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Rhodium-Catalyzed Tandem Vinylcyclopropanation of Strained Alkenes

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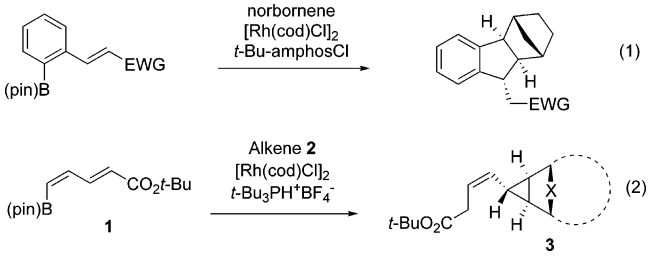
The rhodium-catalyzed addition of organoboronic acids and esters to unsaturated carbon−carbon bonds is a powerful tool for preparing structurally complex molecules.[1] Recently, we reported a rhodium-catalyzed tandem carbocyclization of aryl boronate esters bearing a Michael acceptor and strained alkenes or alkynes (eq 1).[2] When we reacted the vinyl boronate ester **1**, we isolated a novel and unexpected vinylcyclopropane product, presumably arising from a rare rhodium-catalyzed 1,6-addition (eq 2).[3] Herein, we report our preliminary results on the exploration of reaction scope as well as some preliminary mechanistic studies.[4]

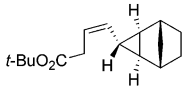
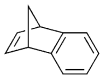
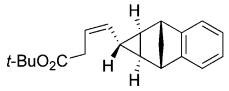
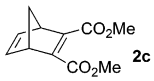
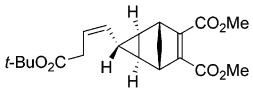
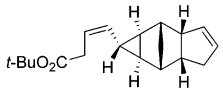
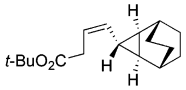
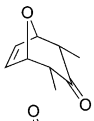
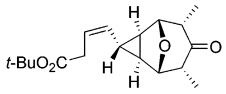
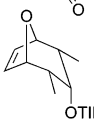
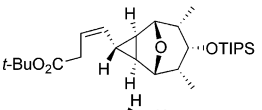
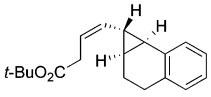
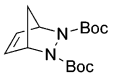
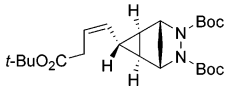
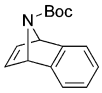


Modification of our previously published conditions showed that phosphine ligands play a crucial role in the success of the reaction. Bidentate ligands, such as dppf and dppe, gave a poor yield of the expected product. Monodentate ligands, however, performed well, as the use of either PPh_3 or t-$Bu_3PH^+BF_4^-$ [5] afforded product **3a** when **1** was coupled with norbornene (**2a**). Overall, t-$Bu_3PH^+BF_4^-$ was the optimal ligand, providing **3a** in 84% isolated yield (Table 1, entry 1).[6]

To confirm the structure of the vinylcyclopropane product, X-ray crystal structures were obtained for product **3f** (Figure 1) and the derivative of **3a**.[7] These structures unambiguously show the cyclopropane moiety and the unusual β,γ-unsaturated ester with a *Z*-olefin geometry.

We further examined the scope of the reaction by using a variety of strained and unstrained alkenes as coupling partners. Benzonorbornene **2b** showed lower reactivity; however, by doubling the catalyst loading, we obtained the corresponding product **3b** in 51% yield (entry 2). Norbornene derivatives **2c** and **2d** both displayed chemoselective vinylcyclopropanation at the strained and/or nonconjugated alkene in moderate to good yields (entries 3 and 4). The reaction of bicyclo[2.2.2]oct-2-ene **2e** gave a lower yield (entry 5), presumably due to reduced bond strain versus **2a**. Oxabicyclic alkenes **2f** and **2g** afforded the corresponding product in good to excellent yields (entries 6 and 7) and demonstrate the mildness and selectivity of this reaction with such highly functionalized substrates. Interestingly, unstrained 1,2-dihydronaphthalene **2h** was also reactive under the typical reaction conditions, affording **3h**, albeit in low yield (entry 8). The introduction of nitrogen-containing strained alkenes proved to be problematic, and diazabicyclic alkene **2i** gave the interesting product **3i** in low yield (entry 9). However, this example is potentially interesting as it allows access to bicyclo-[3.2.1]-1,3-diamines.[8] Moving the nitrogen atom closer to the reaction site led to reaction in reduced yields or no reaction as observed for the Boc-protected azabicyclic alkene **2j** (entry 6).

Table 1. Rhodium-Catalyzed Vinylcyclopropanation of **1** and Alkene Partner **2**[a]

entry	alkene	product	yield (%)[b]
1	 **2a**		**3a**, 84
2	 **2b**		**3b**, 39 (51)[c]
3	 **2c**		**3c**, 74
4	 **2d**		**3d**, 63
5	 **2e**		**3e**, 15
6	 **2f**		**3f**, 97
7	 **2g** OTIPS		**3g**, 79
8	 **2h**		**3h**, 20
9	 **2i**		**3i**, 32
10	 **2j**	----	**N.R.**

[a] All reactions were run under the following conditions: **1** (0.2 mmol, 1.0 equiv), **2** (0.2−0.22 mmol, 1.0−1.2 equiv), $[Rh(cod)Cl]_2$ (3 mol %), t-$Bu_3PH^+BF_4^-$ (6.6 mol %), KF (0.4 mmol, 2.0 equiv), dioxane (3 mL), H_2O (0.3 mL). [b] Isolated by column chromatography. [c] Yield obtained using $[Rh(cod)Cl]_2$ (6 mol %) and t-$Bu_3PH^+BF_4^-$ (13.2 mol %).

The proposed mechanism for this unusual vinylcyclopropanation is believed to follow the path shown in Scheme 1. $L_nRh(OH)$ (**I**),[9,10] which is generated in situ, transmetalates with boronate ester **1** to

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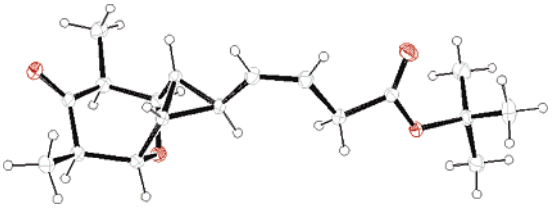
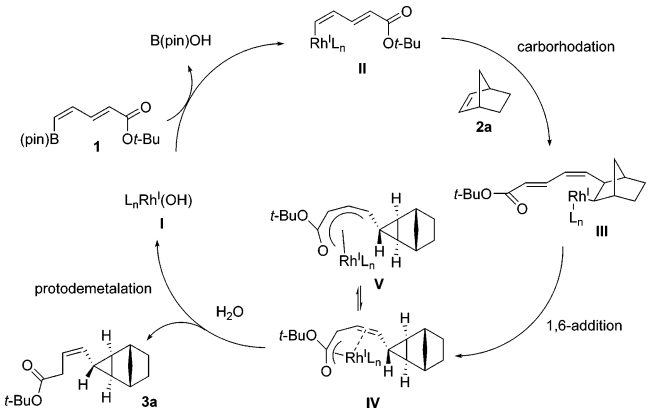


Figure 1. ORTEP plot of **3f** at 30% probability.

Scheme 1. Proposed Catalytic Cycle for the Rhodium-Catalyzed Tandem Addition/Cyclization Reaction

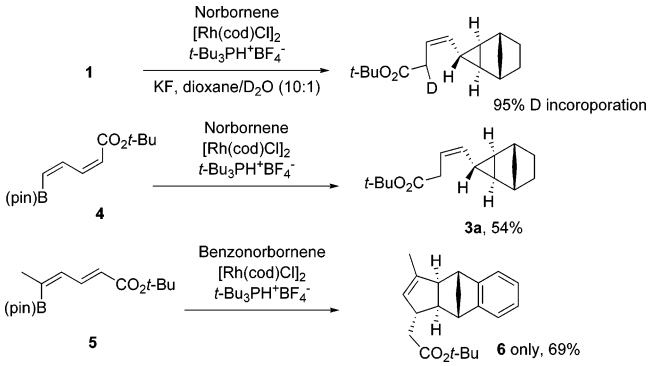


give the vinylrhodium(I) species **II** and B(pin)OH. Subsequent carborhodation at the *exo* face of norbornene gives intermediate **III**, which undergoes 1,6-addition preferentially to 1,4-addition. While rhodium-catalyzed 1,6-additions of phenylboronic acid have been reported previously by Csákÿ and co-workers,[3a] these types of reactions are very rare. The reasons for the regioselectivity have not yet been elucidated. Protodemetalation of the resulting (oxo-π-allyl)rhodium(I) complex **IV** produces the vinylcyclopropane product **3a** and regenerates the active catalyst **I**. The exclusive formation of a *Z*-olefin is proposed to be favored because of internal coordination of the carbonyl group in intermediate **IV**, which locks the (oxo-π-allyl)rhodium into one conformation. Murakami and co-workers also reported a similar rhodium-catalyzed vinylcyclopropanation reaction; however, their proposed mechanism involves a β-methoxy elimination to regenerate the active catalyst, and their study did not address the question of alkene stereochemistry.[4]

A deuterium quenching study showed that protodemetalation occurs preferentially at the α-carbon (Scheme 2) with over 95% deuterium incorporation in the product; supporting the presence of (oxo-π-allyl)rhodium(I) species **IV**. More interestingly, the reaction of olefin isomer **4** under the same reaction conditions also gave product **3a**. This suggests that the olefin geometry of the α,β-unsaturation is not critical for the vinylcyclopropane formation, and the mechanism must involve an olefin isomerization step, possibly via an equilibrium between (oxo-π-allyl)rhodium(I) **IV** and (oxo-π-pentadienyl)rhodium(I) **V**.

In addition, we tested the effect of substitution on the boronate ester. When the methyl-substituted boronate ester **5** was used with benzonorbornene, the cyclopentene product **6** was obtained in moderate yield. This result suggests that the substituent α to the boron plays a significant role on the relative rates of 1,4- versus 1,6-addition.

Scheme 2



In conclusion, a new vinylcyclopropanation formation reaction involving a rare 1,6-addition of an alkylrhodium(I) species has been developed. We are currently exploring substrate scope and mechanistic studies and will report our results in due course.

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Supporting Information Available: Experimental procedures and spectroscopic characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(4) During the preparation of our manuscript, Murakami and co-workers also reported a similar rhodium-catalyzed vinylcyclopropanation of norbornene derivatives. See: Miura, T.; Sasaki, T.; Harumashi, T.; Murakami, M. *J. Am. Chem. Soc.* **2006**, *128*, 2516.

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(7) See Supporting Information.

(8) For preparation of chiral 1,3-diamines, see: (a) Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1679. (b) López-García, M.; Alfonso, I.; Gotor, V. *Chem.—Eur. J.* **2004**, *10*, 3006. For 1,3-diamines as ligand, see: (c) Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844.

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(10) By using $[Rh(cod)OH]_2$ as catalyst precursor, the product was obtained in lower yield. Additional details will appear in our full account.

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