JOC Article

Addition of Bifunctional Organoboron Reagents to Strained Alkenes. Carbon−Carbon Bond Formation with Rh(I) Catalysis in Aqueous Media

Mark Lautens* and John Mancuso[†]

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

mlautens@chem.utoronto.ca

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Arylboronate esters bearing a pendant Michael-type acceptor olefin undergo transmetalation with a rhodium-based catalytic complex to generate a functionalized organorhodium intermediate that can cyclize onto strained olefins in good to excellent yields. The catalytic system involves the use of an electron-rich, sterically bulky ligand to stabilize the organorhodium intermediate and reduce the incidence of protodeboronation in aqueous media.

Introduction

Transition metal-catalyzed cross-coupling reactions have proven vital in the assembly and construction of various compounds for pharmaceutical usage, the synthesis of natural products, and the generation of novel supramolecular constructs.[1] Protocols in frequent use involve the Stille,[2] Suzuki,[3] and Heck[4] couplings which established palladium catalysis[5] as a robust method for carbon−carbon σ-bond formation. A major area of research focuses on the solubilization of transition metal complexes in water through the use of water-soluble phosphines to carry out catalysis in aqueous media.[6,7]

As an alternative to palladium catalysis, rhodium-catalyzed cross-couplings[8,9] are gaining in popularity due to the seminal studies by Miyaura[10] and Hayashi,[11] who demonstrated conjugate addition of arylboronic acids to enones and aldehydes. Further studies by both groups have shown that the coupling process can be rendered asymmetric with the electrophilic component replaced with activated olefins.[12] An important aspect of these reactions was that water was necessary as cosolvent (or additive) to promote the coupling process through the generation of a catalytically active hydroxorhodium(I) intermediate from Rh−X (X = acac, Cl, etc.).[13] In addition, reactivity differences between Rh and Pd have been

[†] Present address: Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260.

(1) For general references on cross-coupling reactions, see: (a) Miyaura, N., Ed. *Cross-coupling reactions*: *a practical guide*; Springer: New York, 2002. (b) Murahashi, S.-i., Davies, S. G., Eds. *Transition Metal Catalyzed Reactions*; Blackwell Science: Oxford, UK, 1999. (c) Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: New York, 1998. (d) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; Wiley-VCH: New York, 2000.

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(3) For reviews on the Suzuki coupling, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 5**,** 2457. (b) Miyaura, N. *Organoboron Compounds* in Topics in Current Chemistry, **2002**, Vol. 219, Springer-Verlag: Heidelberg, p 11. (c) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

(4) For reviews on the Heck reaction see: (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (b) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

(5) Tsuji, J. *Palladium Reagents and Catalysis*: *Innovations in Organic Synthesis*; Wiley & Sons: New York, 1995.

(6) For reviews on transition metal catalysis with water-soluble ligands, see: (a) Pinault, N.; Bruce, D. W. *Coord. Chem. Rev.* **2003**, *241*, 1. (b) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (c) Sinou, D. *Adv. Synth. Catal.* **2002**, *344*, 221.

(7) For a review on organometallic chemistry in water, see: Herrmann, W. A. In *Aqueous-Phase Organometallic Chemistry*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, Germany, 1998; pp 35−45.

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(12) Asymmetric addition to enones: (a) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1999**, *40*, 6957. (c) Yamamoto, Y.; Fujita, M.; Miyaura, N. *Synlett* **2002**, *5*, 767. Asymmetric addition to acrylates: (d) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron*: *Asymmetry* **1999**, *10*, 4047. (e) Sakuma, S.; Miyaura, N. *J. Org. Chem.* **2001**, *68*, 8944. Asymmetric addition to vinylphosphonates: (f) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591. Asymmetric addition to vinyl nitro compounds: (g) Hayashi, T.; Senda, T.; Ogaswara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716.

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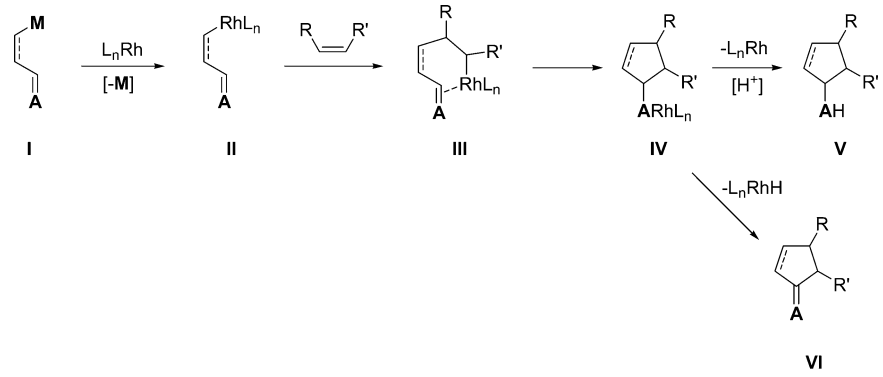
SCHEME 1



observed. For example, the tolerance of rhodium for aryl−halide bonds has been demonstrated, which positions this methodology as complementary to Pd-based methods. Previous reports have indicated that the C−Br bond in aryl bromides is not readily prone to oxidative insertion by rhodium and aryl C−I insertion is promoted only at high temperatures (>100 °C).[14] Furthermore, in boron-based couplings, the waste product of the catalytic cycle is usually boric acid, a relatively nontoxic species as compared to metal halide salts generated by other coupling processes.

We demonstrated recently that a cross-coupling between arylboronic acids and styrene-type olefins or 2-vinyl(azaheteroaromatics) could occur in neat water using SDS (sodium dodecyl sulfate) as a surfactant with a Rh(I) catalyst.[15] The hydrophilic ligand, TPPDS (dipotassium bis(*p*-sulfonatophenyl)phenylphosphine),[16] was used to solubilize the catalyst in the aqueous phase. Styrene-type olefins were found to generate unsaturated products, presumably arising from a Heck-type process. Vinyl(azaheteroaromatics) followed a conjugate addition−protonation pathway, resulting in a net hydroarylation process. Protodemetalation of the boronic acid partner could be attenuated through the use of SDS, but still required it be used in excess (2.5 equiv) with respect to alkene.

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 with rhodium catalysis focus on intermolecular processes with the metal mediating the formation of only *one* carbon−carbon bond. In contrast, several studies have demonstrated the flexibility of palladium chemistry, through the creation of tandem or "cascade" processes,[17] promoting the formation of several C−C and C−X bonds in a "one-pot" fashion.

In theory, rhodium catalysis could be used to effect a similar cascade sequence. The success of this process is reliant on the generation of organorhodium intermediates which cannot undergo undesirable side reactions such as *β*-hydride elimination or protodemetalation by water. These intermediate species should have sufficient longevity and reactivity to proceed in further carborhodative steps, ultimately building fused ring systems. The proposed concept is shown in Scheme 1, whereby the use of a bifunctional donor/acceptor **I**, containing group M (a metal/metalloid moiety) and group A (an acceptor moiety; i.e., O, NR, CH-EWG, etc.).

Group M would allow for a transmetalation reaction to occur in the presence of a rhodium catalyst to generate an organorhodium intermediate **II**. The organorhodium intermediate can coordinate another olefin and undergo migratory insertion, resulting in the carborhodated species **III**. Internal coordination of the rhodium center to the acceptor group A may be possible and cyclization can occur to give **IV**. At this stage, protodemetalation by a protic donor would give **V** or *β*-hydride elimination of Rh−H from **IV** would generate **VI**, the unsaturated product.

The key to the success of this endeavor is avoiding protodemetalation at an intermediate stage in the process. Indeed, one of the drawbacks of working in aqueous organorhodium chemistry is the propensity for reaction with water to occur faster than carborhodation of the olefin. This is often compensated for by the addition of several equivalents (2.5−10) of arylboron substrate thus dramatically reducing the practical utility[18] of the reaction. From a financial perspective, the cost of organoboron reagents, in particular functionalized or heterocyclic species, remains high. To render the proposed cascade reaction synthetically attractive, it was necessary to devise a method whereby only 1 equiv of the organoboron substrate can be used, allowing yields to be based on this coupling partner.

In this article, we present a comprehensive study on the generation of functionalized indanes from bifunctional arylboronate esters and norbornyl olefins, which had appeared previously as a communication.[19] In addition, we also describe our efforts to generate products from thiophene-based boronate ester substrates.

Results and Discussion

A communication by Miura disclosed the "merry-go-round" alkylation of phenyboronic acid by norbornene in

(14) Our previous study demonstrated that halide substituents on the boronic acid coupling partner survive the cross-coupling conditions; see ref 15 and for other examples indicating the resistance of Rh insertion into aryl halide bonds at low temperature; see: (a) Ishiyama, T.; Hartwig, J. *J. Am. Chem. Soc.* **2000**, *122*, 12043. (b) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003.

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

(16) This ligand is commercially available from Strem Chemicals.

(17) Selected reviews on Pd cascade reactions: (a) Heumann, A.; Réglier, M. *Tetrahedron* **1996**, *52*, 9289. (b) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65.

(18) (a) Trost, B. M. *Science* **1991**, *254*, 1471. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *24*, 259.

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

SCHEME 2

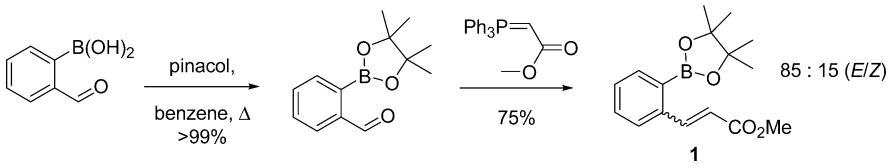
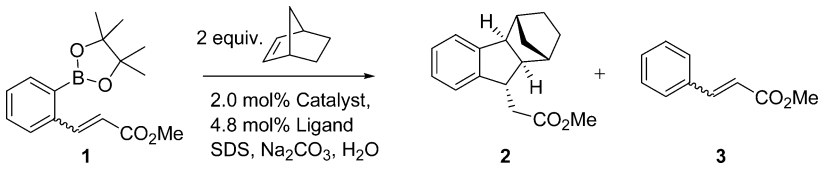


TABLE 1. Optimization of the Bifunctional Addition with a Rh(I) Catalyst and Water-Soluble Ligands



entry[a]	catalyst/ligand	conditions	conv, %[b]	(2:3)[c]
1	$[Rh(cod)Cl]_2$	80 °C, 2 h	13	69:31
2	$[Rh(cod)Cl]_2$/TPPDS[d]	80 °C, 2 h	>99	27:73
3	$[Rh(cod)Cl]_2$/*t*-Bu-amphos-Cl	80 °C, 2 h	>99	—[e]
4[f]	$[Rh(cod)Cl]_2$/*t*-Bu-amphos-Cl	80 °C, 2 h	>99 (95)	>99:<1
5[f,g]	$[Rh(cod)Cl]_2$/*t*-Bu-amphos-Cl	80 °C, 2 h	>99	96:4
6[f]	$[Rh(cod)Cl]_2$/*t*-Bu-amphos-Cl	rt, 14 h	>99	>99:<1
7[f]	$[Rh(cod)Cl]_2$/Cy-amphos-Cl	rt, 14 h	NR	
8[f]	$[Rh(cod)OH]_2$/*t*-Bu-amphos-Cl	80 °C, 2 h	>99	>99: <1

[a] Reactions run in 0.2 M degassed water under nitrogen with 0.6 equiv of SDS and 1 equiv of Na_2CO_3. [b] Determined by ^1H NMR. Isolated yield in parentheses. [c] Determined by ^1H NMR. [d] 8.0 mol % of ligand used. [e] Variable results. [f] 1:1 water:toluene (degassed) was used as the solvent. [g] 1 equiv of norbornene was used.

the presence of a rhodium catalyst.[20] Through carborhodation of norbornene and a series of Rh migrations, it was observed that norbornyl groups were introduced at multiple positions around the phenyl ring. Furthermore, this experiment demonstrated the resistance of norbornylrhodium intermediates toward β-hydride elimination and showed that norbornene could function as a potential "trapping" agent for organorhodium intermediates.

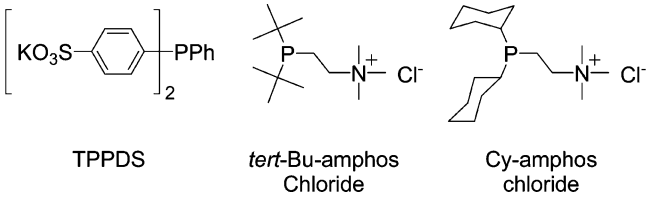
Test substrate **1** was synthesized from the readily available 2-formylphenylboronic acid, which was esterified as its pinacol derivative to facilitate product recovery and purification following the Wittig coupling (Scheme 2). Compound **1** was isolated as a mixture of *E*/*Z* isomers, with the *E* isomer being predominant.

Substrate **1** was designed to incorporate a pendant acrylate group, a moiety that is known to be highly reactive as an electrophile with organorhodium nucleophiles. It was tested initially with a catalytic amount of $[Rh(cod)Cl]_2$ in water with SDS and norbornene under the same conditions which were successful for the styrene/boronic acid coupling.[15] Consumption of **1** was slow and although the desired product **2** was detected, it was in very low yield as protodemetalation to generate **3** was a problematic side reaction (Table 1, entry 1).

The desired indane **2** was isolated as a single diastereomer and a ROESY 2D-NMR experiment was used to assign the stereochemical configuration as the *exo* adduct. To improve the conversion and reduce the incidence of deboronated compound **3**, a variety of water-soluble ligands were tested (Scheme 3).

In addition to the TPPDS ligand, which has been proven to be ideal for several transition metal-mediated

SCHEME 3



reactions in aqueous media,[21] the amphos ligands were a viable alternative as they could be readily prepared.[22] Recently, Shaughnessy and co-workers have reported the use of *tert*-butyl-amphos chloride as a soluble ligand in a water/acetonitrile-based Suzuki coupling system giving excellent yields.[23] Grubbs and co-workers have also demonstrated the use of Cy-amphos chloride for the solubilization of Ru metathesis catalysts in water and methanol.[24]

As seen in Table 1, entry 2, the use of the TPPDS ligand allowed for complete consumption of the starting material, with protodemetalation as the predominant reaction pathway. The use of the *tert*-butyl-amphos ligand gave excellent product conversion but the ratio of products **2** and **3** was variable. Problems with irreproducibility were believed to result from poor solubilization of the substrate or intermediates in the organic phase

(20) Oguma, K.; Miura, M.; Satoh, T.; Nomura, M. *J. Am. Chem. Soc.* **2000**, *122*, 10464.

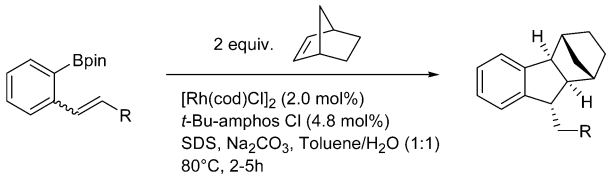
(21) Some recent articles concerning the use of TPPDS in catalysis: (a) Peng, Q. R.; Yang, Y.; Wang, C. J.; Liao, X. L.; Yuan, Y. Z. *Catal. Lett.* **2003**, *88*, 219. (b) Chen, H.; Li, Y. Z.; Chen, J. R.; Cheng, P. M.; Li, X. J. *Catal. Today* **2002**, *74*, 131. (c) Li, Y. Z.; Chen, H.; Chen, J. R.; Cheng, P. M.; Hu, J. Y.; Li, X. J. *Chin. J. Chem.* **2001**, *19*, 58.(d) Thorpe, T.; Brown, S. M.; Crosby, J.; Fitzjohn, S.; Muxworthy, J. P.; Williams, J. M. J. *Tetrahedron Lett.* **2000**, *41*, 4503.

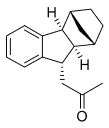
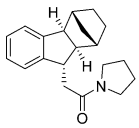
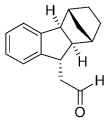
(22) Smith, R. T.; Baird, M. C. *Inorg. Chim. Acta* **1982**, *62*, 135.

(23) Shaughnessy, K. H.; Booth, R. S. *Org. Lett.* **2001**, *3*, 2757.

(24) (a) Lynn, D. M.; Mohr, B.; Grubbs, R. H.; Henling, L. M.; Day, M. W. *J. Am. Chem. Soc.* **2000**, *122*, 6601. (b) Mohr, B.; Lynn, D. M.; Grubbs, R. H. *Organometallics* **1996**, *15*, 4317.

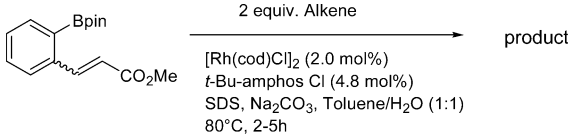
TABLE 2. Screening of Heck Acceptor Olefin

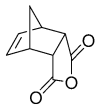
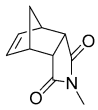
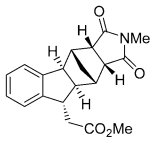
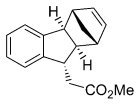
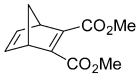
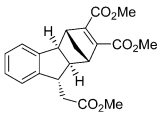


entry	R		product, isolated yield (%)[a]
1	-COMe	**4**	 **5**, 88
2		**6**	 **7**, 87
3	-CHO	**8**	 **9**, 62[b]
4	-CN	**10**	---- N.R.
5	-SO_2pTol	**11**	---- ----[c]

[a] Isolated by column chromatography. [b] Slow addition of boronate ester to reaction mixture over 12 h at rt. [c] Protodeboronation of the substrate only.

TABLE 3. Screening of Diels–Alder Adducts and Norbornadiene Derivatives as Coupling Partners



entry[a]	alkene		product, isolated yield (%)[b]
1		**12**	**3** only >99
2		**13**	 **14**, 90
3		**15**	 **16**, 94
4		**17**	 **18**, 82

[a] Ratio of boronate ester to alkene is 1:2. [b] Isolated by column chromatography. Diastereomeric excess is >20:1 for all entries.

provided by the surfactant. It was gratifying to discover that this problem could be alleviated through the use of an organic cosolvent. Entries 4–8 employ the use of a 1:1 toluene-to-water system containing SDS as a surfactant. This system resulted in the formation of an opaque yellow emulsion and allowed complete conversion of substrate to product with very little protodemetalation. Entry 5 indicated that excess olefin was unnecessary as only 1 equiv of norbornene gave no significant decrease in yield. Entry 6 demonstrated that conversion at room temperature was feasible, albeit with longer reaction time. However, the use of cyclohexyl-amphos chloride did not result in any conversion at room temperature (entry 7). Entry 8 supported our hypothesis that a hydroxorhodium(I) intermediate was the active catalytic species, as the addition of pregenerated $[Rh(cod)OH]_2$[25] showed no difference from the standard chloride catalyst precursor.

It is also interesting to note that the geometric configuration of the double bond in the arylboronate substrate **1** seemed to have no effect on the diastereoselectivity. Variations in the ratio of *E*-to-*Z* isomers were tolerated and gave the same product diastereomer.

tert-Butyl-amphos was chosen for further studies as it exhibited higher activity as compared to cyclohexyl-amphos or TPPDS. Functionality on the arylboronate ester component was examined further by testing various pendant Heck-acceptor groups (Table 2).

Entries 1 and 2 illustrate that both enone and acrylamide functionalites are compatible. The relative stereochemical configuration of the products was assigned based on NMR analysis and comparison to compound **2**. A boronate ester **8** containing an α,β-unsaturated aldehyde moiety gave a mixture of products. In this case, competitive 1,2-addition to the aldehyde by another equivalent of substrate might occur. To improve the yield of **9**, it was necessary to slowly add the substrate as a solution in toluene to the reaction mixture by syringe pump at room temperature (entry 3). An acrylonitrile-based substrate **10** (entry 4) was found to hinder the rate of transmetalation at room temperature, presumably by coordination of multiple cyano groups to the rhodium center, thus attenuating the metal's reactivity. The use of the α,β-unsaturated sulfone **11** (entry 5) allowed for transmetalation of the substrate, as evidenced from isolation of protodemetalated material, but did not yield any desired product.

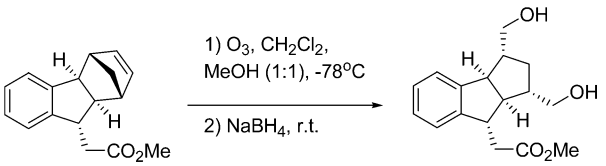
Norbornyl derivatives with increased functionality were examined (Table 3). The Diels–Alder adduct of cyclopentadiene and maleic anhdydride (**12**) resulted in a strongly exothermic reaction with no conversion to the desired product (entry 1). It was speculated that rhodium insertion into the C–O bonds of the anhydride group had occurred as it has been previously shown by Frost that anhydrides can be used to acetylate arylboronic acids with use of a rhodium catalyst.[26] The Diels–Alder adduct of *N*-methylmaleimide (**13**) proceeds to give the pentacycle **14**.

Norbornadiene-based coupling partners[27] were also investigated and entry 3 demonstrates the addition to

(25) Uson, R.; Oro, L. A.; Cabeza, J. A. *Inorg. Synth.* **1985**, *23*, 126.

(26) Frost, C. G.; Wadsworth, K. J. *Chem. Commun.* **2001**, *22*, 2316.

SCHEME 4



16 **19** (99%)

norbornadiene. The stereochemistry of compound **16** was verified by hydrogenation, which yielded compound **2**. Entry 4 indicates that the reaction is compatible with substituted norbornadiene **17** and coupling is selective for the unsubstituted double bond.

An example of a postsynthetic modification to yield functionalized tricyclic systems is shown in Scheme 4. Ozonolysis of **16** followed by reductive workup with $NaBH_4$ gave the diquinane **19** in quantitative yield. Compound **19** bears five stereocenters, three of which are created in the coupling step.

Since norbornyl- and norbornadienyl-alkenes were successful coupling partners, coupling partners containing heteroatoms were examined. A variety of oxabicyclic alkenes were screened and the results are listed in Table 4.

Entry 1 indicated that oxabenzonorbornadiene **20** inhibited the reaction, a surprising result since previous studies with oxabicyclic systems and arylboronic acids with rhodium catalysis showed this substrate was compatible with the reaction conditions.[28] Oxidative addition into one of the strained C−O bonds of the oxabicyclic bridge is a possibility and may account for termination of the reaction.

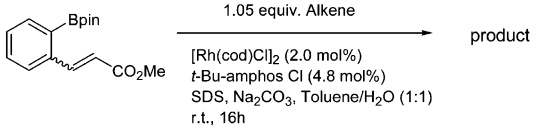
Entries 2−4 indicate the generality of the reaction as both [2.2.1] and [3.2.1] systems add very well. Interestingly, no ring-opened products could be detected. [3.2.1] systems are known to be resistant to ring opening but the integrity of the [2.2.1] system, a substrate that is known to be a highly reactive strained olefin, is preserved in this case.

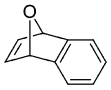
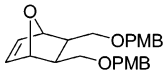
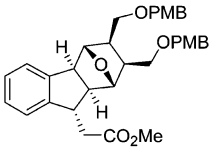
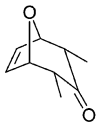
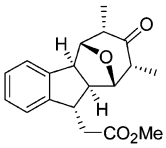
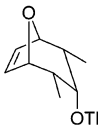
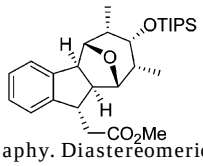
An interesting aspect of the reaction was discovered when substituents were placed at the bridgehead carbons of the oxabicyclic systems (Table 5).

Entry 1 suggests that double bridgehead substitution prevents attack of the arylrhodium nucleophile onto the alkene, presumably due to a steric shielding effect by the methyl groups. However, placement of only one methyl group (entry 2) yields a product in near quantitative yield as one diastereomer and regioisomer. The relative stereochemistry was confirmed by single-crystal X-ray analysis.

Further investigation showed that a larger group such as $-CH_2CH_2OTHP$ (entry 3) gives a lower yield of product but still as only one diastereomer and regioisomer. A similar trend is noted for the [3.2.1] systems

TABLE 4. Screening of Oxabicyclic Alkenes as Coupling Partners



entry	alkene		product, isolated yield (%)[a]	
1		**20**	----	N.R.
2		**21**		**22**, 90%
3		**23**		**24**, 97%
4		**25**		**26**, 91%

[a] Isolated by column chromatography. Diastereomeric excess is >20:1 for all entries.

which are less strained, but are expected to be more sensitive to substitution patterns as the bridgehead substituents "shield" the alkene to a greater extent, due to increased bond angles within the ring. Substrate **32** (entry 4) gives only deboronated material as expected for a disubstituted system while substrate **33** (entry 5) gives the desired product **34** as a single regio- and diastereoisomer, and its relative configuration was confirmed by X-ray analysis. Entry 6 shows that the presence of a single sterically encumbering bridgehead substituent prevents addition completely, resulting only in deboronation. Entry 7 demonstrates that a phenyl group at the bridgehead is not tolerated, resulting in a complete shutdown of the reaction. In a similar process seen for oxabenzonorbornadiene, it is possible that the benzylic C−O bond is weakened and prone to oxidative insertion by the metal, resulting in a Rh−substrate complex that is inactive and sequesters the metal.

Bicyclic alkenes containing nitrogen atoms were also briefly examined (Table 6).

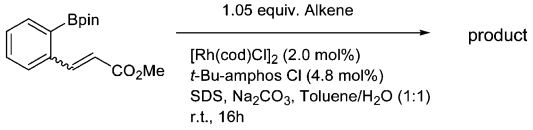
An azabenzonorbornadiene substrate **37** gave similar results as the oxygen analogue and did not yield the desired product (entry 1) even when changing the *N*-group from Boc to Ts or Ph. The Diels−Alder adduct of di-*tert*-butyl azodicarboxylate and cyclopentadiene (**38**) could be coupled to give the product **39** with the hydrazido bond intact (entry 2).[29] The Diels−Alder adduct of *N*-Boc-pyrrole and DMAD **40** failed, resulting only in deboronation of the substrate. Substrate **41** (entry 4), a

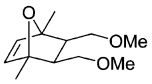
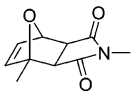
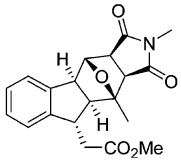
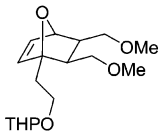
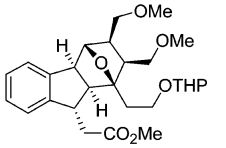
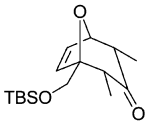
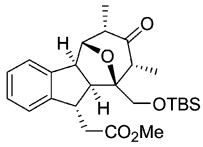
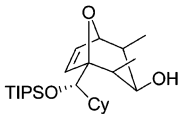
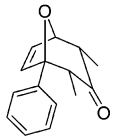
(27) The ratio of arylboronate substrate to alkene deserves some comment. In cases where the alkene is volatile and any excess can be easily removed by application of vacuum, 2 equiv are usually used to ensure complete reaction conversion. In cases where the alkene is heavily functionalized, or the coupling partner has a similar R_f to the product on silica gel, the loading is reduced to 1.05−1.1 equiv. In all cases, this reduction has no detrimental effect on selectivity or yield of the reaction.

(28) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311.

(29) The N−N bond in cyclic compounds of this type can be cleaved with Na/NH_3, see: Mellor, J. M.; Smith, N. M., *J. Chem. Soc., Perkin Trans. 1* **1984**, *12*, 2927.

TABLE 5. Screening of Bridgehead-Substituted Oxabicyclic Alkenes



entry	alkene		product, isolated yield (%)[a]	
1		**27**	**3** only	>99%
2		**28**		**29**[b], 99%
3		**30**		**31**[c], 87%
4		**32**	**3** only	>99%
5		**33**		**34**[b], 60%
6		**35**	**3** only	>99%
7		**36**	----	N.R.

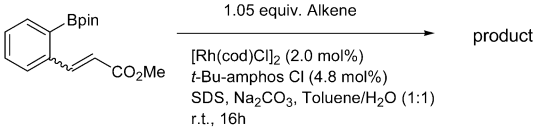
[a] Products isolated by column chromatography. Diastereomeric excess is >20:1 for all entries. Product isolated as one diastereomer and regioisomer. [b] Relative stereo- and regiochemistry verified by X-ray single-crystal diffraction. [c] Relative stereo- and regiochemistry assigned based on carbon and proton NMR spectroscopy.

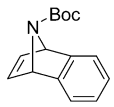
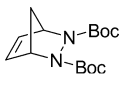
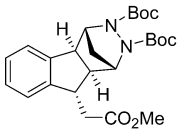
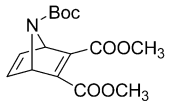
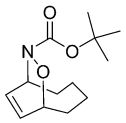
[4.2.2] bicyclic ring system, did not undergo any coupling, implying that the alkene may not be activated enough as ring strain is not as predominant as it is in the [3.2.1] and [2.2.1] ring systems.

Azabicycles based on the [3.2.1] system are known collectively as the tropane class of alkaloids, and have a seven-membered ring with a bridging aminomethyl group as the core structure. Members of this class are of interest as pharmaceutical agents as they exhibit high and diverse biological activity.[30] It was of interest to determine if the present coupling methodology could be used to synthesize new analogues of tropane alkaloids. Prior studies in the literature concerning the generation of tropane analogues have pointed to the utility of scopolamine as a starting scaffold for further elaboration. (−)-Dehydrohyoscamine (**42**) could be easily generated from commercial (−)-scopolamine as substrate for the cross-coupling reaction (Scheme 5).[31]

(30) For a general review on the tropane class of alkaloids, see: Fodor, G.; Dharanipragada, R. *Nat. Prod. Rep.* **1994**, *11*, 443.

TABLE 6. Screening of Azabicyclic Alkenes as Coupling Partners



entry	alkene		product, isolated yield (%)[a]	
1		**37**	----	N.R.
2		**38**		**39**, 76%
3		**40**	----	N.R.
4		**41**	**3** only	>99%

[a] Products isolated by column chromatography. Diastereomeric excess is >20:1 for all entries.

Coupling with the boronate ester **1** under standard conditions with KF as base gave the desired adduct **43** in good yield and as a mixture of diastereomers in a 1:1.3 ratio. More importantly, neither epimerization of the α-center nor hydrolysis of the tropic acid side chain was observed, emphasizing the mild conditions of the coupling process.

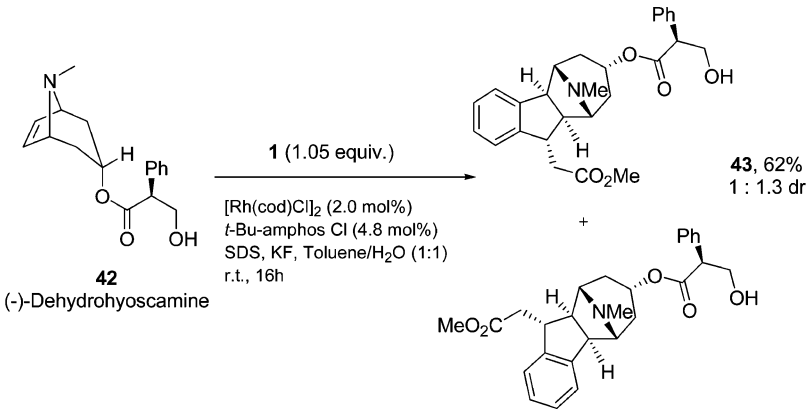
In general, the catalytic cycle of this tandem cyclization is believed to involve the presence of hydroxorhodium(I) intermediates[25,32] (Scheme 6). The rhodium(cyclooctadiene)chloride dimer is known to hydrolyze at room temperature in a basic aqueous solution to generate the corresponding hydroxorhodium(I) species.[33] 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

(31) (a) Aberle, N. S.; Ganesan, A.; Lambert, J. N.; Saubern, S.; Smith, R. *Tetrahedron Lett.* **2001**, *42*, 1975. (b) Hayakawa, Y.; Baba, Y.; Makino, S.; Noyori, R. *J. Am. Chem. Soc.* **1978**, *100*, 1786.

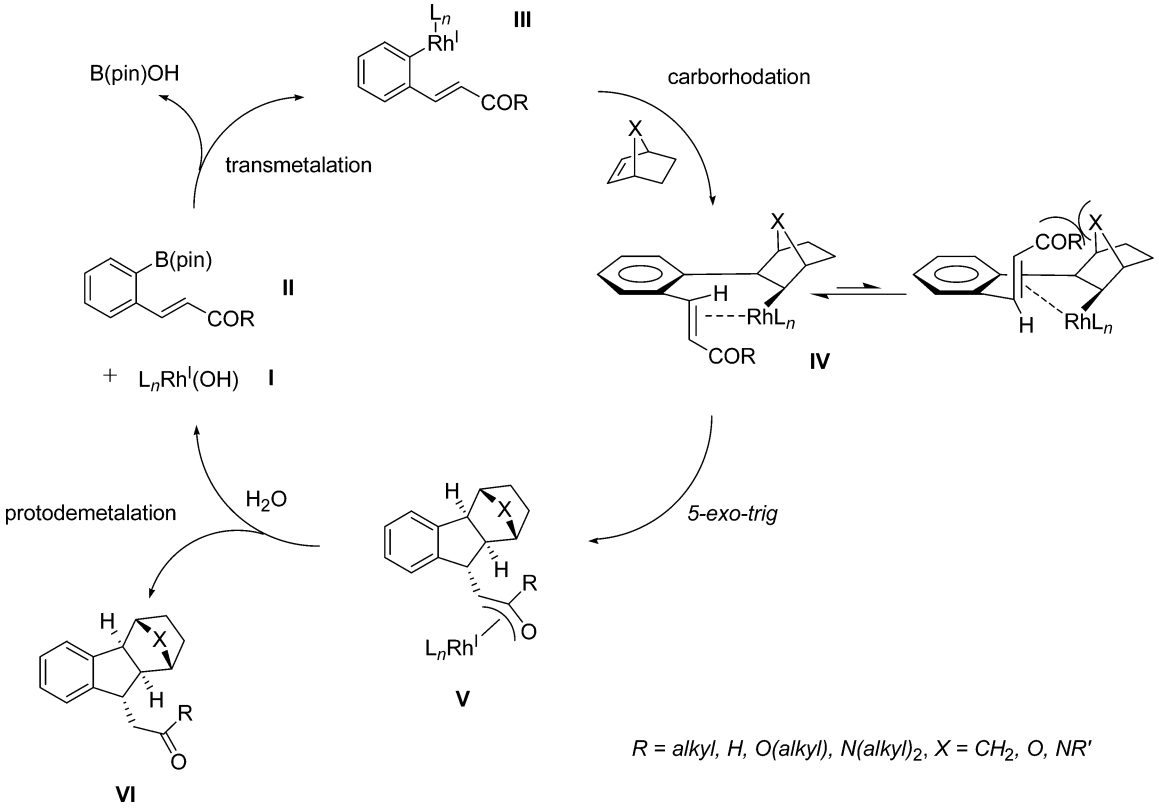
(32) (a) Brune, H.-A.; Unsin, J.; Hemmer, R.; Reichardt, M. *J. Organomet. Chem.* **1989**, *369*, 335. (b) Grushkin, V. V.; Kuznetsov, V. F.; Bensimon, C.; Alper, H. *Organometallics* **1995**, *14*, 3927. (c) Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

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

SCHEME 5



SCHEME 6



the Suzuki coupling. Two equivalents of fluoride are believed to promote the formation of an $Ar(BF_nOH_{3-n})^-$ species, which transmetalates more readily.[34] Indeed, the reduced basicity of fluoride has proven beneficial in cases where very acidic protons are present within the coupling partners, thus rendering the use of protecting groups unnecessary.

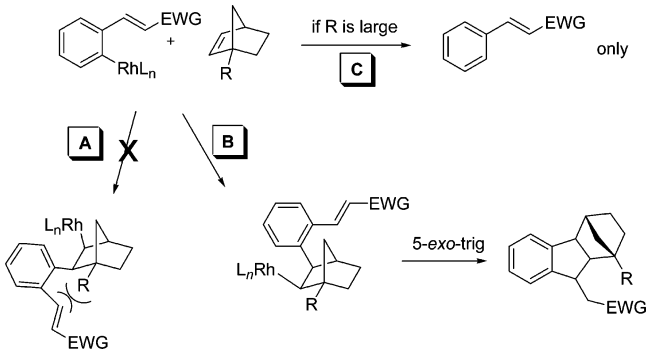
The catalytic cycle is initiated by transmetalation of $L_nRh(OH)$ **I** with the arylboronate substrate **II** to generate the arylrhodium(I) species **III** and release B(pin)OH. Coordination of the alkene followed by selective carborhodation on the *exo* face ensues to give **IV** in which the rhodium is presumably coordinated to the internal pendant olefin. This coordination may be crucial for cases such as the oxa[2.2.1]bicyclic substrates whereby the ring closure becomes kinetically favored over ring opening of the strained system by β-deoxyrhodation.

The 5-*exo*-trig ring closure is rendered diastereoselective due to the significant steric interactions between the −COR group of the pendant acceptor alkene and the bridge group (apical $-CH_2-$, −O−, or −NR′). Thus, the conformer in which the R group is oriented toward the *endo* face of the norbornyl system is favored and leads to the (oxa-π-allyl)rhodium species **V**. This is rapidly protodemetalated by water, which releases the product **VI** and regenerates the hydroxorhodium(I) species.

In cases where there is a substituent at one of the bridgeheads, the selectivity of the *syn*-carborhodation process is dictated by sterics; the aryl group adds at the most sterically accessible carbon, placing the rhodium group proximal to the bridgehead substituent (Scheme 7, path B favored over path A). When the bridgehead

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

SCHEME 7



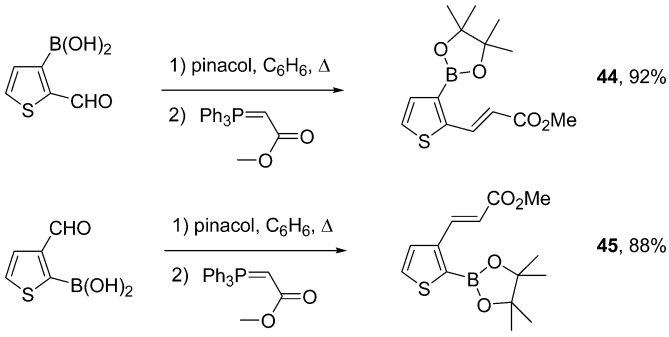
group is very large, both orientations are disfavored by steric factors, thus addition is prevented and the competing protodemetalation pathway becomes predominant (C).

An alternate catalytic pathway involving oxidative addition of Rh(I) into the C−B bond of the phenylboronic acid could be proposed; however, Hayashi's mechanistic studies and NMR analysis on the conjugate addition of boronic acids to enones have indicated that only rhodium-(I) intermediates are present within the catalytic cycle.[32c]

Our previous catalytic system, used for the coupling of arylboron substrates with vinylpyridines and styrenes,[15] was reactive enough to couple these weakly reactive alkenes, but suffered from selectivity issues, preferring protodemetalation.[35] Although yields could be improved by increasing the boronic acid loading to 2.5 equiv and heating at 80 °C, the high cost of these substrates limits large-scale applications. In the present case, the ligand promotes the transmetalative step, resulting in smooth conversion at room temperature. Since there is no appreciable difference between loading of 2 equiv of ligand with respect to the metal over 1 equiv, it is believed that the active species is a monoligated metal intermediate stabilized by the high basicity of the amphos ligand. In addition, the large cone angle of *tert*-butyl-amphos Cl (approximately 185°)[36] may prevent strong binding of another equivalent of ligand to the metal center.

Substitution of the phenyl nucleus of arylboronate ester **1** with other heterocyclic rings would provide access to new structural motifs and compounds with useful properties. Heterocycles are present as core structures and often act as isosteres for the phenyl group within many natural products and pharmaceuticals. Thiophene was a suitable choice for a heterocyclic backbone as its aromatic character is more similar to benzene than either pyrrole or furan. The requisite boronate ester substrates **44** and **45** were synthesized from the corresponding commercially available boronic acids.

SCHEME 8



Thienylboronate ester **44** was tested under a variety of conditions and the results are reported in Table 7.

Under the standard conditions employed previously with the phenylboronate ester, no reaction was observed with substrate **44**, using sodium carbonate (entry 1) or potassium fluoride (entry 2) as base at room temperature. Using potassium fluoride (entry 3) with heating led to the formation of two products, the desired tetracyclic species **46** as a minor component and a hydroarylated product **47**, believed to arise from a C−H insertion process (vide infra).[37] These two products were inseparable by column chromatography. The use of the cyclohexyl-amphos ligand (entry 4) also resulted in a similar reaction outcome, giving a mixture of **46** and **47**. Switching the base to silver oxide (entry 5) led to deboronation. The use of sodium hydroxide at room temperature led to a mixture of starting material and deboronated material (entry 6). Repeating the reaction at higher temperatures simply accelerated the deboronation process (entry 7).

Concerning the mechanism for the formation of the C−H insertion product **47** from the boronate ester **44**, it is possible that a rhodium(I)−rhodium(III) manifold is being followed. There are two possible divergent pathways that can be followed after the carborhodation of the strained alkene (Scheme 9, intermediate **A**). One is the expected attack onto the pendant alkene to generate the cyclized product **46**. The other pathway generates the hydroarylated (C−H inserted) product **47**. For C−H insertion to occur, the intermediate must be at the organorhodium(I) stage, as the resulting rhodacycle **B**, from C−H insertion at the 4-position of the thienyl ring, contains Rh in the higher valent state.[38] Reductive elimination then occurs to give **C**, with the overall result in the rhodium "jumping" from the oxabicycle to the thienyl ring.[39] Performing the reaction in deuterium oxide showed >95% incorporation of deuterium at the 4-position (**47A**). It is interesting to note that C−H insertion occurs only with the thienyl system and was never observed with the phenylboronate esters.

(35) A control reaction was undertaken to determine the relative propensity of a strained alkene and a Michael acceptor toward carborhodation in the present system. When 1.5 equiv each of norbornene and ethyl acrylate were mixed with 1 equiv of phenylboronic acid under standard reaction conditions, only ethyl cinnamate was obtained, indicating that the arylrhodium species generated in this reaction is highly nucleophilic in character. Increasing the amount of norbornene to 5 equiv did not change the outcome of the reaction.

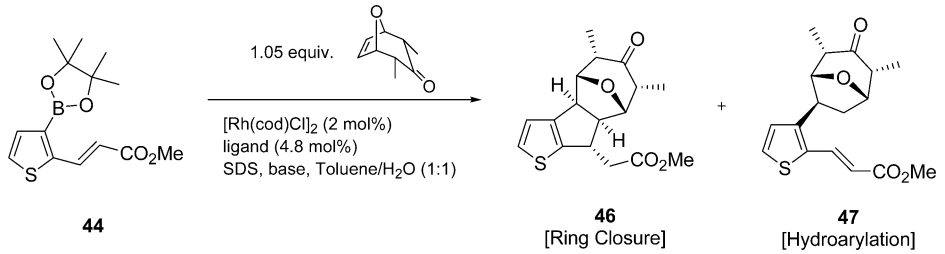
(36) Grubbs has tested Cy-amphos Cl and has determined its Tolman cone angle to be very similar to that of Cy_3P (170°). Although *t*-Bu-amphos chloride has not been measured, its cone angle is assumed to be similar to that of *t*-Bu_3P (185°). See ref 24b.

(37) The more reactive [2.2.1]oxabicyclic alkenes were also tested, as well as norbornene, and did not yield any desired ring-closed products.

(38) The C−H insertion product as well as the minor cyclized product was only observed when fluoride was used as base at high temperatures. Fluoride may promote the oxidative process required for C−H insertion, by stabilizing the Rh(III) state.

(39) Presumably, installation of a functional group at the 4-position, such as a methyl group, would prevent this C−H insertion process and promote formation of the desired cyclized product. This process is under examination.

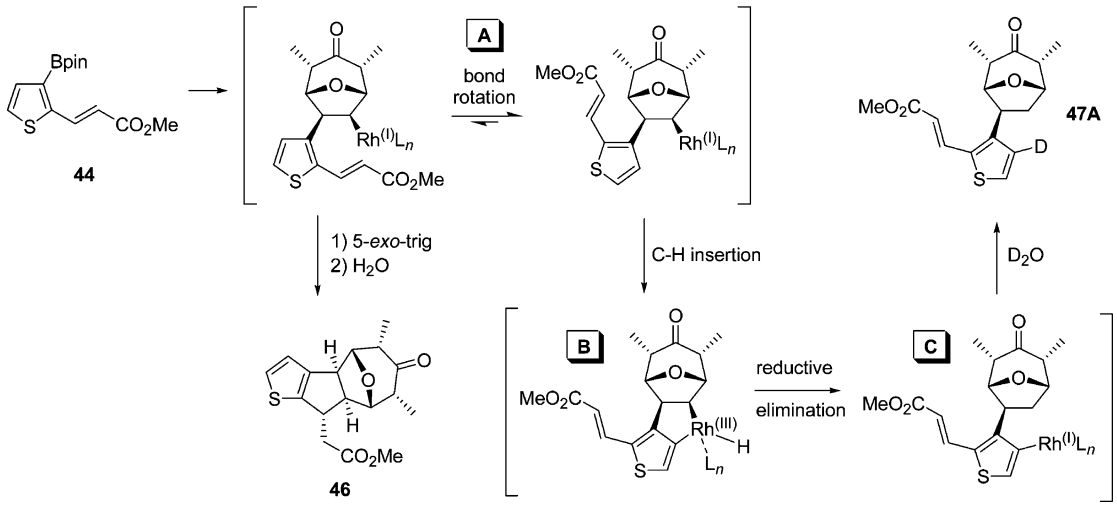
TABLE 7. Screening of Reaction Conditions for Coupling of Compound 44



entry	base	temp/°C	ligand	**46**[a]	**47**[a]	deboronated
1	Na_2CO_3	rt	*t*-Bu-amphos Cl			
2	KF	rt	*t*-Bu-amphos Cl			
3	KF	70	*t*-Bu-amphos Cl	14	60	
4	KF	70	Cy-amphos Cl	9	52	
5	Ag_2O	rt	*t*-Bu-amphos Cl			>99
6	5 M NaOH	rt	*t*-Bu-amphos Cl			>50
7	5 M NaOH	70	*t*-Bu-amphos Cl			>99

[a] Yields estimated by ^{1}H NMR.

SCHEME 9



The thienylboronate ester **44** seems to be very sensitive to reaction conditions; in particular, the choice of base is important. The use of stronger bases accelerates the transmetalation to rhodium, but the resultant thienylrhodium species either reacts too quickly with water or poorly coordinates the strained alkene coupling partner.

Thienylboronate ester **45** could not be successfully coupled to any strained alkene and simply underwent deboronation under conditions involving a variety of bases (Na_2CO_3, KF, CsF, $Ba(OH)_2$, NaOH, and Tl_2CO_3), temperatures, and ranges of water content. Difficulties in encouraging this substrate to add to oxabicyclic alkenes can be assigned to the fact that the boron group is proximal to the thienyl sulfur. B−C hydrolytic cleavage is known to be accelerated by α-heteroatoms (i.e. 2-pyridylboronic acid) or the presence of an adjacent Lewis basic substituent (i.e. *o*-formylphenyl boronic acid).[40,41]

Conclusions

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

Arylboronic esters bearing a pendant Michael acceptor react with strained olefins to give highly functionalized indanes in excellent diastereoselectivity. Both oxa- and azabicycles were compatible as strained olefin coupling partners and an example involving the synthesis of a tropane alkaloid analogue was provided. The steric and electronic character of the bifunctional partner is important and may require modification of the reaction conditions, including investigation of other amphos ligands, to generate desired products, especially in the case of heterocyclic systems. This observation is consistent with cross-coupling reactions such as the Suzuki and Stille couplings in which a variety of conditions have been developed for the successful carbon−carbon bond formation for specific substrate classes. Investigations into the

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(41) (a) Kuivilla, H. G.; Nahabedian, K. V. *J. Am. Chem. Soc.* **1961**, *83*, 2159. (b) Kuivilla, H. G.; Nahabedian, K. V. *J. Am. Chem. Soc.* **1961**, *83*, 2164. (c) Kuivilla, H. G.; Nahabedian, K. V. *J. Am. Chem. Soc.* **1961**, *83*, 2167. (d) Kuivila, H. G.; Reuwer, J. F.; Mangravite, J. A. *J. Am. Chem. Soc.* **1964**, *86*, 2666.

use of other heteroaromatic boronic esters as well as couplings involving acyclic vinyl boronic esters are currently underway.

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Supporting Information Available: Detailed experimental procedures, as well as NMR spectra for all new compounds, and ORTEP diagrams and X-ray crystallographic data for compounds **29** and **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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