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Rhodium-Catalyzed Addition of Arylboronic Acids to Isatins: An Entry to Diversity in 3-Aryl-3-Hydroxyoxindoles

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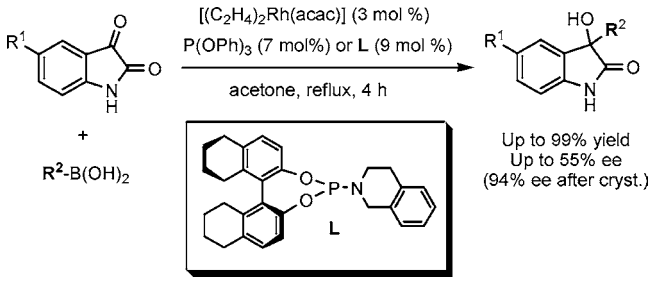
ABSTRACT



A general method for the catalytic 1,2-addition of aryl and alkenyl boronic acids to isatins is described using a rhodium(I)/triphenylphosphite catalyst. The application of this transformation allows the synthesis of a variety of 3-aryl-3-hydroxyoxindole building blocks in high yields. An enantioselective version of this reaction using a rhodium(I)/phosphoramidite system is also presented.

3-Substituted 3-hydroxyoxindoles are encountered in a large variety of natural products with a wide spectrum of biological activities, such as convolutamydines,[1a] donaxaridines,[1b,c] maremycins,[1d] dioxibrassinines,[1e] celogentin K,[1f] 3′-hydroxy hydroxyglucoisatisins,[1g] and TMC-95A.[1h] Molecules that include this structural unit constitute major targets in the development of drug candidates. 3-Alkenyl- and 3-aryl-substituted 3-hydroxyoxindoles,[2] and derivatives thereof,[3] have been used in a number of recent pharmaceutical studies. Biological activities were found to be extremely sensitive to the substitution pattern of the aryl substituent as well as the absolute configuration of the stereogenic center. Until now, no general synthetic procedure has been reported for the preparation of this type of compound with a large variety of aryl groups.[4] Such a procedure, preferably in an enantioselective fashion, would be essential for its biological

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(1) (a) Kamano, Y.; Zhang, H.-P.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Pettit, G. R. *Tetrahedron Lett.* **1995**, *36*, 2783. (b) Rasmussen, H. B.; MacLeod, J. K. *J. Nat. Prod.* **1997**, *60*, 1152. (c) Kawasaki, T.; Nagaoka, M.; Satoh, T.; Okamoto, A.; Ukon, R.; Ogawa, A. *Tetrahedron* **2004**, *60*, 3493. (d) Balk-Bindseil, W.; Helmke, E.; Weyland, H.; Laatsch, H. *Liebigs Ann.* **1995**, 1291. (e) Monde, K.; Sasaki, K.; Shirata, A.; Tagusuki, M. *Phytochemistry* **1991**, *30*, 2915. (f) Suzuki, H.; Morita, H.; Shiro, M.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 2489. (g) Fréchard, A.; Fabre, N.; Péan, C.; Montaut, S.; Fauvel, M.-T.; Rollin, P.; Fourasté, I. *Tetrahedron Lett.* **2001**, *42*, 9015. (h) Kohno, J.; Koguchi, Y.; Nishio, M.; Nakao, K.; Kuroda, M.; Shimizu, R.; Ohnuki, T.; Komatsubara, S. *J. Org. Chem.* **2000**, *65*, 990.

(2) (a) Hewawasam, P.; Meanwell, N. A.; Gribkoff, V. K.; Dworetzky, S. I.; Biossard, C. G. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1255. (b) Hewawasam, P.; Erway, M.; Moon, S. L.; Knippe, J.; Weiner, H.; Biossard, C. G.; Post-Munson, D. J.; Gao, Q.; Huang, S.; Gribkoff, V. K.; Meanwell, N. A. *J. Med. Chem.* **2002**, *45*, 1487.

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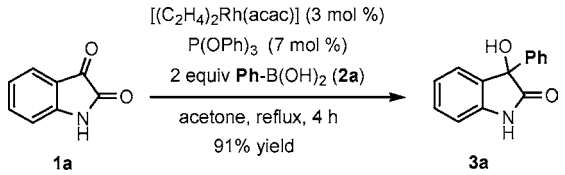
evaluation by systematic structural variation in a library approach.

There are a number of recent reports on the catalytic enantioselective formation of quaternary carbon centers at the 3-position of oxindoles.[5] However, the catalytic enantioselective formation of a tertiary alcohol at this position has been elusive until now.[6] The formation of quaternary carbon centers[7] via addition of carbon nucleophiles to ketone derivatives still constitutes a major challenge for synthetic chemistry.[8] Catalytic enantioselective synthesis of α-hydroxycarbonyl compounds via addition of organometallic nucleophiles to α-dicarbonyl substrates has so far been limited to alkynylations[9] and alkylation reactions using zinc reagents.[10] Inspired by the progress in the field of rhodium-catalyzed additions of sp^2-hybridized carbon nucleophiles to a variety of electrophiles,[11,12] we decided to investigate the arylation and alkenylation of isatin substrates using a combination of boronic acids[13,14] and rhodium catalysts to achieve the synthesis of 3-substituted 3-hydroxyoxindoles.

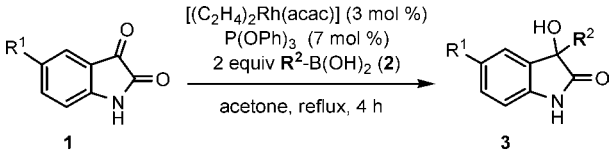
Experiments conducted with isatin **1a** and 2 equiv of phenylboronic acid **2a** in the presence of a catalyst generated *in situ* from 3 mol % of $[(C_2H_4)_2Rh(acac)]$ and 7 mol % of $P(OPh)_3$ lead to full conversion and 91% isolated yield of **3a** after 4 h at reflux temperature (Scheme 1). Although this class of substrates represents highly activated carbonyl compounds, to the best of our knowledge, this is the first report of rhodium-catalyzed arylboronic acid addition to ketones.[6,15]

Scheme 1. Rhodium/Triphenylphosphite-Catalyzed Addition of Arylboronic Acids to Isatin



This reaction was applied to isatin substrates **1a**−**c** and a variety of arylboronic acids **2a**−**k** (Table 1). As already observed by Frost for the addition of arylboronic acids to

Table 1. Rhodium/Triphenylphosphite-Catalyzed 1,2-Addition of Aryl- and Alkenylboronic Acids to Isatins



Boronic Acids:

2a: R^2 = Phenyl
2b: R^2 = *p*-Tolyl
2c: R^2 = 3,5-Dimethylphenyl
2d: R^2 = *o*-Tolyl
2e: R^2 = *p*-Methoxyphenyl
2f: R^2 = 2-Naphthyl
2g: R^2 = *m*-Nitrophenyl
2h: R^2 = *p*-Ethoxycarbonylphenyl
2i: R^2 = *o*-Fluorophenyl
2j: R^2 = 3-Thiophene
2k: R^2 = 2-*trans*-phenylvinyl

entry[a]	isatin (R^1)		boronic acid	product	yield[b]
1	**1a**	(H)	**2a**	**3a**	91%
2	**1b**	(Me)	**2a**	**3b**	79%
3	**1c**	(Cl)	**2a**	**3c**	99%
4	**1a**	(H)	**2b**	**3d**	99%
5	**1a**	(H)	**2c**	**3e**	99%
6	**1a**	(H)	**2d**	**3f**	99%
7	**1a**	(H)	**2e**	**3g**	98%
8	**1a**	(H)	**2f**	**3h**	87%
9	**1a**	(H)	**2g**	**3i**	66%
10	**1c**	(Cl)	**2h**	**3j**	62%
11	**1a**	(H)	**2i**	**3k**	43%
12	**1a**	(H)	**2j**	**3l**	54%
13	**1a**	(H)	**2k**	**3m**	96%

[a] All reactions were performed on 0.2 mmol scale in 2 mL of acetone at reflux for 4 h with 2 equiv of arylboronic acid (**2**) in the presence of a catalyst generated *in situ* from 3 mol % of $[(C_2H_4)_2Rh(acac)]$ and 7 mol % of triphenylphosphite. [b] Isolated yields of **3** after column chromatography.

(3) (a) Hewawasam, P.; Meanwell, N. A.; Gribkoff, V. K. U.S. Patent 5,602,169, **1997**; *Chem. Abstr.* **1997**, *126*, 181369. (b) Gribkoff, V. K.; Starrett, J. E., Jr.; Dworetzky, S. I.; Hewawasam, P.; Boissard, C. G.; Cook, D. A.; Frantz, S. W.; Heman, K.; Hibbard, J. R.; Huston, K.; Johnson, G.; Krishnan, B. S.; Kinney, G. G.; Lombardo, L. A.; Meanwell, N. A.; Molinoff, P. B.; Myers, R. A.; Moon, S. L.; Ortiz, A.; Pajor, L.; Pieschl, R. L.; Post-Munson, D. J.; Signor, L. J.; Srinivas, N.; Taber, M. T.; Thalody, G.; Trojnacki, J. T.; Weiner, H.; Yeleswaram, K.; Yeola, S. W. *Nat. Med.* **2001**, *7*, 471. (c) Natarajan, A.; Fan, Y.-H.; Chen, H.; Guo, Y.; Iyasere, J.; Harbinski, F.; Christ, W. J.; Aktas, H.; Halperin, J. A. *J. Med. Chem.* **2004**, *47*, 1882. (d) Natarajan, A.; Guo, Y.; Harbinski, F.; Fan, Y.-H.; Chen, H.; Luus, L.; Diercks, J.; Aktas, H.; Chorev, M.; Halperin, J. A. *J. Med. Chem.* **2004**, *47*, 4979. (e) Cliffe, I. A.; Lien, E. L.; Mansell, H. L.; Steiner, K. E.; Todd, R. S.; White, A. C.; Black, R. M. *J. Med. Chem.* **1992**, *35*, 1169.

(4) The synthesis of enantiomerically enriched 3-aryl-3-hydroxyoxindoles has been accomplished via the highly diastereoselective arylation of mandelic acid: (a) Barroso, S.; Blay, G.; Cardona, L.; Fernández, I.; García, B.; Pedro, J. R. *J. Org. Chem.* **2004**, *69*, 6821. For the synthesis of enantiomerically enriched 3-aryl-3-hydroxyoxindoles by asymmetric hydroxylation using chiral oxaziridines, see ref 2b.

(5) Palladium-catalyzed intramolecular α-arylation: (a) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. Intramolecular Heck reaction: (b) Dounay, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261. Organocatalytic acyl transfer: (c) Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 3921. Biocatalytic desymmetrization of prochiral substrates: (d) Akai, S.; Tsujino, T.; Akiyama, E.; Tanimoto, K.; Naka, T.; Kita, Y. *J. Org. Chem.* **2004**, *69*, 2478. Lewis-catalyzed α-fluorination of carbonyl groups: (e) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164. Palladium-catalyzed allylation of prochiral nucleophiles: (f) Trost, B. M.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 308. Organocatalytic aldol reaction: (g) Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 7418.

(6) After submission of this manuscript, the group of Hayashi reported the rhodium-catalyzed asymmetric addition of aryl- and alkenylboronic acids to isatins: Shintani, R.; Inoue, M.; Hayashi, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3353.

(7) For reviews on the formation of quaternary carbon centers, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Denissova, I.; Barriault, L. *Tetrahedron* **2003**, *59*, 10105. (c) Ramón, D. J.; Yus, M. *Curr. Org. Chem.* **2004**, *8*, 149. (d) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *247*, 1473. (e) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (f) Christoffers, J., Baro, A., Eds. *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2005.

(8) For a recent review on enantioselective addition to ketones using zinc reagents, see: (a) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284. For leading references in the field of catalytic enantioselective additions of organometallic aryl and alkenyl reagents to carbonyl compounds, see: (b) García, C.; Walsh, P. J. *Org. Lett.* **2003**, *5*, 3641. (c) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 8355. (d) Tomita, D.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 4138.

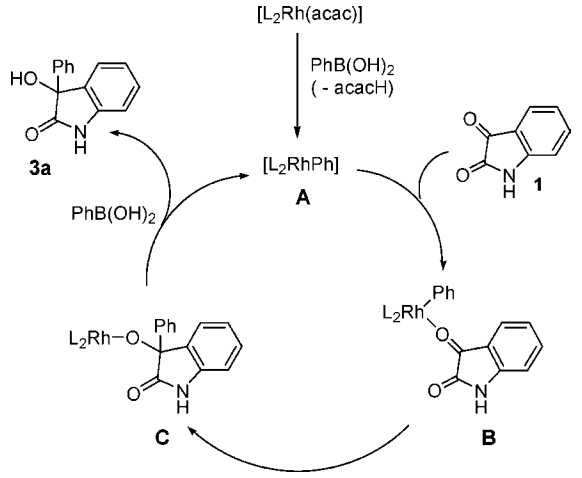
(9) (a) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451. (b) Dhondi, P. K.; Chisholm, J. D. *Org. Lett.* **2006**, *8*, 67.

(10) (a) DiMauro, E. F.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2002**, *124*, 12668. (b) DiMauro, E. F.; Kozlowski, M. C. *Org. Lett.* **2002**, *4*, 3781. (c) Funabashi, K.; Jachmann, M.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5489.

aldehydes,[16] this 1,2-addition reaction is influenced by the electronic substitution pattern of both reaction partners. Electron-donating groups on the isatin substrate lower the reactivity (entry 2), while electron-withdrawing substituents cause an increase of reactivity (entry 3). Electron-donating substituents on the boronic acid result in high yields (entries 4−8), while electron-withdrawing ones lead to moderate values (entries 9−11). Steric hindrance of the boronic acid does not influence the yield (compare entries 4−6). Phenyl groups with electrophilic substituents, which are generally not tolerated by organomagnesium or organolithium reagents, were introduced here with success (entries 9−11).[14] Also *ortho*-fluorophenyl, for which the Grignard reagent is not available, was successfully introduced (entry 11). An additional advantage of the present strategy is the fact that it proceeds without protecting the amide functionality of the substrate.

In contrast with the initial report of Miyaura on the rhodium-catalyzed arylboronic acid addition to aldehydes,[17] our system does not require the presence of any added protic source.[18] Although the substrate is protic itself, similar observations using aldehydes as substrates seem to indicate that the alkoxy species **C** (Scheme 2) resulting from the

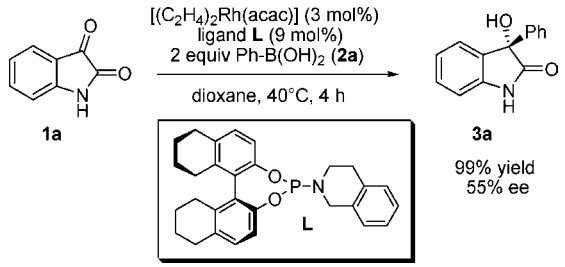
Scheme 2. Proposed Mechanism of the Rhodium-Catalyzed 1,2-Addition of Arylboronic Acids



arylation of the carbonyl function is acting as a nucleophile in the transmetalation step to regenerate the catalytic active intermediate **A**.[12d]

In relation with previous studies[12d,e] conducted in our group on asymmetric 1,2-arylations using substrates with carbon−heteroatom double bonds, we investigated an array of binol-based phosphoramidite ligands,[19] a class of cheap, easily prepared ligands, successful in the rhodium-catalyzed conjugate addition of arylboronic acids to enones.[12a−c] This led to the discovery of moderate enantioselectivities using the new phosphoramidite ligand **L** (Scheme 3).

Scheme 3. Enantioselective Rhodium/Phosphoramidite-Catalyzed 1,2-Addition of Arylboronic Acid to Isatin



In preliminary experiments, a series of chiral phosphoramidite ligands was tested with model substrate **1a** and phenylboronic acid **2a**. In the presence of a catalyst generated from 3 mol % of $[(C_2H_4)_2Rh(acac)]$ and 9 mol % of ligand **L**,[20] 3-phenyl-3-hydroxyoxindole (**3a**) was obtained in virtually quantitative yield and 55% ee.[21] Upon recrystallization from 2-propanol, the supernatant gave the enantioenriched product in 59% yield and 94% ee.

In conclusion, we have discovered the 1,2-addition of arylboronic acids to isatin substrates based on a combination of a rhodium(I) precursor and 2 equiv of triphenylphosphite. This method represents a general procedure for the formation of 3-aryl-3-hydroxyoxindoles in good to excellent yields. Promising enantioselectivities are obtained in an asymmetric version of this reaction employing a phosphoramidite ligand. Further studies to expand this methodology to other classes of substrates and to improve the enantioselectivity of the asymmetric addition are currently in progress.

(11) For reviews on this topic, see: (a) Hayashi, T. *Synlett* **2001**, 879. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (c) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169.

(12) (a) Boiteau, J.-G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 681; *Org. Lett.* **2003**, *5*, 1385. (b) Boiteau, J.-G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2003**, *68*, 9481. (c) Duursma, A.; Hoen, R.; Schuppan, J.; Hulst, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 3111. (d) Jagt, R. B. C.; Toullec, P. Y.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Org. Biomol. Chem.* **2006**, *4*, 773. (e) Jagt, R. B. C.; Toullec, P. Y.; Geerdink, D.; de Vries, J. G.; Feringa, B. L.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2789.

(13) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Hall, D. G., Ed. *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*; Wiley-VCH: Weinheim, Germany, 2005.

(14) For a discussion of the advantages of arylboronic acids in 1,2-addition reactions regarding functional group tolerance, see: Fürstner, A.; Krause, H. *Adv. Synth. Catal.* **2001**, *343*, 343.

(15) For the asymmetric addition of arylzinc reagents, generated in situ from arylboronic acids and diethylzinc to acetophenones, see: (a) Prieto, O.; Ramón, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2003**, *14*, 1955. Also see: (b) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850.

(16) Moreau, C.; Hague, C.; Weller, A. S.; Frost, C. G. *Tetrahedron Lett.* **2001**, *42*, 6957.

(17) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 3279.

(18) For a comprehensive mechanistic rationale of the rhodium-catalyzed arylboronic acid conjugate addition to enones and a discussion of the crucial role of the protic source in the catalytic activity, see: Hayashi, T.; Takahashi, M.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **2002**, *124*, 5052.

(19) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346.

(20) A ligand/rhodium ratio of 3/1 gave the optimum enantioselectivity. Using a lower ratio, the ee decreases slightly. This is probably due to competitive chelating properties of both substrate **1** and product **3**. Using a higher ratio, dramatically lower activity was observed.

(21) Ligand (*S*)-**L** provided product (*S*)-**3a**. For determination of the absolute configuration of compound **3a**, see: Barroso, S.; Blay, G.; Cardona, L.; Fernandez, I.; Garcia, B.; Pedro, J. R. *J. Org. Chem.* **2004**, *69*, 6821 and the discussion in the Supporting Information.

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Supporting Information Available: Experimental details, chromatographic, and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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