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Rhodium-Catalyzed Annulation of Ynamides with Bifunctional Arylboron Reagents

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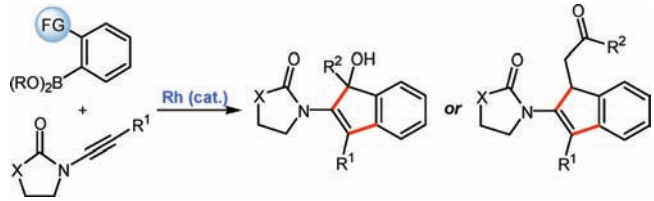
ABSTRACT



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 reactions[3] with various organometallic reagents.[4,5] We recently became interested in rhodium-catalyzed[6] 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 carborhodation of the ynamide **1** (Scheme 1).[7]

The annulation of *ortho*-functionalized arylboron reagents has previously been accomplished using alkynes[8] 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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(6) For a review of rhodium-catalyzed carbon−carbon bond-forming reactions of organometallic compounds, see: Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169–196.

(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.

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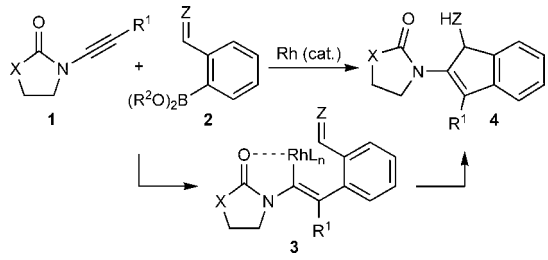
Scheme 1. Proposed Rh-Catalyzed Annulation of Ynamides with Bifunctional Arylboron Reagents



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 compounds[13] and functional materials.[14] Second, it was of fundamental interest to ascertain whether the directing effect[15] 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.

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 comparison purposes. Regarding the bifunctional arylboron reagent, commercially available 2-acylphenylboronic acids **6a** and **6b** were examined first (Figure 2). An initial survey of reaction conditions revealed that reaction of ynamides **1** with 2-formylphenylboronic acid (**6a**) in the presence of

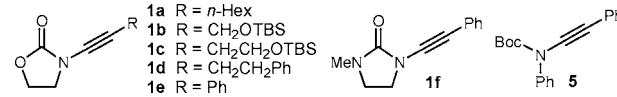


Figure 1. Ynamides employed in this study.

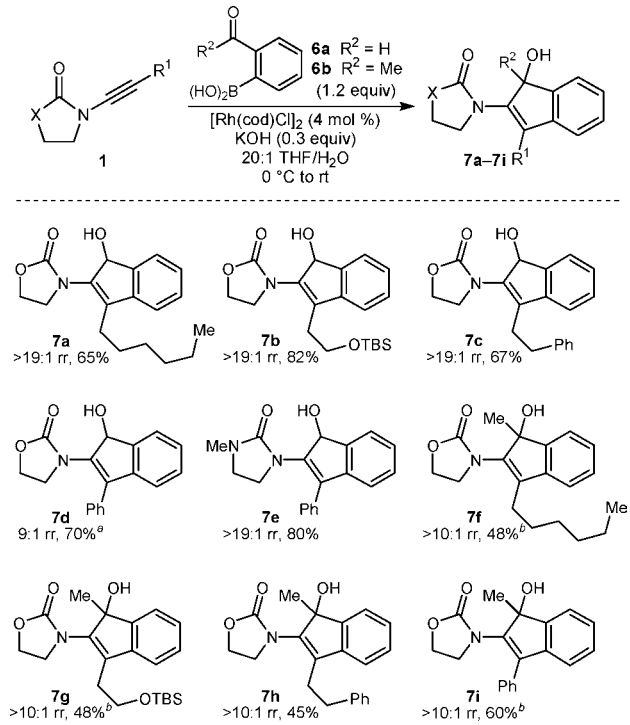


Figure 2. Rhodium-catalyzed annulation of ynamides with 2-acylphenylboronic acids. rr = Regioisomeric ratio as determined by ^{1}H NMR analysis of the unpurified reaction mixtures. Unless stated otherwise, cited yields are of isolated major regioisomers. Notes: (a) Isolated as a 9:1 inseparable mixture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

(8) Using rhodium catalysis: (a) Lautens, M.; Marquardt, T. *J. Org. Chem.* **2004**, *69*, 4607–4614. (b) Shintani, R.; Okamoto, K.; Hayashi, T. *Chem. Lett.* **2005**, *34*, 1294–1295. (c) Matsuda, T.; Makano, M.; Murakami, M. *Chem. Lett.* **2005**, *34*, 1416–1417. (d) Miura, T.; Murakami, M. *Org. Lett.* **2005**, *7*, 3339–3341. (e) Harada, Y.; Nakanishi, J.; Fujihara, H.; Tobisu, M.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 5766–5771. (f) Miyamoto, M.; Harada, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2008**, *10*, 2975–2978. (g) Tobisu, M.; Onoe, M.; Kita, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 7506–7507. Using palladium catalysis: (h) Yang, M.; Zhang, X.; Lu, X. *Org. Lett.* **2007**, *9*, 5131–5133. (i) Liu, G.; Lu, X. *Adv. Synth. Catal.* **2007**, *349*, 2247–2252. (j) Tsukamoto, H.; Kondo, Y. *Org. Lett.* **2007**, *9*, 4227–4230. (k) Zhou, F.; Yang, M.; Lu, X. *Org. Lett.* **2009**, *11*, 1405–1408.

(9) (a) Lautens, M.; Mancuso, J. *Org. Lett.* **2002**, *4*, 2105–2108. (b) Lautens, M.; Mancuso, J. *J. Org. Chem.* **2004**, *69*, 3478–3487. (c) Nishimura, T.; Yasuhara, Y.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 7506–7507. (d) Nishimura, T.; Yasuhara, Y.; Nagaosa, M.; Hayashi, T. *Tetrahedron: Asymmetry* **2008**, *19*, 1778–1783. (e) Tseng, N.-W.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 1809–1811.

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(12) For related reactions involving *o*-haloaromatic aldehydes and ketones, see: (a) Quan, L. G.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3545–3546. (b) Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089–4092. (c) Rayabarapu, D. K.; Cheng, C.-H. *Chem. Commun.* **2002**, 942–943. (d) Rayabarapu, D. K.; Yang, C.-H.; Cheng, C.-H. *J. Org. Chem.* **2003**, *68*, 6726–6731. (e) Chang, K.-J.; Rayabarapu, D. K.; Cheng, C.-H. *J. Org. Chem.* **2004**, *69*, 4781–4787. (f) Zhang, X.; Larock, R. C. *Org. Lett.* **2005**, *7*, 3973–3976.

(13) For examples, see: (a) Ishiguro, Y.; Okamoto, K.; Ojima, F.; Sonoda, Y. *Chem. Lett.* **1993**, *22*, 1139–1140. (b) Karaguni, I.-M.; Glusenkamp, K.-H.; Langerak, A.; Geisen, C.; Ullrich, V.; Winde, G.; Möröy, T.; Müller, O. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 709–713. (c) Müller, O.; Gourzoulidou, E.; Carpintero, M.; Karaguni, I.-M.; Langerak, A.; Herrmann, C.; Möröy, T.; Klein-Hitpaß, L.; Waldmann, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 450–454.

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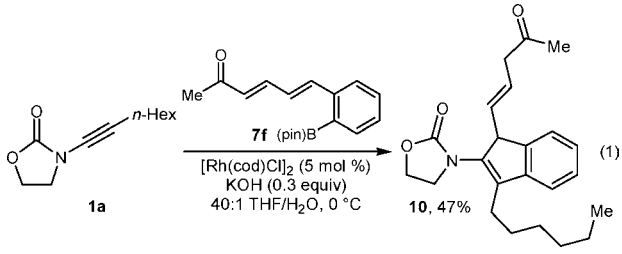
$[Rh(cod)Cl]_2$ (4 mol %) and KOH (0.3 equiv) in 20:1 THF/H_2O was successful to provide a range of 2-amidoindenols **7a**−**7e** with generally high regioselectivities[17] and good yields. Aliphatic or aromatic substituents on the ynamide were tolerated. 2-Acetylphenylboronic acid (**6b**) was also 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 rates[18] 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-amidoindenes **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 Et_3N, 2-amidoindenol **7e** underwent a facile formal 1,3-hydrogen rearrangement reaction[23] to provide indanone **11** as a 4:1 inseparable mixture of diastereomers in 77% yield (eq 2).[24]

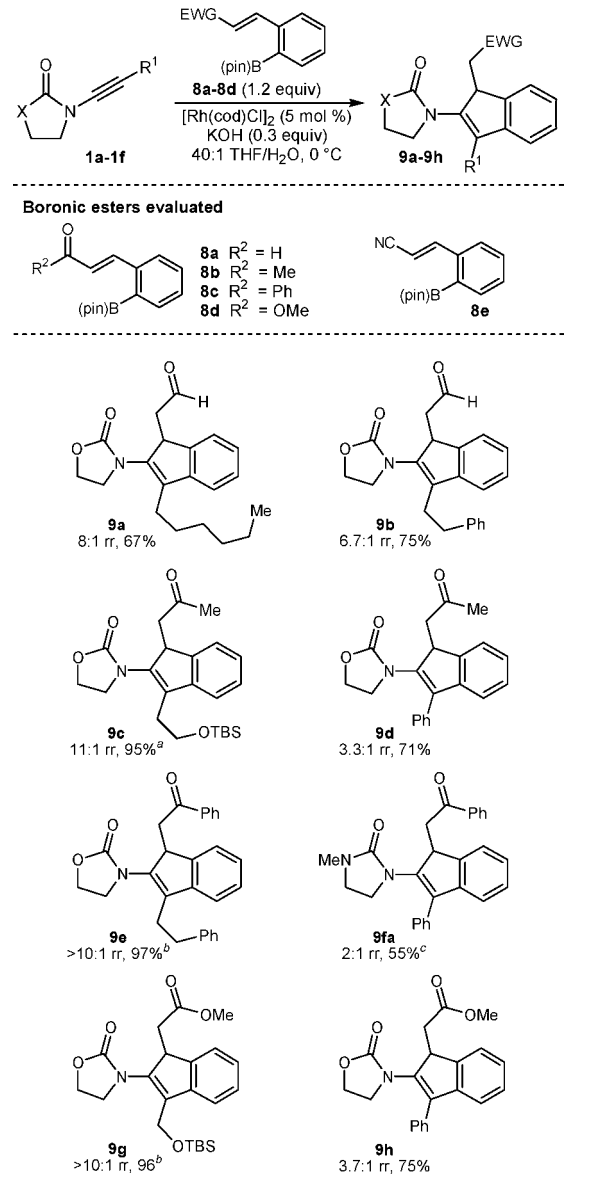


Figure 3. Rhodium-catalyzed annulation of ynamides with 2-alkenylphenylboronic esters. rr = Regioisomeric ratio as determined by ^1H NMR analysis of the unpurified reaction mixtures. Unless stated otherwise, cited yields are of isolated major regioisomers. Notes: (a) Product was isolated as an 11:1 inseparable 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.

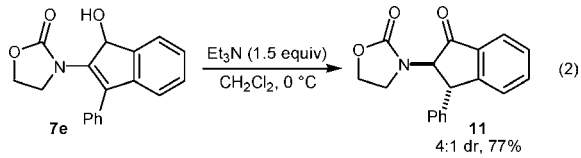
(21) Single X-ray crystallography of indene **9h** allowed confirmation of the regiochemical outcome.

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

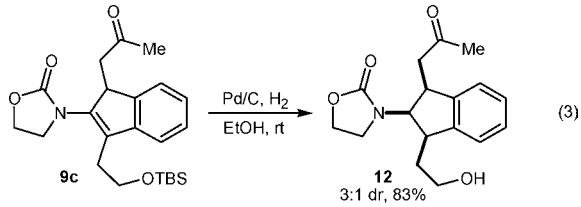
(23) This reaction most likely proceeds via a series of base-induced [1,5] hydrogen shifts; see: (a) Clark, W. M.; Tickner-Eldridge, A. M.; Huang, G. K.; Pridgen, L. N.; Olsen, M. A.; Mills, R. J.; Lantos, I.; Baine, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 4550–4551. See also: (b) Hedberg, C.; Andersson, 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 CD_2Cl_2 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]



(2)



(3)

In summary, rhodium-catalyzed annulation reactions of ynamides with arylboron compounds containing an aldehyde, 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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(25) The diastereochemical outcome of this reaction was established through NOESY ^{1}H NMR spectra. See Supporting Information for details.