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Rhodium-Catalyzed Enantioselective 1,6-Addition of Arylboronic Acids to Enynamides: Asymmetric Synthesis of Axially Chiral Allenylsilanes

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Abstract: Rhodium-catalyzed asymmetric 1,6-addition of arylboronic acids to β-alkynyl acrylamides substituted with a silyl group on the alkyne terminus took place to give high yields of axially chiral allenylsilanes with 94−99% enantioselectivity, which was realized by use of a rhodium/chiral diene complex.

Axially chiral allenes (1,2-propadienes) are attractive compounds as chiral building blocks in organic synthesis, and useful synthetic approaches to this class of compounds starting from prochiral compounds have recently been developed.[1,2] The 1,6-addition of carbon nucleophiles to conjugated enyne−carbonyl compounds is one of the most efficient approaches for the preparation of functionalized allenes.[3] Copper reagents or catalysts have been used for the selective 1,6-addition of organometallic reagents to enynoates leading to allenes,[4] but the asymmetric variant catalyzed by copper complexes has not been reported to date. In this context, we recently reported the enantioselective synthesis of axially chiral allenes by means of 1,6-addition of aryltitanates to enynones in the presence of chlorotrimethylsilane, which is catalyzed by a rhodium/chiral bisphosphine complex.[5] The 1,6-addition products were obtained as β-allenylidene silyl enolates with high enantioselectivity, but the substrates were limited to β-alkynylated cycloalkenones, which effectively shield the competing 1,4-addition reaction. Here we report the asymmetric 1,6-addition of arylboronic acids to linear enynamides to give axially chiral allenylsilanes[6] in high yields with high enantioselectivity.

We found that enynamide **1a** substituted with a terminal silyl group on the alkyne is a good substrate that gives allenylsilane derivatives with high enantioselectivity in the addition of arylboronic acids. Thus, treatment of **1a** with phenylboronic acid (**2m**, 2 equiv) in the presence of the rhodium/chiral diene[7] catalyst [RhCl((*S*,*S*)-Fc-tfb*(**L1**))]$_2$ (Fc = ferrocenyl)[8] (5 mol % Rh) and K_3PO_4 (20 mol %) in 1,4-dioxane and H_2O at 50 °C for 3 h gave allenylsilane **3am** with 98% ee together with a small amount of **4am** (total yield 87%, **3am**/**4am** = 98/2), whereas the formation of the corresponding 1,4-adduct was not observed (Scheme 1). The characteristic 1,6-selectivity observed in the addition to **1a** arises from the amide functionality. For example, the reaction of a *tert*-butyl ester of the same enyne moiety gave a mixture of the corresponding 1,6- and 1,4-addition products (82% yield, 1,6-/1,4-adduct = 1/1).

Scheme 1

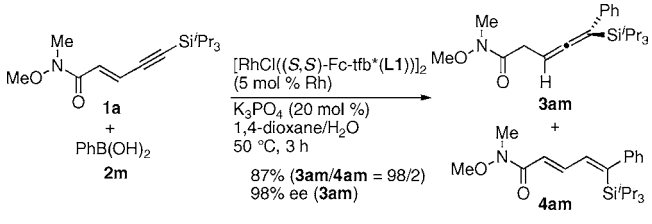
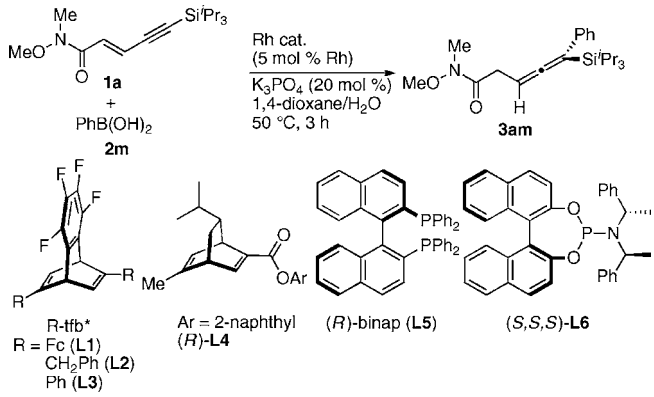


Table 1. Rhodium-Catalyzed Asymmetric 1,6-Addition of Phenylboronic Acid (**2m**) to Enynamide **1a**[a]



entry	Rh cat.	time (h)	conv. (%)[b]	yield (%)[b]
1	[RhCl((*S*,*S*)-**L1**)]$_2$	3	100	85 (98% ee)
2	[RhCl((*R*,*R*)-**L2**)]$_2$	3	24	16
3	[RhCl((*R*,*R*)-**L3**)]$_2$	3	27	19
4	[RhCl((*R*,*R*)-**L3**)]$_2$	9	40	22 (89% ee)
5[c]	[RhCl(C$_2$H$_4$)$_2$]$_2$/(*R*)-**L4**	3	26	18
6	[RhCl((*R*)-**L5**)]$_2$	3	0	0
7	[Rh(OH)((*R*)-**L5**)]$_2$	3	3	0
8[d]	[RhCl(C$_2$H$_4$)$_2$]$_2$/(*S*,*S*,*S*)-**L6**	3	0	0

[a] Reaction conditions: **1a** (0.20 mmol), **2m** (0.40 mmol), Rh catalyst (5 mol % Rh), K_3PO_4 (0.040 mmol), 1,4-dioxane (1.0 mL), H_2O (0.1 mL) at 50 °C for 3 h. [b] The conversion of **1a** and the yield of **3am** were determined by ^{1}H NMR spectroscopy. Values in parentheses are ee's of **3am** determined by HPLC analysis. [c] **L4** (6 mol %). [d] **L6** (12 mol %).

The choice of ligand is important for the catalytic activity in the present reaction (Table 1). Complete consumption of starting **1a** was observed when diene ligand **L1** substituted with ferrocenyl groups was used (entry 1). In contrast, the use of diene ligands substituted with benzyl (**L2**) and phenyl (**L3**) gave **3am** in 16 and 19% yield, respectively, with recovery of a significant amount of unreacted **1a** (entries 2 and 3). The yield of **3am** was low (22%) in the reaction catalyzed by [RhCl(**L3**)]$_2$, even with a prolonged reaction time (9 h) (entry 4), indicating that the catalyst lost its activity during the reaction (see below). Ligand **L4**[9] also displayed low activity, giving **3am** in 18% yield (entry 5). The formation of the addition products was not observed with binap **L5**[10] or phosphoramidite **L6**[11] (entries 6−8).

The absolute configuration of **3am** was determined to be (*S*)-(+) by X-ray crystallographic analysis of compound **6**, which was derived from **3am** in two steps (Scheme 2).[12] Thus, reduction of the Weinreb amide in **3am** by treatment with $NaBH_4$[13] followed by Mitsunobu-type amination with phthalimide and (cyanomethylene)tributylphosphorane[14] gave **6** in good yield without loss of its enantiomeric purity.

10.1021/ja1066509

Scheme 2

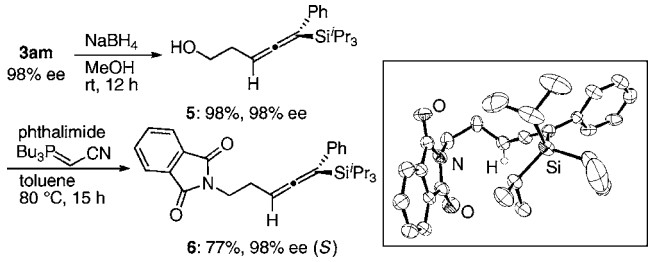
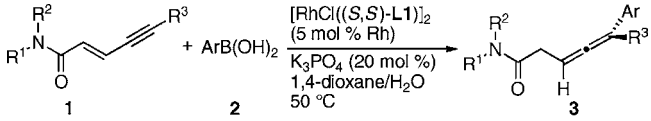


Table 2. Rhodium-Catalyzed Asymmetric 1,6-Addition of Arylboronic Acids to Enynamides **1**[a]



1a: R^1 = OMe, R^2 = Me, R^3 = Si^iPr_3 **1d**: R^1 = R^2 = ^{i}Pr, R^3 = Si^iPr_3
1b: R^1 = OMe, R^2 = Me, R^3 = $SiMe_2{}^tBu$ **1e**: R^1 = R^2 = CH_2Ph, R^3 = Si^iPr_3
1c: R^1 = OMe, R^2 = Me, R^3 = $SiEt_3$ **1f**: R^1 = R^2 = Ph, R^3 = Si^iPr_3

entry	1	Ar	time (h)	yield (%)[b]	ee (%)[c]
1	**1a**	Ph (**2m**)	3	87 (**3am**)	98 (*S*)
2	**1a**	4-MeC_6H_4 (**2n**)	3	89 (**3an**)	97 (*S*)
3	**1a**	3-MeC_6H_4 (**2o**)	3	86 (**3ao**)	97 (*S*)
4	**1a**	4-$MeOC_6H_4$ (**2p**)	3	86 (**3ap**)	97 (*S*)
5[d]	**1a**	3,4-$(OCH_2O)C_6H_3$ (**2q**)	12	87 (**3aq**)	96 (*S*)
6	**1a**	4-ClC_6H_4 (**2r**)	36	80 (**3ar**)	96 (*S*)
7	**1a**	4-BrC_6H_4 (**2s**)	36	74 (**3as**)	96 (*S*)
8	**1a**	4-$CF_3C_6H_4$ (**2t**)	24	79 (**3at**)	95 (*S*)
9	**1b**	Ph (**2m**)	6	80 (**3bm**)	94 (*S*)
10	**1c**	Ph (**2m**)	3	75 (**3cm**)	96 (*S*)
11	**1d**	Ph (**2m**)	72	70 (**3dm**)	94 (*S*)
12	**1e**	Ph (**2m**)	24	82 (**3em**)	96 (*S*)
13	**1f**	Ph (**2m**)	12	86 (**3fm**)	99 (*S*)

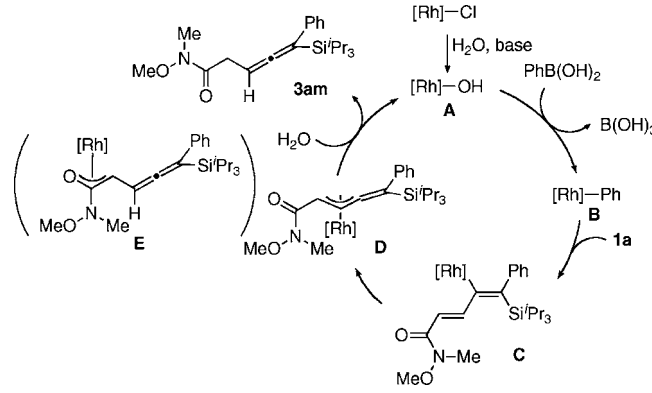
[a] Reaction conditions: **1** (0.20 mmol), $ArB(OH)_2$ (**2**) (0.40 mmol), $[RhCl((S,S)\text{-}\mathbf{L1})]_2$ (5 mol % Rh), K_3PO_4 (0.040 mmol), 1,4-dioxane (1.0 mL), H_2O (0.1 mL) at 50 °C. [b] Isolated yields. Inseparable isomers are included in entries 1−10 (2−5%). [c] Determined by HPLC analysis. The absolute configurations were assigned by analogy with entry 1. [d] Performed with $(ArBO)_3$ (0.13 mmol).

The results obtained for the rhodium-catalyzed 1,6-addition of several arylboronic acids to enynamides are summarized in Table 2. Arylboronic acids with aryl groups bearing a variety of substituents (**2m**−**t**) were successfully introduced into the reaction of **1a**, giving the corresponding addition products (**3am**−**at**) in good yields with enantioselectivities ranging from 95 to 98% ee (entries 1−8).[15] The addition of **2m** to enynamides substituted with *tert*-butyldimethylsilyl (**1b**) and triethylsilyl (**1c**) groups on the alkyne proceeded well to give **3bm** and **3cm**, respectively, with high enantioselectivity (entries 9 and 10).[16] Diisopropyl- (**1d**), dibenzyl- (**1e**), and diphenylamide (**1f**) were also good substrates, giving the corresponding addition products (**3dm**−**fm**) in good yields with 94−99% ee (entries 11−13).

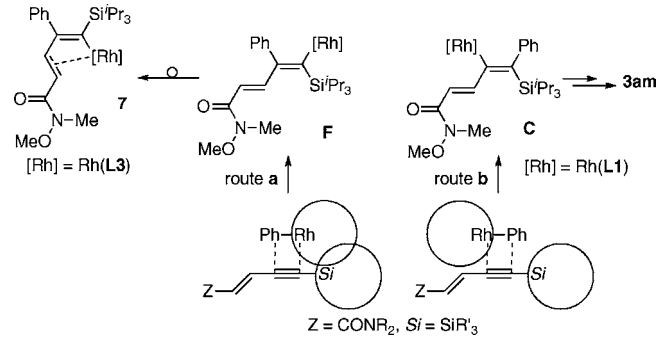
A proposed catalytic cycle for the present reaction is shown in Scheme 3. Transmetalation of a phenyl group from the boron to the rhodium center forms phenylrhodium species **B**. Insertion of an alkyne into the phenyl−rhodium bond with regiochemistry in which the phenyl is placed proximal to a silyl group on **1a** generates alkenylrhodium **C**, and isomerization by coordination of an alkene moiety forms benzylidene−π-allylrhodium **D**.[17] Hydrolysis of **D** or oxa-π-allylrhodium **E** gives the allene **3am** and hydroxorhodium species **A**.[18]

It was found that the catalyst deactivation observed in the reaction with chiral diene ligand **L3** (Table 1, entries 3 and 4) is caused by

Scheme 3. Proposed Catalytic Cycle



Scheme 4



the formation of a stable alkenylrhodium species (Scheme 4). Thus, in the reaction of **1a** with **2m** in the presence of a catalytic amount of $[RhCl(\mathbf{L3})]_2$ (Table 1, entry 4), alkenylrhodium complex **7** was isolated by column chromatography on silica gel with hexane/ethyl acetate under air. The structure of **7** was assigned by analogy with **8**, which was separately prepared by a stoichiometric reaction of $[RhCl(\mathbf{L3})]_2$ with **1f** and the neopentyl glycolate ester of **2m** (Figure 1).[19] The formation of **7** can be explained by alkyne insertion with regioselectivity opposite to that leading to **3am** (Scheme 4). Thus, insertion of the alkyne into the phenyl−rhodium bond that places the phenyl group away from the silyl group generates alkenylrhodium **F** (route **a**). Subsequent geometrical isomerization produces alkenylrhodium **7**. Complex **7** is too stable to regenerate an active catalytic species. Actually, the reaction of **1a** with **2m** in the presence of a catalytic amount of **7** (5 mol %) in a separate experiment did not give the addition products at all. The high catalytic activity of the rhodium complex coordinated with **L1** is attributed to the regioselective alkyne insertion leading to alkenyl-

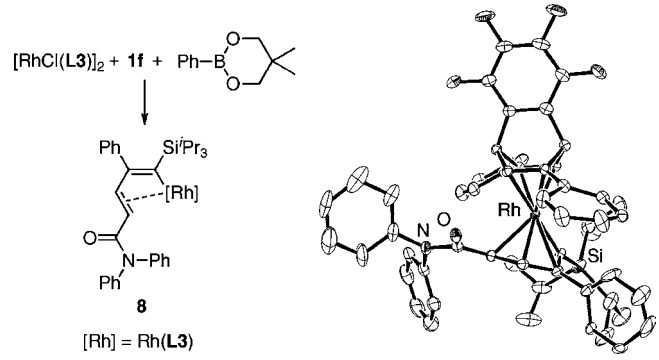
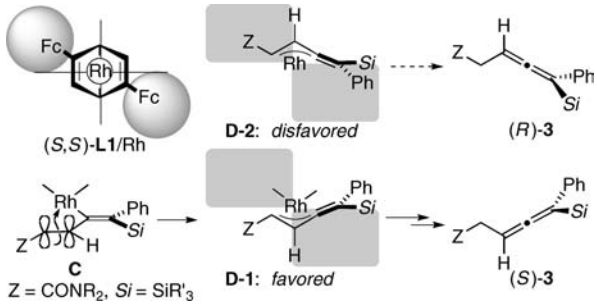


Figure 1. (left) Synthesis of **8**. (right) ORTEP illustration of **8** with thermal ellipsoids drawn at the 30% probability level. Hydrogen atoms and a solvent molecule have been omitted for clarity.

Scheme 5. Proposed Stereochemical Pathway



rhodium **C** (route **b**). The selectivity may be caused by the bulkiness of the ferrocenyl substituents on **L1**, which places the rhodium away from the bulky silyl group.

The formation of addition products having the *S* configuration is presumably explained by the stereochemical model shown in Scheme 5. The rhodium complex coordinated with (*S*,*S*)-**L1** constructs an effective C_2-symmetric environment with the ferrocenyl substituents located at upper-left and lower-right positions.[8] When isomerization of the alkenyl species **C** into the benzylidene−π-allylrhodium **D** occurs in the catalytic cycle, the bottom face of the double bond intramolecularly coordinates to the rhodium center in a manner that avoids the steric repulsions between the substituent on the diene ligand and the benzylidene moiety (and/or the amide Z). Thus, the formation of the **D-1** structure to give (*S*)-**3** is favorable.

In summary, we have developed a rhodium-catalyzed asymmetric 1,6-addition of arylboronic acids to enynamides that gives axially chiral allenylsilanes with high enantioselectivity, which was realized by use of a rhodium/chiral diene complex.

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Supporting Information Available: Experimental procedures, spectroscopic and analytical data for the substrates and products, and crystallographic data (CIF) for **6** and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The reaction of **1a** with (*E*)-2-phenylethenylboronic acid did not give the corresponding allene, and 80% of the starting **1a** was recovered.

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(18) The addition to **1f** with phenylboroxine in the presence of D_2O instead of H_2O gave the 2-deuterated product [D]**3fm** (91% D) in 86% yield with high diastereoselectivity (>95%).

(19) Crystal data for **8** are reported in the Supporting Information.

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