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Effect of Chiral Diene Ligands in Rhodium-Catalyzed Asymmetric Addition of Arylboronic Acids to α,β-Unsaturated Sulfonyl Compounds

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Supporting Information

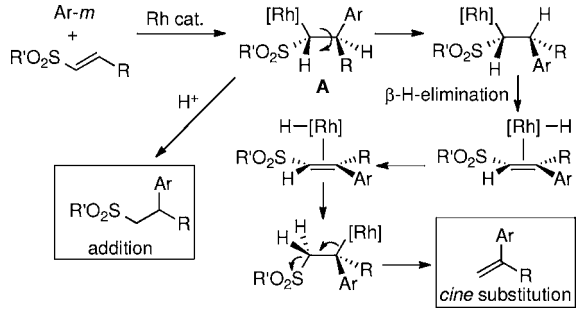
ABSTRACT: Asymmetric addition of arylboronic acids to α,β-unsaturated sulfonyl compounds proceeded in the presence of a rhodium catalyst coordinated with a chiral diene ligand to give high yields of the addition products with high enantioselectivity (96−>99.5% ee). The diene ligand was proved to be essential for the formation of the addition products, while the use of a bisphosphine ligand mainly gave the *cine*-substitution product.

Recent progress in the rhodium-catalyzed asymmetric addition of organoboron reagents to electron-deficient alkenes provides one of the most reliable methods available for the synthesis of chiral carbonyl compounds, where a variety of aryl and alkenyl groups are introduced with high enantioselectivity.[1] Since the first report on the asymmetric addition of arylboronic acids to conjugated enones by use of a Rh/binap catalyst in 1998,[2] this type of asymmetric catalysis has been extended to the addition to α,β-unsaturated esters,[3] amides,[4] aldehydes,[5] phosphonates,[6] and nitro compounds.[7] Borylalkenes[8] and electron-deficient alkenylarenes[9] have also been reported as a new class of substrates in the rhodium-catalyzed asymmetric arylation and alkenylation.

Chiral sulfonyl compounds have great versatility in organic synthesis, and they are also important as biologically active substances in medicinal chemistry.[10] Successful examples of rhodium-catalyzed asymmetric addition of arylboronic acids to alkenyl 2-pyridyl sulfones have been reported by Carretero and co-workers.[11] The selective addition is achieved by use of a rhodium/chiral bisphosphine catalyst, where it is proposed that the distinctive reactivity of the alkenyl 2-pyridyl sulfone is due to the formation of a stable five-membered intermediate by intramolecular coordination of the pyridyl group to rhodium. Copper-catalyzed asymmetric alkylation of alkenyl 2-pyridyl sulfones has also been reported by Bechara/Charette[12] and Feringa.[13,14] Unfortunately, however, applicable substrates in their reports have so far been limited to 2-pyridyl sulfones, and thus development of a new catalytic system is desirable.[15,16]

One of the unique reactivities of the α,β-unsaturated sulfonyl compounds toward nucleophiles is the *cine*-substitution.[17] The first catalytic *cine*-substitution of alkenyl sulfones with aryltitanium reagents was reported in 2003 by use of a rhodium/bisphosphine (binap) complex (Scheme 1).[18,19] The reaction pathway of the *cine*-substitution has been proposed as shown in Scheme 1, where β-hydrogen elimination from an alkylrhodium intermediate **A**, formed via *syn* addition of an arylrhodium species, is a key reaction step leading to the *cine*-substitution product. Thus, to achieve the addition reaction, protonation of the intermediate **A** needs to be faster than β-hydrogen elimination. Here we report that the use of a chiral diene ligand enables the rhodium-catalyzed asymmetric addition of arylboronic acids to a wide variety of α,β-unsaturated sulfonyl compounds with very high enantioselectivity.

Scheme 1. Rhodium-Catalyzed Arylation of α,β-Unsaturated Sulfonyl Compounds



A significant difference in reactivity between a Rh/bisphosphine and a Rh/diene catalyst was observed in the addition of an arylboronic acid to an alkenylsulfonate (Scheme 2). Thus, treatment of alkenylsulfonate **1a** with *p*-tolylboronic acid (**2m**, 2 equiv) in the presence of $[RhCl((R)\text{-binap})]_2$[20] (3 mol % of Rh) and K_3PO_4 in 1,4-dioxane/H_2O (9:1) at 60 °C for 3 h gave the substitution product **3** in 43% yield, where the formation of only a 9% yield of the addition product **4am** was observed (Scheme 2a). In sharp contrast, the reaction in the presence of a rhodium catalyst coordinated with a chiral diene ligand[21] $[RhCl((S,S)\text{-Fc-tfb*})]_2$[22] (tfb: tetrafluorobenzobarrelene) gave the addition product **4am** in 98% yield as a sole product with 96% ee (Scheme 2b). These results indicate that the nature of the ligand determines the selectivity toward the addition or substitution, despite the fact that both catalysts promote the asymmetric addition of arylboronic acids to α,β-unsaturated carbonyl compounds.[20,23]

Of the chiral diene ligands at hand, tetrafluorobenzobarrelenes (tfb's)[23] were found to display high catalytic activity and enantioselectivity (Table 1). Thus, the reaction by use of a chiral tfb ligand substituted with phenyl groups (Ph-tfb*) gave

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Scheme 2. Arylation of Sulfonate 1a

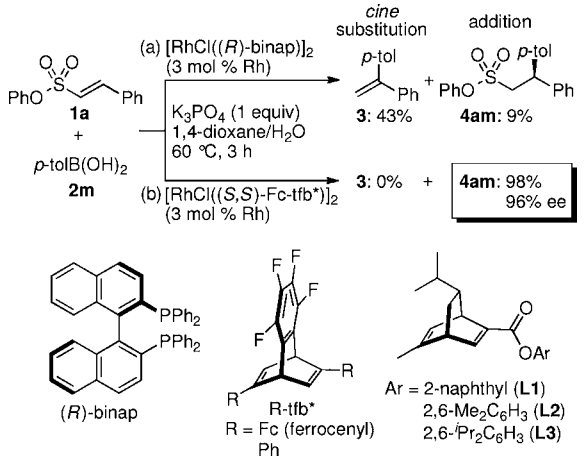
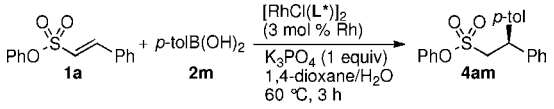


Table 1. Rhodium-Catalyzed Asymmetric Addition of *p*-Tolylboronic Acid (2m) to Sulfonate 1a[a]



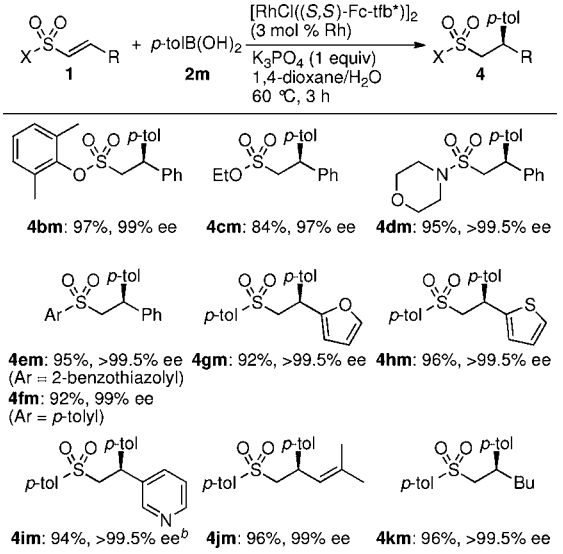
entry	ligand	yield (%)[b]	ee (%)[c]
1	(*S*,*S*)-Fc-tfb*	98[d]	96
2	(*R*,*R*)-Ph-tfb*	86[d]	95
3	(*R*)-**L1**	39	83
4	(*R*)-**L2**	38	91
5	(*R*)-**L3**	33	94

[a]Reaction conditions: **1a** (0.20 mmol), **2m** (0.40 mmol), [RhCl(**L***)]$_2$ (3 mol % of Rh), K_3PO_4 (0.20 mmol), 1,4-dioxane (0.72 mL), H_2O (0.08 mL) at 60 °C for 3 h. [b]Determined by ^{1}H NMR. [c]Determined by chiral HPLC analysis. [d]Isolated yield.

the addition product **4am** in 86% yield with 95% ee (entry 2). Although high enantioselectivity was observed by using chiral diene ligands **L1**−**L3**[9,24] derived from a natural product (*R*)-phellandrene, the catalytic activities of their rhodium complexes were lower than those of tfb-based ligands (entries 3−5).[25]

The Rh/Fc-tfb* catalyst displayed high catalytic activity and enantioselectivity in the addition of *p*-tolylboronic acid (**2m**) to diverse alkenyl sulfonyl compounds (Scheme 3). The addition to (*E*)-2,6-dimethylphenyl styrylsulfonate (**1b**) gave the addition product **4bm** in 97% yield with 99% ee. In the reaction of ethyl sulfonate **1c**, a slightly lower yield (84%) of the addition product **4cm** with 97% ee than those obtained with aryl sulfonates **1a** and **1b** was observed in spite of the complete conversion of **1c**, probably due to the decomposition of **1c** or **4cm** to the sulfonic acid salts. A very high enantioselectivity (>99.5% ee) was observed in the reaction of alkenylsulfonamide **1d** giving the addition product **4dm** in 95% yield. Alkenyl sulfones **1e**−**1k** are also good substrates in the present reaction. Thus, the reaction of 2-benzothiazolyl sulfone **1e** gave the addition product **4em**, which would be employed in the modified Julia olefination,[26] in 95% yield with over 99.5% ee. The addition to alkenyl sulfones substituted at the *β*-position with phenyl (**1f**), 2-furyl (**1g**), 2-thienyl (**1h**), 3-pyridyl (**1i**), alkenyl (**1j**), and butyl (**1k**) gave the corresponding addition products **4fm**−**4km** in high yields with over 99% ee.

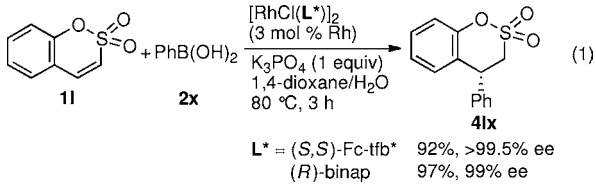
Scheme 3. Rhodium-Catalyzed Asymmetric Addition of *p*-Tolylboronic Acid (2m) to 1[a]



[a]Reaction conditions: **1** (0.20 mmol), **2m** (0.40 mmol), [RhCl((*S*,*S*)-Fc-tfb*)]$_2$ (3 mol % of Rh), K_3PO_4 (0.20 mmol), 1,4-dioxane (0.72 mL), H_2O (0.08 mL) at 60 °C for 3 h. The yields are isolated yields, and the ee's were determined by chiral HPLC analysis. [b]Performed with 0.50 mmol of **2m** at 80 °C for 15 h.

The results obtained for the addition of several arylboronic acids **2** to alkenylsulfonate **1b** are summarized in Table 2. The addition of *p*-tolylboroxine **2m′** to **1b** was catalyzed by 0.3 mol % of rhodium, and the reaction for 24 h gave **4am** in 99% yield with 99% ee (entry 2). A variety of aryl groups substituted with both electron-donating and -withdrawing functionalities were introduced into **1b** to give the corresponding addition products in high yields with over 97% ee (entries 3−12).

The asymmetric addition of phenylboronic acid (**2x**) to cyclic sulfonate **1l** catalyzed by the Rh/Fc-tfb* complex proceeded to give the addition product **4lx** in 92% yield with >99.5% ee (eq 1). The same reaction was also catalyzed by the



(1)

Rh/binap complex, which favors the substitution in the reaction of the linear sulfonate **1a**, to give **4lx** in 97% yield with 99% ee. This is probably because the alkylrhodium intermediate formed via the *syn* phenylrhodation has no *β*-hydrogens to be eliminated in *syn* fashion.

The absolute configurations of the sulfonate (*R*)-**4bv** and (*R*)-**4lx** produced by use of (*S*,*S*)-Fc-tfb* were determined by X-ray crystallographic analysis.[27] The absolute configurations are in good agreement with the stereochemical model previously proposed for the addition to *α*,*β*-unsaturated carbonyl compounds by use of C_2-symmetric chiral diene ligands.[28]

A deuterium-labeling experiment provided mechanistic insight into the protonation step (Scheme 4). Treatment of alkenyl sulfone **1g** with *p*-tolylboroxine **2m′** and D_2O, where *p*-

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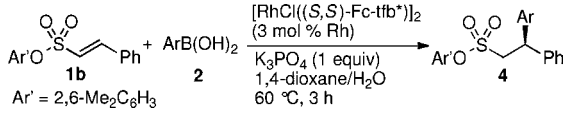
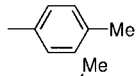
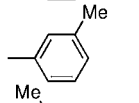
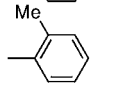
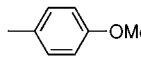
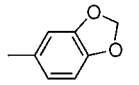
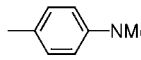
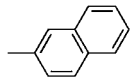
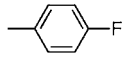
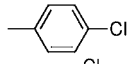
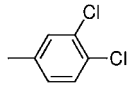
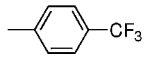
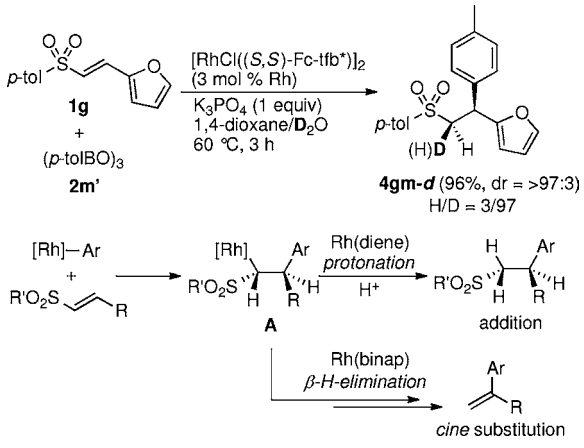
Table 2. Rhodium-Catalyzed Asymmetric Addition of Arylboronic Acids 2 to 1b[a]



entry	—Ar		isolated yield (%)	ee (%)[b]
1		(**2m**)	**4bm**: 97	99
2[c]			**4bm**: 99	99
3		(**2n**)	**4bm**: 97	99
4		(**2o**)	**4bo**: 99	>99.5
5		(**2p**)	**4bp**: 97	99
6[d]		(**2q**)	**4bq**: 99	99
7[e]		(**2r**)	**4br**: 97	97
8[d]		(**2s**)	**4bs**: 94	99
9		(**2t**)	**4bt**: 97	>99.5
10		(**2u**)	**4bu**: 96	>99.5
11[d]		(**2v**)	**4bv**: 94	>99.5
12		(**2w**)	**4bw**: 96	>99.5

[a]Reaction conditions: **1b** (0.20 mmol), **2** (0.40 mmol), [RhCl((*S*,*S*)-Fc-tfb*)]$_2$ (3 mol % of Rh), K_3PO_4 (0.20 mmol), 1,4-dioxane (0.72 mL), H_2O (0.08 mL) at 60 °C for 3 h. [b]Determined by chiral HPLC analysis. [c]5-Fold scale reaction using (*p*-tolBO)$_3$ (2 equiv B) and 0.3 mol % of Rh in 1,4-dioxane/H_2O (9:1, 0.50 M) for 24 h. [d](ArBO)$_3$ (0.13 mmol) was used instead of ArB(OH)$_2$. [e]Performed at 80 °C for 12 h.

Scheme 4. A Deuterium-Labeling Experiment



tolB(OD)$_2$ is generated in situ, in the presence of the rhodium catalyst and K_3PO_4 at 60 °C for 3 h gave the addition product **4gm-*d***, whose deuterium content at the α-carbon was 97% (dr = >97:3). It was also confirmed that the deuterium on **4gm-*d*** was *syn* to the *p*-tolyl group.[29] The result indicates that the alkylrhodium intermediate **A** directly undergoes protonation with retention of stereochemistry at the rhodium to give the addition product without an extra step such as β-hydrogen elimination or migration of rhodium onto the aryl group by 1,4-Rh shift.[30] In the present reaction, faster protonation of the alkylrhodium intermediate **A** than β-hydrogen elimination enabled the selective formation of the addition product, which was realized by using the diene ligand.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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