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Regioselective Rhodium(I)-Catalyzed Hydroarylation of Protected Allylic Amines with Arylboronic Acids

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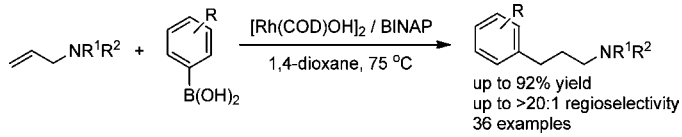
ABSTRACT



A novel regioselective rhodium(I)-catalyzed hydroarylation of unactivated alkenes with arylboronic acids is described. The catalytic system employs $[Rh(COD)OH]_2$ and BINAP to effect the addition of various arylboronic acids to protected allylic amines. The regioselectivity was found to be highly dependent on the protecting group, favoring the linear addition product with up to 92% yield and >20:1 regioselectivity.

Rhodium-catalyzed carbon−carbon bond formation has been the subject of extensive studies in recent years.[1] In particular, significant advances have been made in rhodium(I)-catalyzed addition of arylboronic acids to alkenes activated by conjugated electron-withdrawing groups (Miyaura−Hayashi reaction).[2] The net outcome of the process is the addition of hydrogen and aryl groups across the double bond (hydroarylation).[3] However, the addition to unactivated alkenes still remains a major challenge in this area. Strained alkenes, such as norbornene, have been reported to insert into a rhodium-aryl bond as a key step for facilitating multiple alkylation of aromatic rings.[4,5] In an earlier communication, we reported a rhodium-catalyzed cross-coupling of styrenes with arylboronic acids.[6] The method afforded *trans*-stilbene products in good yield, which were formed via a Heck-type addition−elimination process. In contrast, heteroaromatic alkenes such as 2-vinylpyridine led to the addition products exclusively via an addition-hydrolysis process. Although these reports contributed to broaden the scope of alkenes that can undergo rhodium-catalyzed addition reactions, to the best of our knowledge, rhodium-catalyzed hydroarylation of simple alkenes, e.g., alkenes that are not conjugated or

(1) (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (c) *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005. (d) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394. (e) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217.

(2) For additions to enones, see: (a) Sakai, M.; Hayashi, M.; Miyaura, N. *Organometallics* **1997**, *16*, 4229. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. For additions to α,β-unsaturated esters, see: (c) Sakuma, S.; Sakai, M.; Itooka, R.; Miyaura, N. *J. Org. Chem.* **2000**, *65*, 5951. For additions to vinyl phosphonates, see: (d) Hayashi, T.; Senda, T.; Takaya, Y.; Ogasawara, M. *J. Am. Chem. Soc.* **1999**, *121*, 11591. For additions to vinyl nitro compounds, see: (e) Hayashi, T.; Senda, T.; Ogasawara, M. *J. Am. Chem. Soc.* **2000**, *122*, 10716. For additions to α,β-unsaturated aldehydes, see: (f) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850.

(3) For examples of transition-metal-catalyzed hydroarylation of alkenes, see: (a) Jana, R.; Tunge, J. A. *Org. Lett.* **2009**, *11*, 971. (b) Harada, H.; Thalji, R. K.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2008**, *73*, 6772. (c) Bhalla, G.; Oxgaard, J.; Goddard, W. A., III; Periana, R. A. *Organometallics* **2005**, *24*, 3229. (d) Oxgaard, J.; Periana, R. A.; Goddard, W. A., III *J. Am. Chem. Soc.* **2004**, *126*, 11658. (e) Han, X.; Widenhoefer, R. A. *Org. Lett.* **2006**, *8*, 3801. (f) Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 4042. (g) McKeown, B. A.; Foley, N. A.; Lee, J. P.; Gunnoe, T. B. *Organometallics* **2008**, *27*, 4031. (h) Youn, S. W.; Pastine, S. J.; Sames, D. *Org. Lett.* **2004**, *6*, 581. (i) Martinez, R.; Genet, J.-P.; Darses, S. *Chem. Commun.* **2008**, 3855. (j) Foley, N. A.; Lee, J. P.; Ke, Z.; Gunnoe, T. B.; Cundari, T. R. *Acc. Chem. Res.* **2009**, *42*, 585. (k) Bartoli, G.; Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Synlett* **2008**, 2508.

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

(5) For related hydroarylation of other [2.2.1]bicyclic alkenes, see: (a) Menard, F.; Lautens, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2085. (b) Panteleev, J.; Menard, F.; Lautens, M. *Adv. Synth. Catal.* **2008**, *350*, 2893.

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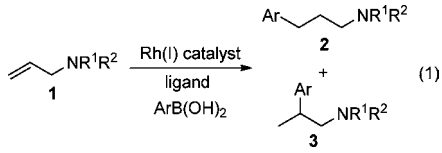
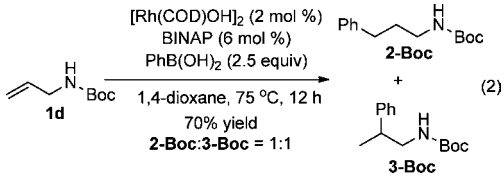
part of strained systems, has not been reported.

We envisaged the use of simple protected allylic amines **1** as substrates for the hydroarylation reaction (eq 1). Acylated allylic amines are widely used in medicinal chemistry,[7] and allyl groups can be utilized to install various aryl groups at a late stage in SAR studies of drug discovery. The alkene moiety of these allylic amines is not activated, yet we speculated the protecting groups could potentially coordinate to the rhodium catalyst to facilitate the reaction. Two possible regioisomeric products, the linear **2** and branched **3** products, can be formed upon arylrhodation. Since both products are common motifs in biologically active compounds,[7] developing a regioselective method to access either product would be valuable. Moreover, the branched product **3** is amenable to enantioselective hydroarylation, which could provide useful chiral amine building blocks.[8] The chemoselectivity of the reaction also needs to be addressed: addition followed by β-hydride elimination could lead to a Heck-type product, or the substrate could isomerize to an enamine in the presence of the rhodium catalyst.[9]



(1)

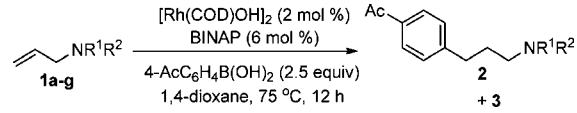
We initially studied the reaction of Boc-protected allylic amine **1d** with phenylboronic acid in the presence of $[Rh(COD)OH]_2$ and BINAP. Linear and branched products **2-Boc** and **3-Boc** were obtained in 70% yield in a 1:1 ratio (eq 2). No Heck-type products or isomerized starting material was observed in these conditions. Optimization of the reaction conditions was then undertaken to improve the yield and regioselectivity. Various parameters were studied, including the catalyst source, ligand, organoboron reagent, solvent, temperature, reaction time, and additives (see Supporting Information). The initial $[Rh(COD)OH]_2$/BINAP conditions gave the best yield of the desired products.



(2)

Preferential formation of the linear product **2** was observed with allylic amines bearing different protecting groups. The yield and regioselectivity were found to be dependent on the protecting group. Substrates **1a**−**g**, including phthalimide, sulfonamides, carbamates, and amides, reacted successfully with 4-acetylphenylboronic acids under the above optimal conditions (Table 1).

Table 1. Rh-Catalyzed Hydroarylation of Protected Allylic Amines with 4-Acetylphenylboronic Acids



entry	NR^1R^2	yield (%)[a]	**2**:**3**[b]	product
1	*N*-phthalyl, **1a**	91	7:1	**2aa**
2	$NHSO_2p$-Tol, **1b**	92	6:1	**2ba**
3	$NHSO_2$Me, **1c**	83	4:1	**2ca**
4	$NHCOO^t$Bu, **1d**	92	2:1	**2da**
5	*N*HCOOBn, **1e**	86	2:1	**2ea**
6	*N*HCOOEt, **1f**	65	2:1	**2fa**
7	*N*HC(O)Me,[c] **1g**	50	2:1	**2ga**

[a] Isolated yields. [b] Determined by crude ^{1}H NMR (400 MHz). [c] Allyl-*N*HC(O)*t*Bu, -*N*HC(O)Ph, -*N*HPh, -*N*HBn, -*N*Ts$_2$, and -*N*TsBoc gave <5% crude yield of desired products; allyl-*N*Boc$_2$ gave 20% crude yield, using phenylboronic acid.

The phthalyl and tosyl groups gave the highest regioselectivities (entries 1 and 2), followed by the mesyl group (entry 3). The carbamates and amide (entry 4−7) gave poor regioselectivities. Good yields (up to 92%) of the hydroarylation products were obtained. Ethyl carbamate and methyl amide gave moderate yields (entries 6 and 7). More sterically hindered amides (pivaloyl and benzoyl groups), aniline, benzylamine, and substrates with two protecting groups (-Ts$_2$, -TsBoc, -Boc$_2$) did not provide the desired products in satisfactory yields (0−20%).

The scope of arylboronic acids was studied using allylic phthalimide **1a**, sulfonamide **1b**, and carbamate **1d** as substrates (Table 2). Excellent regioselectivities (up to >20:1) were achieved in the phthalimide series (entries 1−7). Moderate to good yields were obtained, though higher catalyst loadings were required for some boronic acids (entries 1, 4, 5, and 7). In the sulfonamide series (entries 8−14), although moderate yields or varying degrees of regioselectivity were obtained, the majority of the cases gave good regioselectivities (6:1 to 8:1). In the carbamate series (entries 15−20), moderate yields and poor regioselectivities (1:1 to 2:1) were obtained. Electron-withdrawing groups at the *para*-position of the arylboronic acid (-Ac, -CF$_3$, -CO$_2$Me) gave better yields than an electron-donating group (-MeO) at the same position (compare entries 1/7, 8/13, and 15/19). *Meta*- and *ortho*-substituents (3-Ac, 3-MeO and 2-Me) were also tolerated, affording the products in moderate yields. The 2-Me group in the sulfonamide series (entry 14) led to poorer regioselectivity. It was found that adding a small amount of water (dioxane/water = 100:1 v/v) had a beneficial effect on regioselectivity in some cases (entries 2, 11, and 13). For example, compared to the result without added water, the regioselectivity in **2aa** increased significantly from

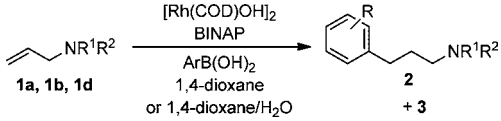
(7) (a) Huang, Y.-T.; Blagg, B. S. J. *J. Org. Chem.* **2007**, *72*, 3609. (b) Chae, J.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 3336. (c) Svenson, J.; Brandsdal, B.-O.; Stensen, W.; Svendsen, J. S. *J. Med. Chem.* **2007**, *50*, 3334.

(8) For an enantioselective synthesis of branched amines, see: Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4793.

(9) (a) Akutagawa, S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 23, 41.4. (b) Inoue, S.-I.; Takaya, H.; Tani, K.; Otsuka, S.; Sato, T.; Noyori, R. *J. Am. Chem. Soc.* **1990**, *112*, 4897.

7:1 to 15:1 (entry 2; cf. Table 1, entry 1), with a slight decrease in yield. This effect was not observed in the carbamate series.

Table 2. Scope of Arylboronic Acid Using Allyl-*N*-phthalimide, Allyl-*N*HTs, and Allyl-*N*HBoc[a]



entry	NR^1R^2	R	yield (%)[b]	**2**:**3**[c]	product
1[d]	*N*-phthalyl, **1a**	4-CF_3	76	20:1	**2ab**
2[e,f]	*N*-phthalyl, **1a**	4-Ac	84	15:1	**2aa**
3	*N*-phthalyl, **1a**	3-Ac	66	>20:1	**2ac**
4[d]	*N*-phthalyl, **1a**	4-CO_2Me	67	11:1	**2ad**
5[d]	*N*-phthalyl, **1a**	3-MeO	55	>20:1	**2ae**
6	*N*-phthalyl, **1a**	H	65	>20:1	**2af**
7[d]	*N*-phthalyl, **1a**	4-MeO	35	>20:1	**2ag**
8	*N*HTs, **1b**	4-CF_3	79	8:1	**2bb**
9	*N*HTs, **1b**	3-Ac	79	6:1	**2bc**
10	*N*HTs, **1b**	4-CO_2Me	56	8:1	**2bd**
11[e]	*N*HTs, **1b**	3-MeO	62	>20:1	**2be**
12	*N*HTs, **1b**	H	65	6:1	**2bf**
13[e,g]	*N*HTs, **1b**	4-MeO	36	15:1	**2bg**
14	*N*HTs, **1b**	2-Me	65	3:1	**2bh**
15	*N*HBoc, **1d**	4-CF_3	69	1:1	**2db**
16	*N*HBoc, **1d**	3-Ac	68	1:1	**2dc**
17	*N*HBoc, **1d**	4-CO_2Me	50	2:1	**2dd**
18	*N*HBoc, **1d**	3-MeO	71	1:1	**2de**
19	*N*HBoc, **1d**	4-MeO	30	1:1	**2df**
20	*N*HBoc, **1d**	2-Me	40	1:1	**2dg**

[a] General conditions: 2 mol % $[Rh(COD)OH]_2$, 6 mol % BINAP, 2.5 equiv of arylboronic acid, 2.5 mL of 1,4-dioxane, 75 °C, 12 h. [b] Isolated yields. [c] Determined by crude ^{1}H NMR (400 MHz). [d] 4 mol % $[Rh(COD)OH]_2$, 12 mol % BINAP. [e] 1,4-Dioxane/H_2O (2.5 mL/25 μL). [f] Adding more water (1,4-dioxane/H_2O = 2.5 mL:250 μL) increased the **2**:**3** ratio (>20:1) but decreased conversion significantly (26% isolated yield). [g] No added water: 33% yield, **2**:**3** = 11:1.

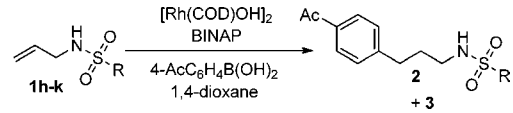
The effects of the sulfonyl substituent group of sulfonamides **1h**−**k** were subsequently studied. The products were obtained in high yields favoring linear product **2** (Table 3). Electron-rich, electron-poor, and *ortho*-substituted aromatic groups all gave good yields and regioselectivities (entries 1−3). On the other hand, a drastic increase in regioselectivity (>20:1) was observed with the CF_3 group directly attached to sulfone (entry 4).

To investigate whether the reaction could be extended to alkenes other than allylic amines, substrates with a differing carbon chain length were tested (Table 4).

The yield decreased significantly as the carbon chain length increased, and a complete loss of regioselectivity was observed (entries 1−2, cf. Table 1, entry 2). Vinyl phthalimide **4c** afforded the linear product **5c** exclusively albeit in a low yield (entry 3). Intriguingly, this result demonstrates a polarity reversal of the reactants since enamides/enamines usually act as nucleophiles.[10]

Methylated sulfonamide **1l** was also submitted to the reaction (eq 3). The *N*-Me group did not impede the reactivity, and product **2l** was obtained in a yield comparable to that with the nonmethylated sulfonamide (cf. Table 2, entry 12). The methyl group had a significant effect on regioselectivity, favoring the linear product **2l** exclusively.

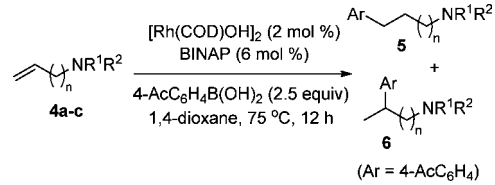
Table 3. Effects of Sulfonamide Substituent Groups[a]



entry	R	yield (%)[b]	**2**:**3**[c]	product
1	4-$MeOC_6H_4$, **1h**	92	6:1	**2h**
2	2-MeC_6H_4, **1i**	88	7:1	**2i**
3	4-FC_6H_4, **1j**	86	8:1	**2j**
4	CF_3, **1k**	43[d]	>20:1	**2k**

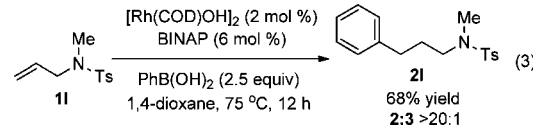
[a] Reaction conditions: $[Rh(COD)OH]_2$ (2 mol %), BINAP (6 mol %), boronic acid (2.5 equiv), 1,4-dioxane (2.5 mL), 75 °C, 12 h. [b] Isolated yields. [c] Determined by crude ^{1}H NMR (400 MHz). [d] Average yield of two runs.

Table 4. Effect of Carbon Chain Length



entry	NR^1R^2	*n*	yield (%)[a]	**5**:**6**[b]	product
1	*N*HTs, **4a**	2	62	1:1	**5a**
2	*N*HTs, **4b**	3	48	1:1	**5b**
3	*N*-phthalyl, **4c**	0	35	>20:1	**5c**

[a] Isolated yields. [b] Determined by crude ^{1}H NMR (400 MHz).

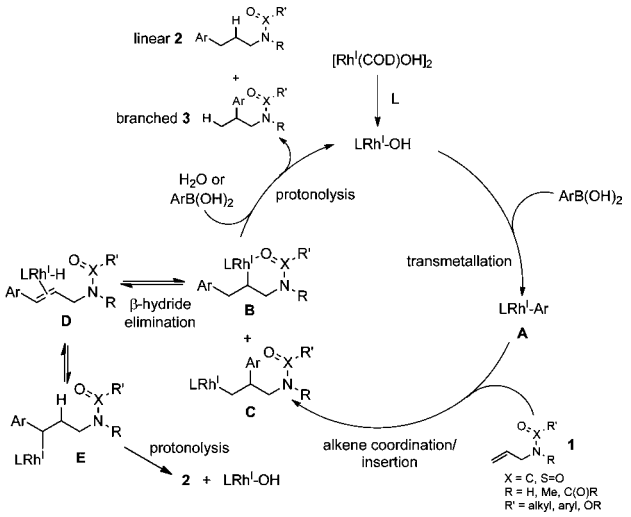


A proposed catalytic cycle for the general reaction is shown in Scheme 1. Fast transmetalation between the rhodium catalyst and arylboronic acid generates Rh−Ar species **A**. Subsequent coordination and insertion of alkene **1** would lead to intermediates **B** and **C**; this step determines the regiochemical outcome of the product. Presumably, certain X═O groups such as phthalyl and tosyl groups are better at coordinating rhodium and thus stabilize intermediate **B** by forming a six-membered rhodacycle, whereas a less stable seven-membered ring would be formed in **C**. As a result, the linear products **2** are formed predominantly upon protonolysis, and the catalyst is regenerated. The fact that

(10) For our earlier report on palladium-catalyzed regioselective hydrostannation of substrate **4d**, see: Lautens, M.; Kumanovic, S.; Meyer, C. *Angew. Chem., Int. Ed.* **1996**, *35*, 1329.

the homoallylic substrate gave no regioselectivity (Table 4, entry 1) may also support this hypothesis since no stabilized rhodacycles would be formed. However, it is also possible that **B** could undergo β-hydride elimination to form a transient styrene-type intermediate **D** and Rh-H, which may be in equilibrium with **B** and **E**. Protonolysis would lead to the same linear product **2**. We also hypothesize that the coordination of the X═O group to rhodium would also

Scheme 1. Proposed Catalytic Cycle for Rh(I)-Catalyzed Hydroarylation of Protected Allylic Amines



explain the reactivity of the otherwise unactivated alkene substrate **1** by bringing the Rh-Ar species close to the alkene component of the substrate prior to insertion. The fact that substrates without an X═O group such as allyl-*N*HPh and -*N*HBn gave no desired product may support this argument (Table 1).

In summary, a novel regioselective Rh(I)-catalyzed hydroarylation of protected allylic amines with arylboronic acids was developed. The regioselectivity was found to be dependent on the nature of the protecting group. Linear products can be obtained in good yields and excellent regioselectivities despite other competing processes such as addition−elimination or isomerization. This represents one of the few examples of Rh(I)-catalyzed addition of arylboronic acids to unactivated alkenes. Notably, the method reported herein is complementary to Pd-catalyzed reactions where β-elimination is more facile and generally the predominant pathway. It should be noted that arylpropylamines **2** are synthetic equivalents to fully reduced hydrocinnamyl amides where variation of the aryl group would not be straightforward. However, the method reported herein allows easy modulation of the aryl group in the last step. Further investigation into the reaction mechanism, *N*-substituent effect, use of other allylic substrates, and formation of branched product is in progress.

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

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