

Rhodium-Catalyzed Annulation of Ynamides with Bifunctional Arylboron Reagents

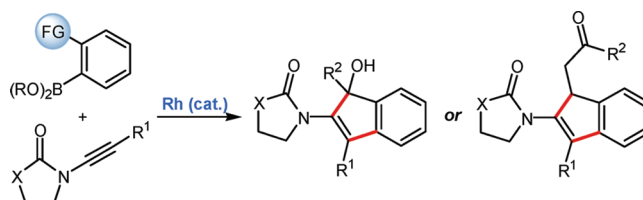
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ABSTRACT



Annulation of ynamides with arylboronic acids or esters containing an electrophilic functional group at the *ortho*-position proceeds under the action of rhodium catalysis to generate 2-amidoindenols or 2-amidoindenes, usually with good regioselectivity.

Ynamides^{1,2} have recently been demonstrated to be valuable substrates in carbometalation reactions³ with various organometallic reagents.^{4,5} We recently became interested in

rhodium-catalyzed⁶ ynamide carbometalations with organoboron reagents, and in particular, arylboron compounds **2** containing an electrophilic functional group at the *ortho*-position to trap the alkenylrhodium intermediates **3** generated upon initial carboration of the ynamide **1** (Scheme 1).⁷

The annulation of *ortho*-functionalized arylboron reagents has previously been accomplished using alkynes⁸ and alkenes,^{8d,e,9} and these processes^{10–12} benefit from mild reaction conditions and broad tolerance of functional groups. To our knowledge, the annulation of ynamides in analogous reactions has not been described previously, and we viewed

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(3) For general reviews on carbometalation reactions, see: (a) Marek, I.; Chinkov, N.; Banon-Tenne, D. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; pp 395–478. (b) Marek, I.; Normant, J. F. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; pp 514–522.

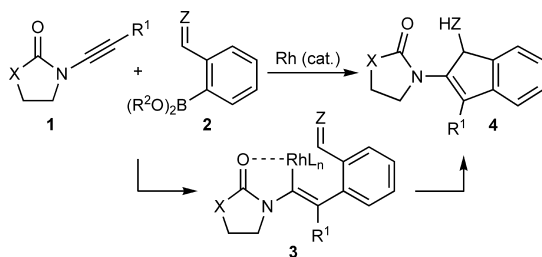
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(7) The carbometalation of ynamides **1** with arylboron reagents lacking an electrophilic functional group at the *ortho*-position will be the subject of a separate report from our laboratories.

Scheme 1. Proposed Rh-Catalyzed Annulation of Ynamides with Bifunctional Arylboron Reagents



the formation of 2-amidoindenes **4** in such a process to be attractive for a number of reasons. First, the indene ring system is present in biologically active compounds¹³ and functional materials.¹⁴ Second, it was of fundamental interest to ascertain whether the directing effect¹⁵ of the carbonyl or sulfonyl group of ynamides as proposed in previous ynamide carbometalations^{4,5} would also be operative here, to provide indenes with high regioselectivities. Third, the enamide moiety present within the products **4** could potentially serve as a useful handle for further manipulations.¹⁶ In this Letter, the successful execution of this strategy is reported.

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(10) For related reactions involving dienylboronate esters, see: (a) Tseng, N.-W.; Mancuso, J.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 5338–5339. (b) Tseng, N.-W.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 2521–2526.

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Because of their efficacy in previous rhodium-catalyzed carbozincations,⁵ ynamides **1a–1f** containing oxazolidin-2-one or imidazolin-2-one rings were chosen for this study (Figure 1). Acyclic ynamide **5** was also studied for com-

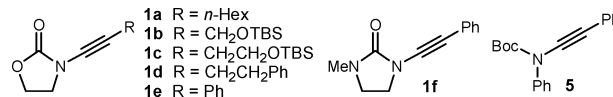


Figure 1. Ynamides employed in this study.

parison purposes. Regarding the bifunctional arylboron reagent, commercially available 2-acylphenylboronic acids **6a** and **6b** were examined first (Figure 2). An initial survey

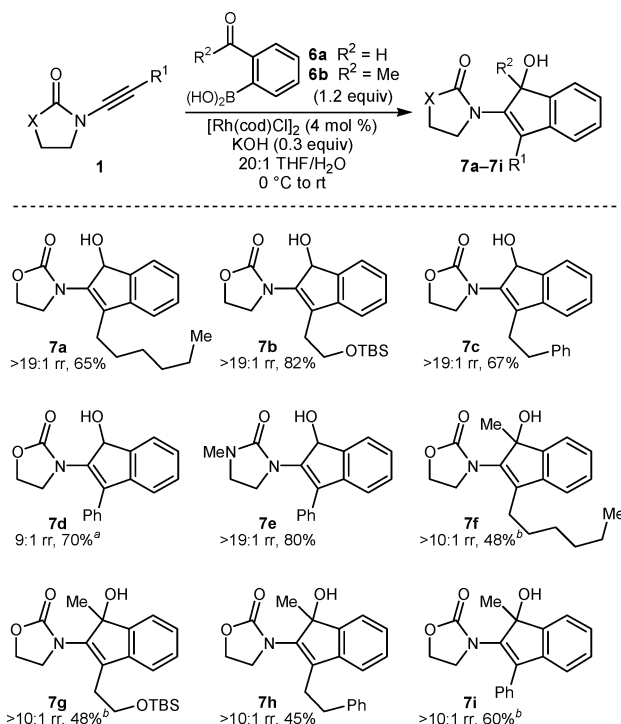


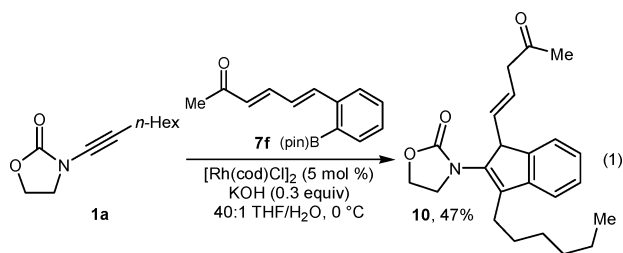
Figure 2. Rhodium-catalyzed annulation of ynamides with 2-acylphenylboronic acids. rr = Regioisomeric ratio as determined by ¹H NMR analysis of the unpurified reaction mixtures. Unless stated otherwise, cited yields are of isolated major regioisomers. Notes: (a) Isolated as a 9:1 inseparable mixture of regioisomers. (b) Products were accompanied by ca. 5–7% of unidentified inseparable impurities.

of reaction conditions revealed that reaction of ynamides **1** with 2-formylphenylboronic acid (**6a**) in the presence of

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[Rh(cod)Cl]₂ (4 mol %) and KOH (0.3 equiv) in 20:1 THF/H₂O was successful to provide a range of 2-amidoindenols **7a–7e** with generally high regioselectivities¹⁷ and good yields. Aliphatic or aromatic substituents on the ynamide were tolerated. 2-Acetylphenylboronic acid (**6b**) was also a competent reaction partner under these conditions, providing tertiary-alcohol-containing 2-amidoindenols **7f–7i** with high regioselectivities. Perhaps unsurprisingly, however, the lower electrophilicity of the ketone in **6b** compared with the aldehyde in **6a** was manifested in decreased reaction rates¹⁸ and isolated yields. In addition, small quantities of unidentified side products were observed in these cases. Consistent with previous reports of rhodium-catalyzed ynamide carbometalations,⁵ annulation of acyclic ynamide **5** with **6a** proceeded successfully but with low regioselectivity.¹⁹

Next, the reactions of ynamides **1** with 2-alkenylphenylboronic esters **8** were evaluated under similar reaction conditions, and 2-amidoindenenes **9** were formed in generally good yields (Figure 3). Arylboron reagents containing α,β -unsaturated aldehydes (**8a**), ketones (**8b** and **8c**), or esters (**8d**) were effective coupling partners, whereas α,β -unsaturated nitrile **8e** did not lead to any indene, even after prolonged heating at 50 °C. The lack of reactivity of **8e** has been documented previously.²⁰ With ynamides **1a–1d** containing aliphatic substituents, the regioselectivities were high (products **9a–9c**, **9e**, and **9g**), but phenyl-substituted ynamides **1e** and **1f** resulted in lower selectivities (products **9d**, **9fa**, and **9h**).²¹ Once again, acyclic ynamide **5** was not an effective substrate with boronic esters **8**, resulting in inseparable mixtures of indene regioisomers with low selectivities.²² Interestingly, reaction of ynamide **1a** with dienone-substituted phenylboronic ester **7f** provided a complex mixture from which 2-amidoindene **10** containing a β,γ -unsaturated ketone was isolated in 47% yield (eq 1).



Further reactions of the 2-amidoindene products are illustrated in eqs 2 and 3. When treated with Et₃N, 2-amidoindene

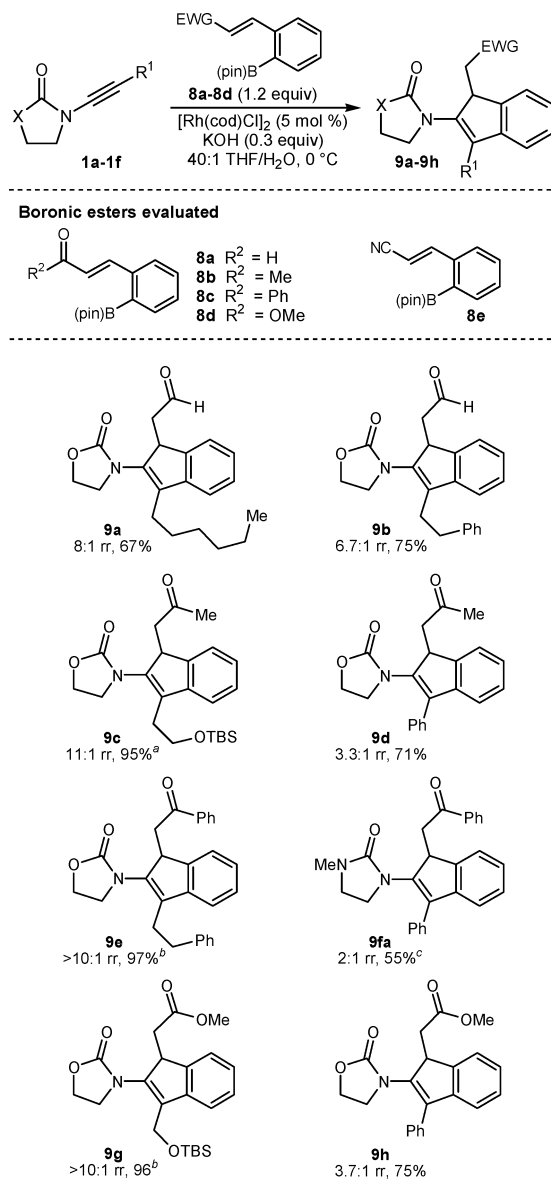


Figure 3. Rhodium-catalyzed annulation of ynamides with 2-alkenylphenylboronic esters. rr = Regioisomeric ratio as determined by ¹H NMR analysis of the unpurified reaction mixtures. Unless stated otherwise, cited yields are of isolated major regioisomers. Notes: (a) Product was isolated as an 11:1 inseparable mixture of regioisomers. (b) Product was isolated as a >10:1 inseparable mixture of regioisomers. (c) The minor regioisomer **9fb** (not shown) was isolated in 28% yield.

(17) The regioselectivity of annulation of ynamide **1c** with arylboronic acid **6a** was established through X-ray crystallography of a derivative of the resulting indene **7b**. See Supporting Information for details.

(18) Reactions employing **6a** were complete within 3 h, whereas reactions employing **6b** required overnight stirring for completion.

(19) This experiment produced a 1.7:1 inseparable mixture of indenols **7ja** and **7jb**, accompanied by small quantities of unidentified impurities. See Supporting Information for details.

(20) Catalyst deactivation through coordination of multiple nitrile groups to rhodium was cited as a possible explanation for the unreactive nature of **8e**. See ref 9b.

(21) Single X-ray crystallography of indene **9h** allowed confirmation of the regiochemical outcome.

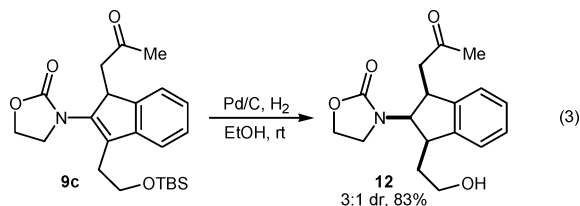
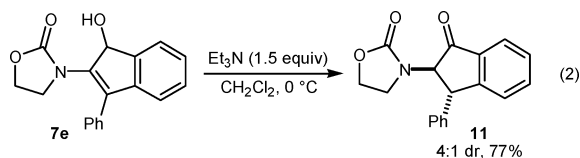
(22) For example, annulation of **5** with **8d** provided a 2:1 inseparable mixture of indenols **9ia** and **9ib** in 95% yield. See Supporting Information for details.

doindenol **7e** underwent a facile formal 1,3-hydrogen rearrangement reaction²³ to provide indanone **11** as a 4:1 inseparable mixture of diastereomers in 77% yield (eq 2).²⁴

(23) This reaction most likely proceeds via a series of base-induced [1,5] hydrogen shifts; see: (a) Clark, W. M.; Tickner-Eldridge, A. M.; Huang, G. K.; Pridgen, L. N.; Olsen, M. A.; Mills, R. J.; Lantos, I.; Baine, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 4550–4551. See also: (b) Hedberg, C.; Andersson, P. G. *Adv. Synth. Catal.* **2005**, *347*, 662–666. (c) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089–4092.

(24) Stirring indanone **11** (4:1 dr) in CD₂Cl₂ with DBU (1.0 equiv) increased the diastereomeric ratio to 7:1 after 5 h, after which time decomposition started to occur.

Hydrogenation of 2-amidoindene **9c** produced indane **12** as a 3:1 inseparable mixture of diastereomers with concomitant deprotection of the silyl group (eq 3).²⁵



In summary, rhodium-catalyzed annulation reactions of ynamides with arylboron compounds containing an aldehyde,

(25) The diastereochemical outcome of this reaction was established through NOESY ^1H NMR spectra. See Supporting Information for details.

a ketone, or an electron-deficient alkene at the *ortho*-position have been developed. The reactions proceed under mild conditions to provide a range of functionalized 2-amidoindenes with generally good levels of regioselectivity. The development of enantioselective variants of these reactions will be the subject of future reports.

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Supporting Information Available: Experimental procedures, full spectroscopic data for all new compounds, and crystallographic data in CIF format. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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