Rhodium Catalysis

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Linear-Selective Rhodium(I)-Catalyzed Addition of Arylboronic Acids to Allyl Sulfones**

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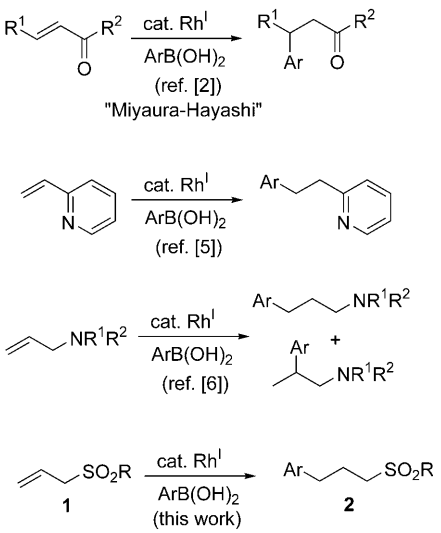
Rhodium-catalyzed C–C bond formation has become one of the most studied and widely used synthetic methods.[1] A particularly powerful transformation is the rhodium-catalyzed 1,4-addition of arylboronic acids to activated alkenes developed by Miyaura and Hayashi (Scheme 1).[2] Since the initial application to the enone systems, this strategy has been successfully extended to other activated alkenes such as α,β-unsaturated esters, aldehydes, amides, phosphonates, sulfones, and nitro compounds.[3] However, the substrates for these transformations are limited to alkenes that are activated by electron-withdrawing groups. The addition to unactivated alkenes remains a challenge. Recent advances on this front include rhodium-catalyzed addition of arylboronic acids to strained bicyclic alkenes and vinylarenes.[4,5] We reported that simple protected allylic amines will also participate in rhodium-catalyzed addition reactions to afford linear and branched (formal) hydroarylated products.[6] The regioselectivity was found to be highly dependent on the protecting group.



Scheme 1. Rhodium-catalyzed addition of arylboronic acids to activated and unactivated alkenes.

To broaden the scope of unactivated alkenes in the rhodium-catalyzed addition reactions, we decided to employ readily available allyl sulfones **1** (Scheme 1). Sulfones have displayed great utility and versatility in synthetic applications.[7] The linear addition products **2** have been used as precursors for further transformations.[8] Rhodium-catalyzed addition of arylboronic acids and aryltitanium reagents to α,β-unsaturated sulfones are known.[3f,9] To the best of our knowledge, no example of addition to allyl sulfones has been reported. There is evidence supporting the directing effect of sulfone in rhodium-catalyzed hydroboration of allylic substrates.[10] We envisioned that the directing/coordinating ability of the sulfone group may enhance the reactivity of the otherwise unreactive alkene component and potentially lead to regioselective product formation in the rhodium-catalyzed addition of arylboronic acids to allyl sulfones.

We began our investigations by using commercially available allyl phenyl sulfone **1a** as the substrate. When reacting **1a** with 2.5 equivalents of phenylboronic acid in the presence of 2 mol% [{Rh(cod)OH}$_2$] (cod = 1,5-cyclooctadiene) and 6 mol% binap (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) in dioxane/H_2O (100:1) at 75 °C for 12 hours, the linear addition product **2a** was obtained exclusively in 90% yield (Table 1, entry 1).

The branched product **3** and "Heck" product **4** (through addition/elimination) were not observed under these conditions. Isomerization of the double bond, which is a known process in rhodium catalysis of allylic substrates,[1c] also did not take place. This result was particularly encouraging because it showed both high reactivity and excellent regioselectivity of the allyl sulfone substrate in the rhodium-catalyzed addition process. The amount of added water affected the reaction yield. Reaction without added water and reaction with a larger amount of water (dioxane/H_2O = 10:1) both led to incomplete conversion. The use of excess arylboronic acid was necessary because of the competing hydrolytic deboronation process under the reaction conditions.[1a] Using [[{Rh(cod)OH}$_2$] without added ligand or [{Rh(cod)Cl}$_2$] as the catalyst source gave very poor conversions (Table 1, entries 2 and 3, respectively). The use of tol-binap or biphep (2,2′-bis(diphenylphosphino)-1,1′-biphenyl) as ligands was also effective (Table 1, entries 4 and 5, respectively), but the use of dppb (1,4-bis(diphenyl-

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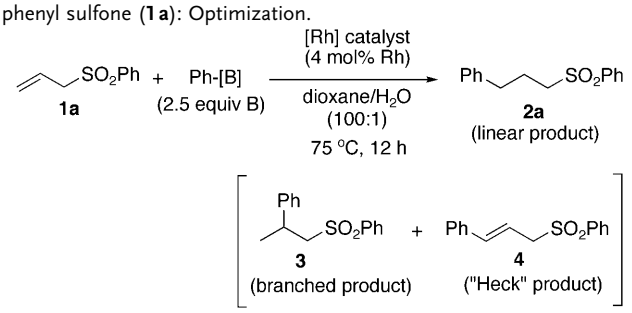
Table 1: Rhodium-catalyzed addition of organoboron reagents to allyl phenyl sulfone (**1a**): Optimization.



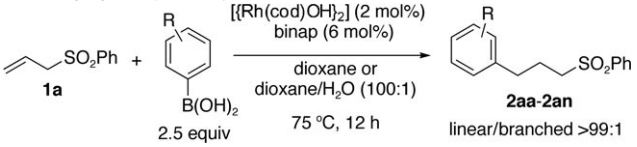
Entry	[Rh] catalyst	Ph-[B]	Yield of **2a** [%]	**2a**:**3**[b]
1	[{Rh(binap)OH}$_2$]	PhB(OH)$_2$	90[a,c]	>99:1
2	[{Rh(cod)OH}$_2$]	PhB(OH)$_2$	5[b]	>99:1
3	[{Rh(binap)Cl}$_2$]	PhB(OH)$_2$	26[b]	>99:1
4	[{Rh(tol-binap)OH}$_2$]	PhB(OH)$_2$	76[b]	>99:1
5	[{Rh(biphep)OH}$_2$]	PhB(OH)$_2$	78[b]	>99:1
6	[{Rh(dppb)OH}$_2$]	PhB(OH)$_2$	9[b,d]	>99:1
7	[{Rh(binap)OH}$_2$]	Ph$_4$BNa	<5[b]	–[e]
8	[{Rh(binap)OH}$_2$]	PhBF$_3$K	37[b]	>99:1
9	[{Rh(binap)OH}$_2$]	PhBPin[f]	45[b]	>99:1
10	[{Rh(binap)OH}$_2$]	(PhBO)$_3$	89[a]	>99:1

[a] Yield of isolated product. [b] Determined by ^{1}H NMR spectroscopy of the crude material. [c] Using dioxane gave 72% of **2a** and 13% of unreacted starting material; using dioxane/H_2O (10:1) gave 67% of **2a** and 13% of unreacted starting material. [d] 45% of unreacted starting material and 21% of **4** were observed. [e] Not determined. [f] PhBPin = phenylboronic acid pinacol ester.

phosphino)butane) gave poor conversion and an increased amount of "Heck" product **4** (Table 1, entry 6). We next investigated the effect of the organoboron reagent. Sodium tetraphenylborate was ineffective and led to no conversion (Table 1, entry 7). Potassium phenyltrifluoroborate and phenylboronic acid pinacol ester only gave modest yields and an increased amount of **4** (Table 1, entries 8 and 9, 8% and 7% of **4**, respectively). Phenylboroxine, an alternative reagent for phenylboronic acid, gave comparable yield of the linear product **2a** (Table 1, entry 10). In all of the above cases, the branched product **3** was not observed.

The scope of arylboronic acids was subsequently studied using allyl phenyl sulfone **1a** as the substrate under the optimized conditions (Table 2). A wide range of functionalized arylboronic acids were employed to afford the linear products **2aa**–**2an** in moderate to high yields and excellent regioselectivities. Electron-rich and electron-poor groups at the 4 and 3 positions gave good yields (Table 2, entries 1–3, 9–11). Functional groups such as ester, carbamate, sulfide, and chloride were tolerated (Table 2, entries 4–8). A methyl group at the 2-position did not hinder the reaction, but a methoxy group at the same position significantly decreased the yield (Table 2, entries 12 and 13, respectively). The 2-naphthylboronic acid gave very high yield of the product (Table 2, entry 14). In most cases, the reaction did not require additional water, presumably the water content in the commercial arylboronic acids facilitates protodemetalation.[11] In some cases, adding water increased the yield significantly (Table 2, entries 8, 11, and 14).

Table 2: Rhodium-catalyzed addition of arylboronic acids to allyl phenyl sulfone (**1a**): Scope of arylboronic acids.

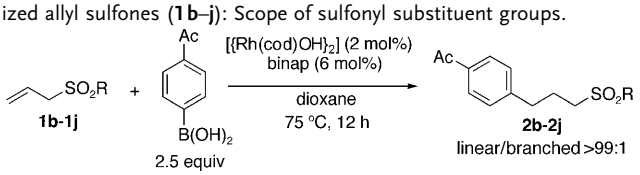


Entry	R	Product	Yield [%][a]
1[b]	4-Ac	**2aa**	91
2[b]	4-OMe	**2ab**	85
3[b]	4-CF$_3$	**2ac**	84
4[b]	4-CO$_2$Me	**2ad**	65
5[b]	4-NHBoc	**2ae**	84
6[b]	4-NHCbz	**2af**	81
7[b]	4-SMe	**2ag**	78
8[c]	4-Cl	**2ah**	67
9[b]	3-Ac	**2ai**	82
10[b]	3-OMe	**2aj**	92
11[c]	3-CF$_3$	**2ak**	75
12[b]	2-Me	**2al**	87
13[b]	2-OMe	**2am**	50
14[c]	2-naphthyl	**2an**	95[d]

[a] Yield of isolated product. [b] Dioxane. [c] Dioxane/H_2O (100:1). [d] 52% Yield without added water. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl.

The effect of the substituent on the sulfonyl group was also studied (Table 3). Linear addition products **2b**–**2j** were obtained with excellent regioselectivities. Electron-rich and electron-poor aromatic groups gave good yields (Table 3, entries 1–4). More sensitive functional groups such as bromide and acetamide and a sterically hindered 2-methyl group required double the catalyst loading to achieve higher yields (Table 3, entries 5–7). Non-aromatic allyl methyl sulfone (**1i**) participated in the reaction albeit a lower yield was obtained (Table 3, entry 8). The synthetically useful benzothiazolyl sulfone (**1j**) gave a poor yield (Table 3, entry 9).[12]

Table 3: Rhodium-catalyzed addition of arylboronic acids to functionalized allyl sulfones (**1b**–**j**): Scope of sulfonyl substituent groups.



Entry	R	Yield [%][a]
1	4-OMeC$_6$H$_4$ (**1b**)	89
2	4-MeC$_6$H$_4$ (**1c**)	87
3	4-FC$_6$H$_4$ (**1d**)	92
4	4-ClC$_6$H$_4$ (**1e**)	90
5[b]	4-BrC$_6$H$_4$ (**1f**)	49
6[b]	4-NHAcC$_6$H$_4$ (**1g**)	71
7[b]	2-MeC$_6$H$_4$ (**1h**)	88
8	Me (**1i**)	60
9	benzothiazolyl (**1j**)	23[c]

[a] Yield of isolated product. [b] [{Rh(cod)OH}$_2$] (4 mol%), binap (12 mol%). [c] No improvement with double catalyst loading.

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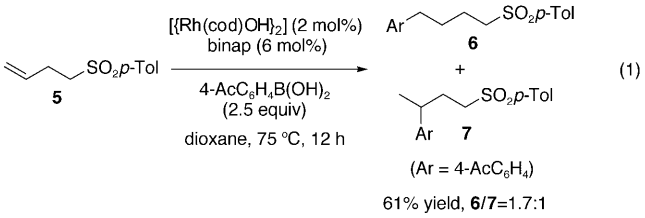
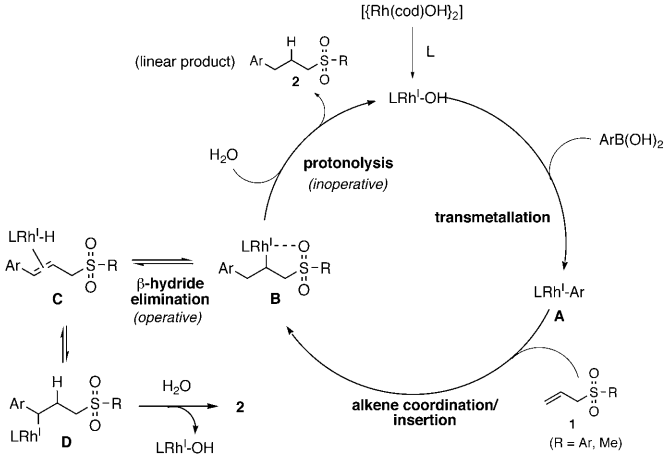
To investigate the effect of carbon-chain length, the homoallyl substrate **5** was employed under the standard conditions [Eq. (1)]. A mixture of linear and branched products (1.7:1) was obtained in 61% yield. The increase of



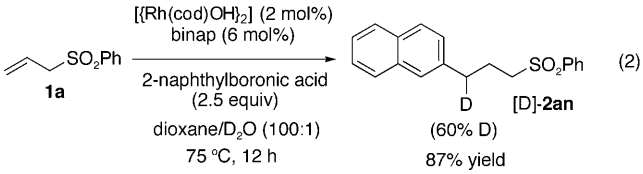
carbon-chain length by one carbon atom caused a substantial decrease in yield and loss of regioselectivity (cf. Table 2, entry 1). On the other hand, no reaction occured with vinyl phenyl sulfone under the same conditions, in accordance with literature reports.[3f,9] We also tested substrates which contain internal alkenes such as cinnamyl phenyl sulfone, crotyl *p*-tolyl sulfone and 3-(phenylsulfonyl)cyclohex-1-ene, as well as a substrate with substituents at the α position (α,α-dimethylallyl phenyl sulfone). No reaction occurred with these more sterically hindered alkenes. The sulfone group was essential for the reactivity since allyl phenyl sulfide and sulfoxide did not react under the same conditions.

The proposed catalytic cycle is shown in Scheme 2. Presumably the sulfone group of substrate **1** plays two roles: 1) enhancing the reactivity of the alkene component by



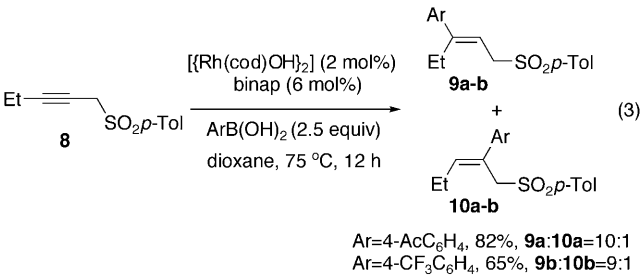
Scheme 2. Proposed catalytic cycle of rhodium(I)-catalyzed addition of arylboronic acids to allyl sulfones (**1**).

coordinating to the rhodium–aryl species **A** prior to insertion; 2) controlling the regioselectivity of the alkene insertion by forming a stabilized five-membered rhodacycle intermediate **B**. Protonolysis of **B** would furnish product **2** and regenerate the catalyst. However, deuterium-quenching experiments using D_2O gave the deuterated product [D]-**2an** with 60% deuterium incorporation exclusively at the benzylic position [Eq. (2)]. This result ruled out the direct formation of product

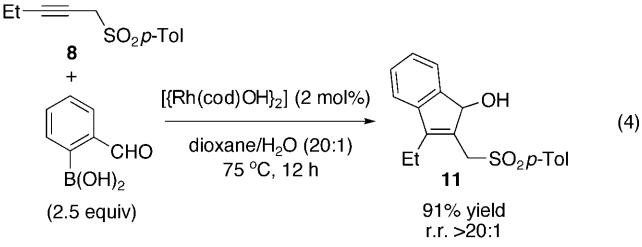


2 from the protonolysis of intermediate **B**, but suggested an alternative β-hydride elimination/re-insertion pathway which generates intermediate **D**. The protonolysis of **D** leads to product **2** formation and catalyst regeneration.

The directing effect of the sulfone group was also shown in the reactions with propargyl sulfone **8**, an unsymmetrical and unactivated alkyne [Eq. (3)]. High regioselectivities favoring



product **9** were obtained, presumably resulting from the analogous five-membered rhodacycle intermediate as proposed in Scheme 1. When 2-formylphenylboronic acid was used, the indenol product **11** was obtained as a single regioisomer (determined by NOE experiments) in high yield through a domino addition/annulation process [Eq. (4)].[13c,d] Regioselective rhodium-catalyzed addition of



arylboronic acids to unsymmetrical alkynes are usually limited to alkynes substituted with electron-withdrawing, aromatic/heteroaromatic, and sterically encumbering groups.[1a,e,5b–d,13] To the best of our knowledge, this is one of the few examples of highly regioselective rhodium-catalyzed addition to unactivated alkynes. The multisubstituted alkenyl products **9** and **11** are useful precursors for further transformations such as Julia olefinations.

In conclusion, we have developed a highly linear-selective rhodium(I)-catalyzed addition of arylboronic acid to allyl sulfones. These studies have extended the scope of unactivated alkenes that can participate in the rhodium-catalyzed

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addition reactions. The method can also be applied to unactivated alkynes such as propargyl sulfones to afford substituted alkenyl products in high regioselectivities. Further studies on mechanism, branched product formation, and utilization of the addition products are currently in progress.

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