthesis of functionalized 1*H*-indene derivatives of potential pharmaceutical interest. The intramolecular cyclization reaction was also achieved with an arylboronate ester bearing a pendant alkyne as Michael acceptor and *tert*-butylacrylate, whereby a third carborhodation

occurred, giving highly functionalized 1-alkylideneindans in excellent yield. The key feature of the intramolecular coupling methodology is that yields are based on consumption of the more expensive arylboron partner. Furthermore, it was found that the reaction proceeds with the best yields in the presence of the commercially available tri-*tert*-butylphosphonium tetrafluoroborate. The stabilization of the arylrhodium intermediates by the ligand is noteworthy and results in a reduction of overall reaction cost and waste generation; vital points for the development of industrial processes.

We are currently investigating the use of heterocyclic arylboronate esters, as well as evaluating alkyl boronates which can undergo similar transformations.

## Experimental Section

**General Procedure for the Rhodium-Catalyzed Cyclization Reaction of Arylboronates Bearing a Pendant Michael Acceptor and Activated Alkynes.** A solution of $[Rh(cod)Cl]_2$ (3.9 mg, 7.86 $\mu$mol), tri-*tert*-butylphosphonium tetrafluoroborate (5.0 mg, 17.3 $\mu$mol, 1:1.2 ligand to Rh), and $Na_2CO_3$ (56 mg, 0.524 mmol) in a degassed 10:1 mixture of dioxane/water (2.2 mL) was vigorously stirred under an inert atmosphere for 30 min at ambient temperature. Thereafter, to the bright yellow solution was added the alkyne (0.341 mmol), followed by addition of the boronate ester derivative (0.262 mmol), and the resulting reaction mixture was stirred for 3 h at 80 °C. After being cooled to room temperature, the colored solution was poured into diethyl ether (10 mL) and the resulting mixture was washed with brine (2 mL). The two phases were separated, and the aqueous phase was extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude material was purified by flash column chromatography on silica gel.

**Ethyl 1-(methoxycarbonylmethyl)-3-methyl-1*H*-indene-2-carboxylate (5):** colorless oil; TLC (hexane/diethyl ether,

(20) (a) For preparation of *t*-Bu-amphos-Cl **3** and an account of its efficiency for Pd-catalyzed Suzuki couplings in aqueous media, see: Shaughnessy, K. H.; Booth, R. S. *Org. Lett.* **2001**, *3*, 2757. (b) Original amphos ligand: Smith, R. T.; Baird, M. C. *Inorg. Chim. Acta* **1982**, *62*, 135.

3:1) $R_f$ = 0.45; ^{1}H NMR (300 MHz, CDCl$_3$) $\delta$ 1.37 (t, $J$ = 6.0 Hz, 3 H), 2.39 (dd, [2]$J$ = 18.0 Hz, [3]$J$ = 9.0 Hz, 1 H), 2.53 (s, 3 H), 3.25 (dd, [2]$J$ = 18.0 Hz, [3]$J$ = 6.0 Hz, 1 H), 3.70 (s, 3 H), 4.15–4.22 (m, 1 H), 4.33 (q, $J$ = 6 Hz, 2 H), 7.33–7.49 (m, 4 H); ^{13}C NMR (75 MHz, CDCl$_3$) $\delta$ 12.8, 14.6, 36.1, 45.8, 51.8, 60.2, 121.5, 123.6, 127.5, 128.4, 132.6, 144.0, 147.5, 151.9, 165.5, 173.0; IR (neat) ṽ 2982, 2953, 1738, 1694, 1609, 1578, 766 cm$^{-1}$; MS (EI) $m/z$ 274 (5) [M$^+$], 228 (80), 200 (100); HRMS (EI) calcd for C$_{16}$H$_{18}$O$_4$ 274.1205, found 274.1197.

**Methyl (2*E*)-3-[5-Methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acrylate (39).** A mixture of 2-(dihydroxyboryl)-5-methoxybenzaldehyde (**38**)[12] (3.81 g, 21.2 mmol) and pinacol (2.76 g, 23.0 mmol) in benzene (60 mL) was placed in a round-bottom flask, and a Dean–Stark trap was attached and filled with benzene. The reaction mixture was heated under reflux until evolution of water had ceased (~12 h). After being cooled to room temperature, the reaction mixture was filtered through a pad of MgSO$_4$ and the solvent was removed in vacuo to yield 5.0 g of crude material (~90%), which was sufficiently pure to be used for the subsequent Wittig reaction.

The crude (pinacol boronate)benzaldehyde (2.5 g, 9.5 mmol) was dissolved in dry toluene (20 mL), and methyl (triphenylphosphoranylidene)acetate (4.15 g, 12.4 mmol) was added all at once. The reaction mixture was heated at 90 °C for 18 h. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure. Diethyl ether was added, and the majority of the white precipitate (Ph$_3$P=O)

was filtered through a glass funnel. The filtrate was concentrated, and the residue was purified by flash column chromatography (hexane/diethyl ether: 2:1) to give 2.3 g (71%) of desired product **39** as a thick, orange oil, from which crystallized, on standing a pink crystalline solid, which was determined to be a mixture of 93:7 trans/cis isomer: mp 58–60 °C; TLC (hexane/diethyl ether, 2:1) $R_f$ 0.42; ^{1}H NMR (400 MHz, CDCl$_3$) $\delta$ 1.36 (s, 12 H), 3.81 (s, 3 H), 3.84 (s, 3 H), 6.37 (d, $J$ = 16.0 Hz, 1 H), 6.91 (dd, [2]$J$ = 8.4 Hz, [3]$J$ = 2.4 Hz, 1 H), 1.17 (d, $J$ = 2.4 Hz, 1 H), 7.79 (d, $J$ = 8.0 Hz, 1 H), 8.60 (d, $J$ = 16.0 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl$_3$) $\delta$ 25.0, 51.8, 55.4, 84.0, 110.9, 115.2, 118.9, 138.3, 142.4, 146.1, 162.0, 167.8; IR (neat) ṽ 2979, 2841, 1721, 1638, 1597, 1349, 859 cm$^{-1}$; MS (EI) $m/z$ 318 (5) [M$^+$], 259 (15), 106 (65), 91 (100), 84 (65); HRMS (EI) calcd for C$_{17}$H$_{23}$BO$_5$ 318.16385, found 318.16392.

**Supporting Information Available:** Characterization data, ^{1}H and ^{13}C NMR spectra of the coupling products, and all new compounds as well as X-ray crystallographic data (CIF file) for compound **42b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO049722P