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Rhodium-Catalyzed Addition of Boronic Acids to Vinylogous Imines Generated *in situ* from Sulfonylindoles

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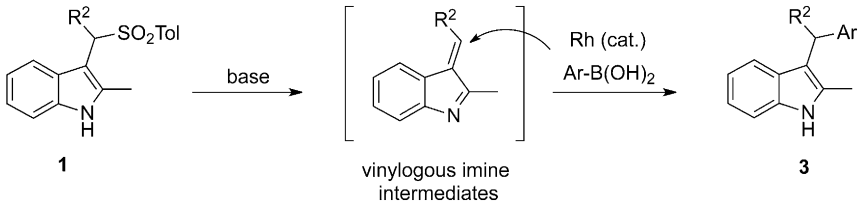
Abstract: The rhodium-catalyzed addition of arylboronic acids to vinylogous imines generated *in situ* from sulfonylindoles has been developed. This procedure provided a rapid approach to C-3 *sec*-alkyl-substituted indoles.

Keywords: boronic acids; rhodium catalysts; sulfonylindoles; vinylogous imines

Substituted indoles are important structures due to their wide distribution in natural products and biologically active molecules.[1] As a particular sub-class of substituted indoles, C-3 *sec*-alkyl-substituted indoles are the core nucleus of many promising therapeutic agents, and the synthesis of such structures is increasing now.[2] Although a variety of synthetic methods has been developed to these compounds,[3] considering the significance of this kind of compounds, a new and efficient synthetic approach to these indole derivatives still remains a highly desirable goal in synthetic chemistry.

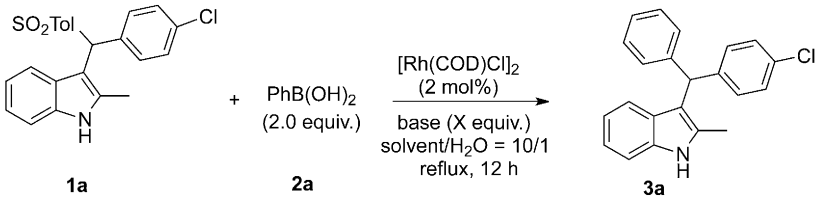
The use of sulfones as an auxiliary group is an important synthetic strategy in organic synthesis; this functional group can modify the polarity of the molecule by acting as an electron-withdrawing group to stabilize carbanions or as a leaving group. Due to this dual chemical behaviour, numerous organic compounds containing sulfones have been designed and applied in organic synthesis.[4] In 2006, a series of 3-(1-arenesulfonylalkyl)indoles was disclosed as good electrophilic precursors by Petrini and co-workers.[5] The sulfonyl moiety at the benzylic position of 3-substituted indoles serves as a good leaving group, which allows the generation of electrophilic species (vinylogous imines) under basic conditions.[6] The intermediate generated *in situ* is equal to an active α,β-unsaturated imine, which can react with various nucleophiles,[7] such as Grignard reagents, Reformatsky reagents, nitroalkanes, aldehydes, and glycine derivatives. Recently the rhodium-catalyzed addition reaction of arylboronic acids with electrophilic organic compounds is attracting increasing attention as a useful method for carbon-carbon bond construction in organic synthesis.[8] Inspired by these elegant studies, we envisioned that these vinylogous imine intermediates might be a suitable receptor in the rhodium-catalyzed addition reaction of arylboronic acids, and by this strategy a rapid entry to biologically active indole derivatives would be supplied (Scheme 1).

We commenced our study by treatment of the sulfonylindole **1a** with phenylboronic acid **2a** (2.0 equiv.) using $[Rh(COD)Cl]_2$ (2.0 mol%) as the catalyst in THF/H_2O (10:1) under basic conditions (KOH



Scheme 1. Nucleophilic addition to vinylogous imines generated *in situ* from sulfonylindoles.

Table 1. Optimizing the conditions for the reaction of arenesulfonylindole **1a** with phenylboronic acid **2a**.[a]



Entry	Sovlent	Base (X equiv.)	Yield[b] [%]
1	THF	KOH (2.0)	70
2	toluene	KOH (2.0)	36
3	CH_2Cl_2	KOH (2.0)	<5
4	dioxane	KOH (2.0)	73
5	dioxane	Cs_2CO_3 (2.0)	<5
6	dioxane	K_2CO_3 (2.0)	<5
7	dioxane	NaOH (2.0)	45
8	dioxane	K_3PO_4 (2.0)	36
9	dioxane	KOH (0.5)	<5
10	dioxane	KOH (1.0)	35
11	dioxane	KOH (3.0)	57
12[c]	**dioxane**	**KOH (2.0)**	**80**

[a] *Reaction conditions:* $[Rh(COD)Cl]_2$ (2 mol%), **1a** (0.2 mmol), **2a** (0.4 mmol), solvent (3 mL), H_2O (0.3 mL), reflux, 12 h.
[b] Isolated yields based on **1a**.
[c] **2a** (0.6 mmol) was used.

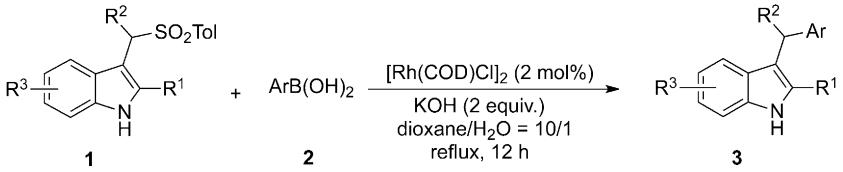
2.0 equiv.). To our delight, the desired product **3a** was obtained in a good yield (Table 1, entry 1). Subsequently, different solvents were examined. Dioxane/water (10:1), the classical solvent system in rhodium-catalyzed addition reactions with boronic acids gave the best result among the solvents tested (entries 2–4). The base played a vital role in this reaction: firstly, it assisted the elimination of arenesulfinic acid to form the vinylogous imine intermediate; secondly, it assisted the generation of the hydroxy-rhodium complex to start the addition reaction. A number of anionic bases was next evaluated, as listed in Table 1 (entries 5–8), Cs_2CO_3, K_2CO_3 were ineffective while NaOH, K_3PO_4 gave moderate yields, and KOH was found to be the most suitable base for this reaction. The yields decreased sharply when the amount of KOH was reduced to 0.5 and 1.0 equiv. (entries 9 and 10), which is probably due to the low efficiency for the elimination of arenesulfinic acid. The use of 3.0 equiv. of KOH did not increase the conversion but resulted in a more complex mixture of products (entry 11). Finally, the effect of the amount of boronic acid on the reactivity was also investigated, 3.0 equiv. of phenylboronic acid can improve the yield to 80% (entry 12).

With the optimized reaction conditions [boronic acids (3.0 equiv.), $[Rh(COD)Cl]_2$ (2 mol%), KOH (2.0 equiv.), in dioxane/water (10:1) as reaction media] in hand, a variety of sulfonylindoles and arylboronic acids has been explored to examine the generality of the reaction. The results are listed in Table 2.

As shown in Table 2, various sulfonylindoles underwent the reaction smoothly and gave the corresponding products with moderate to excellent results. For the substituent R^2, aromatic ones such as phenyl reacted with phenylboronic acid peacefully and a satisfactory yield was obtained (entry 2). Alhough substituting the *para*-position of the phenyl ring with Me or MeO lowered the yields of desired compounds **3c** and **3d** (entries 3 and 5), high yields of **3c** and **3d** were obtained when the corresponding arylboronic acids reacted with substrate **1b** (81% and 89% yields, entries 4 and 6). Sulfonylindoles with aliphatic substituents exhibited much better reactivity than those with aromatic ones in this reaction. Isopropyl and pentyl derivatives all gave full conversions and 99% isolated yields of the products (entries 8 and 9). It is worthy noting that lower yields were obtained when the steric hindrance of R^2 increased (entries 10 and 11). The steric and electronic nature of the indole core had little influence on the outcome of the reaction, and generally high yields were obtained (entries 12–14). For example, the sulfonylindoles with Ph and MeO as substituent at the 2- and 5-positions of the indole ring, respectively, all gave excellent yields.

Subsequently, using **1g** as substrate, the rhodium-catalyzed addition reaction was also examined with a series of arylboronic acids and excellent yields were obtained (Table 2, entries 15–18). Even the electron-deficient 4-(triflouromethyl)phenylboronic acid gave

Table 2. Substrate scope for rhodium-catalyzed reaction of sulfonylindoles **1** with arylboronic acids **2**.[a]



1 2 3

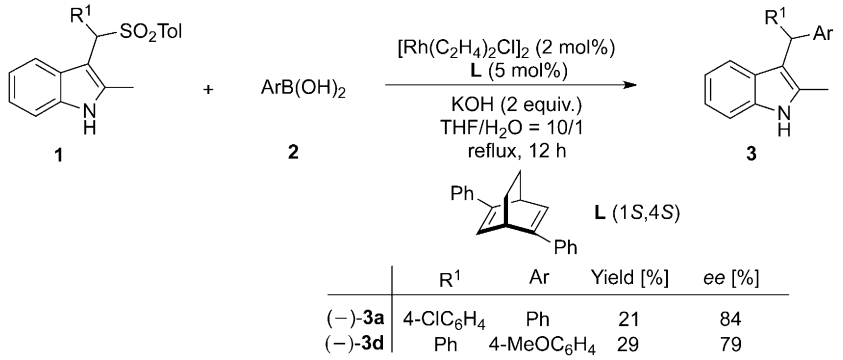
Entry	$R^1/R^2/R^3$ of **1**	Ar	Yield[b] [%]
1	Me/4-Cl-C_6H_4/H (**1a**)	Ph	80 (**3a**)
2	Me/Ph/H (**1b**)	Ph	83 (**3b**)
3	Me/4-Me-C_6H_4/H (**1c**)	Ph	56 (**3c**)
4	Me/Ph/H (**1b**)	4-Me-C_6H_4	81 (**3c**)
5	Me/4-MeO-C_6H_4/H (**1d**)	Ph	52 (**3d**)
6	Me/Ph/H (**1b**)	4-MeO-C_6H_4	89 (**3d**)
7	Me/3-MeO-C_6H_4/H (**1e**)	Ph	75 (**3e**)
8	Me/*i*-Pr/H (**1f**)	Ph	99 (**3f**)
9	Me/*n*-pentyl/H (**1g**)	Ph	99 (**3g**)
10	Me/cylohexyl/H (**1h**)	Ph	80 (**3h**)
11	Me/*t*-Bu/H (**1i**)	Ph	60 (**3i**)
12	H/*n*-pentyl/H (**1j**)	Ph	95 (**3j**)
13	Ph/*n*-pentyl/H (**1k**)	Ph	99 (**3k**)
14	H/*n*-pentyl/5-MeO (**1l**)	Ph	93 (**3l**)
15	Me/*n*-pentyl/H (**1g**)	2-MeO-C_6H_4	99 (**3m**)
16	Me/*n*-pentyl/H (**1g**)	3-MeO-C_6H_4	90 (**3n**)
17	Me/*n*-pentyl/H (**1g**)	4-MeO-C_6H_4	99 (**3o**)
18	Me/*n*-pentyl/H (**1g**)	4-Me-C_6H_4	97 (**3p**)
19	Me/*n*-pentyl/H (**1g**)	4-CF_3-C_6H_4	81 (**3q**)

[a] *Reaction conditions:* $[Rh(COD)Cl]_2$ (2 mol%), **1** (0.2 mmol), **2** (0.6 mmol), KOH (0.4 mmol), dioxane (3 mL), H_2O (0.3 mL), reflux, 12 h.
[b] Isolated yields based on **1**.

an 81% yield of conjugated addition product (entry 19).

Next, a preliminary study on the enantioselective version of this rhodium-catalyzed addition reaction of arylboronic acids to vinylogous imines was carried out (Scheme 2). Using the complex *in situ* generated from $[Rh(C_2H_4)_2Cl]_2$ and Hayashi's ligand **L**[9] as catalyst, low yields (21% and 29%) and moderate enantioseletivities (84% and 79% *ee*) were obtained. The low yields might be ascribed to steric hindrance of the chiral diene ligand. These promising results demonstrated the potential for asymmetric catalysis of current reaction, although more efficient catalytic systems need to be developed.

In conclusion, we have developed an efficient rhodium-catalyzed addition reaction of arylboronic acids to novel electrophiles generated *in situ* from sulfonylindoles, this strategy provided a facile access to the relevant C-3 *sec*-alkyl-substituted indoles in moderate to high yields with a wide range of substrates. Our ongoing studies are focused on an asymmetric version of



1 2 3

	R^1	Ar	Yield [%]	*ee* [%]
(−)-**3a**	4-ClC_6H_4	Ph	21	84
(−)-**3d**	Ph	4-$MeOC_6H_4$	29	79

Scheme 2. Rhodium-catalyzed asymmetric addition of arylboronic acids **2** to sulfonylindoles **1**.

this reaction, and the applications of this methodology in organic synthesis.

Experimental Section

Typical Procedure for the Rhodium-Catalyzed Reactions of Boronic Acids with Sulfonylindoles

A 10-mL Schlenk tube was charged with $[Rh(COD)Cl]_2$ (2.0 mg, 2 mol%), sulfonylindole **1** (0.2 mmol), boronic acid **2** (0.6 mmol), KOH (22.4 mg, 0.4 mmol) and then evacuated under vacuum and placed under a nitrogen atmosphere. Dioxane (3 mL) and water (0.3 mL) were added subsequently. The mixture was stirred at 100 °C for 12 h. Then water (15 mL) was added and the mixture was extracted with CH_2Cl_2 (15 mL) for three times. The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure, the residue was subjected to flash chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 10:1) to yield the corresponding products **3**.

2-Methyl-3-[(4-chlorophenyl)(phenyl)methyl]indole (3a): Yield: 80%; white solid; mp 157–160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.80$ (s, 1H), 7.27–7.17 (m, 8H), 7.13 (d, $J = 8.0$ Hz, 2H), 7.06 (t, $J = 7.5$ Hz, 1H), 6.98 (d, $J = 8.0$ Hz, 1H), 6.90 (t, $J = 7.3$ Hz, 1H), 5.69 (s, 1H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 143.5$, 142.6, 135.4, 132.3, 132.0, 130.7, 129.8, 129.3, 128.5, 128.5, 126.5, 121.1, 119.6, 119.5, 113.7, 110.4, 47.4, 12.5; HR-MS: $m/z =$ 330.1048, calcd. for $C_{22}H_{17}NCl$ $[M-H]^-$: 330.1050.

Acknowledgements

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