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Arylation of Rhodium(II) Azavinyl Carbenes with Boronic Acids

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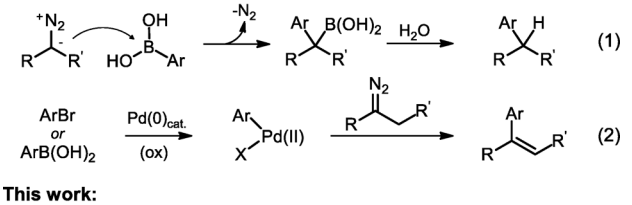
Supporting Information

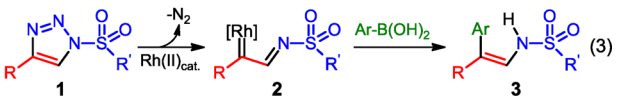
ABSTRACT: A highly efficient and stereoselective arylation of in situ-generated azavinyl carbenes affording 2,2-diaryl enamines at ambient temperatures has been developed. These transition-metal carbenes are directly produced from readily available and stable 1-sulfonyl-1,2,3-triazoles in the presence of a rhodium carboxylate catalyst. In several cases, the enamines generated in this reaction can be cyclized into substituted indoles employing copper catalysis.

Utilization of diazo compounds as versatile reactive species has become a cornerstone in modern organic synthesis.[1] In particular, the diverse reactivity of rhodium carbene complexes derived from diazo compounds has gained considerable attention.[2] Despite the multitude of reactions developed for rhodium carbenes, there are only a few examples of their direct arylation, which are limited to intramolecular processes.[3] The Wang[4a] and Barluenga[4b] groups recently reported that diazo compounds (either directly or generated in situ from tosylhydrazones)[5] react with arylboron nucleophiles in the absence of a transition-metal catalyst (eq 1).

Previous work (Barluenga and Wang):



This work:

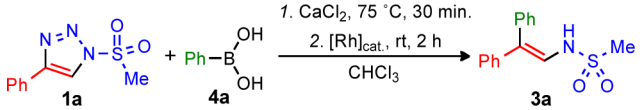


Furthermore, related arylation reactions of diazo compounds via migratory carbene insertion[6] into Pd–aryl intermediates have been described (eq 2).[7] Herein we report a stereoselective Rh(II)-catalyzed reaction of arylboronic acids with azavinyl carbenes derived from 1-sulfonyl-1,2,3-triazoles **1** that provides access to a variety of functional enamine products **3** (eq 3).

It is known that certain 1,2,3-triazoles can undergo ring–chain tautomerization in solution to form the corresponding diazo imines.[8,9f] Initially we attempted to capture the diazo tautomer of **1** by reaction with phenylboronic acid, effectively mimicking the Barluenga and Wang reaction (eq 1). However, no reaction was observed, even under forcing conditions. We attribute the failure of this transformation to a low concentration of the putative diazo tautomer in solution.

We recently demonstrated that readily available 1-sulfonyl-1,2,3-triazoles **1** can serve as direct precursors to rhodium(II) azavinyl carbenes **2**.[9] These structurally unique carbenes share many similarities to the well-studied diazoester derivatives; however, the ready availability and stability of the triazoles allows for simple experimental setup and handling. Following our recent success with the Rh(II)-catalyzed transformations of **1**, we attempted a rhodium-catalyzed arylation utilizing organoboronic acids. We hypothesized that the pendant nitrogen lone pair of the sulfonyl imine of azavinyl carbene **2** could participate in the formation of a boronate complex; subsequent transfer of the nucleophilic organic group could then afford the arylated product. To this end, we examined the reaction of phenylboronic acid **4a** and triazole **1a** in the presence of a 0.5 mol % loading of various Rh(II) catalysts and $CaCl_2$ as an additive (Table 1). We were pleased to find that arylated enamine **3a** was formed at room temperature as the single product.

Table 1. Catalyst Optimization for the Arylation of 1a[a]



entry	catalyst	yield (%)[b]
1	$Rh_2(oct)_4$	<5
2	$Rh_2(piv)_4$	69
3	$Rh_2(esp)_2$	50
4	Rh_2(S-PTAD)$_4$	85
5	Rh_2(S-NTTL)$_4$	75

[a]Performed on a 0.30 mmol scale using 0.5 mol % Rh catalyst and 1.0 equiv of **4a** in 1.0 mL of $CHCl_3$. Since previous studies identified $CHCl_3$ as the optimum solvent for the generation of Rh(II) azavinyl carbenes, no solvent optimization was performed. [b]Determined by LC/MS using *p*-tolyl acetamide as an internal standard.

Although most of the rhodium(II) carboxylate complexes were effective for the arylation of **1a**, Rh_2(*S*-PTAD)$_4$[10] was found to be the optimal catalyst (85% yield of **3a**; Table 1, entry 4). During optimization of the reaction conditions we discovered that $CaCl_2$ is an essential additive for the success of this transformation.[11] A short desiccation period (30 min) was found to be necessary for the formation of an arylboroxine trimer, $(ArBO)_3$, which is likely the active arylating species (see below). Moreover, in the absence of $CaCl_2$, we observed the

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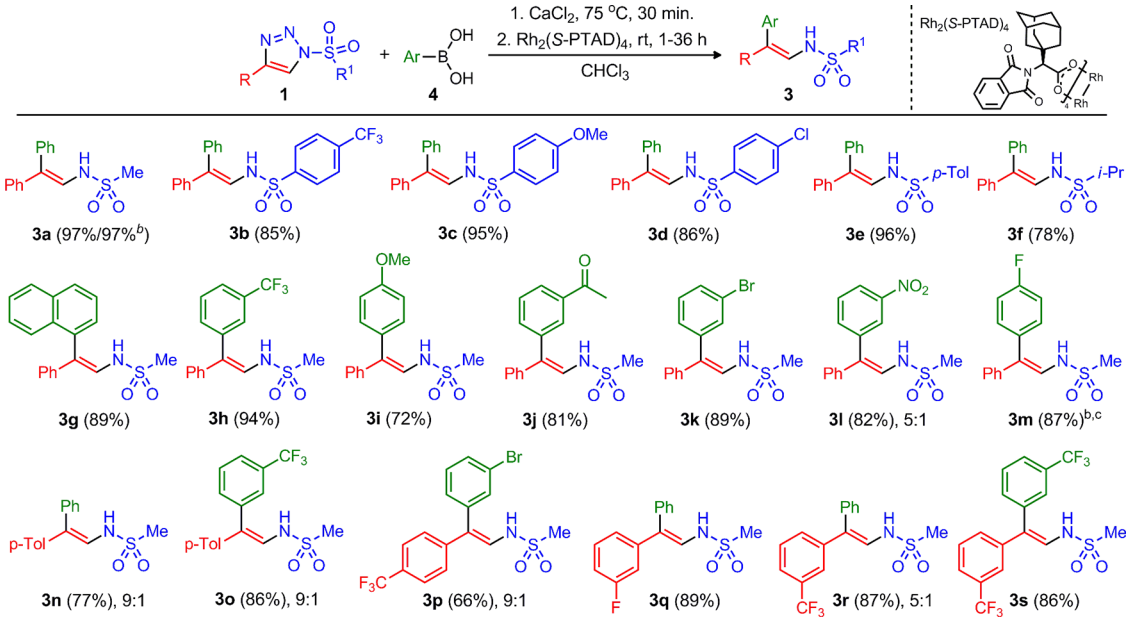
Table 2. Substrate Scope of the Rh(II)-Catalyzed Formation of Substituted Enamines[a]



[a]General reaction conditions: **1** (1.0 equiv, 0.50 mmol), **4** (1.1 equiv, 0.55 mmol), and $CaCl_2$ (4.0 equiv, 2.0 mmol) in 2.0 mL of dry $CHCl_3$ at 75 °C for 30 min, then Rh_2(*S*-PTAD)$_4$ (0.5 mol %) in 0.5 mL of dry $CHCl_3$ at rt for 1−36 h. Values in parentheses are isolated yields. Enamines **3** were isolated in ≥10:1 isomeric purity (by ^{1}H NMR) unless otherwise stated. For the majority of the substrates used, the reaction reached completion within 4 h; however, some exceptions were noted (**3c**, **3p**, **3r**, and **3s**; see the SI for details). [b]$CaCl_2$ was not used. [c]With *p*-fluorophenylboroxine.

significant formation of side products[12] and catalyst deactivation.

With the optimized conditions in hand, we examined the scope of this new reaction with respect to variously substituted 1-sulfonyl-1,2,3-triazoles **1** and arylboronic acids **4**, leading to enamine products **3** (Table 2). Variation of the 1-sulfonyl group at N1 of triazole **1** did not affect the efficiency of the reaction. Accordingly, both aliphatic (**3a** and **3f**) and aromatic (**3b**−**e**) sulfonyl groups were tolerated in the reaction with phenylboronic acid (85−97% yield).

The reaction of 1-mesyl-4-phenyl-1,2,3-triazole **1a** with substituted arylboronic acids **4** to produce unsymmetrical 2,2-diaryl enamines **3** raised the question of the stereoselectivity of the process. To our delight, we found that the enamine products **3g**−**m** were obtained in high isomeric purity, indicating a highly stereoselective arylation reaction. The geometry of the double bond was assigned by performing a single-crystal X-ray analysis of enamine **3g** (Figure 1).[13]

As shown in Table 2, sterically encumbered (**3g**), electron-deficient (**3h**, **3j**, and **3l**), electron-rich (**3i**), and halogen-containing (**3k** and **3m**) boronic acids worked effectively (72−94% yield) for the construction of diversely functionalized 2,2-diaryl enamines. Although ortho-substituted arylboronic acids underwent this arylation process, the reactions were sluggish and led to low conversions. Furthermore, employing triazoles **1** bearing different aryl groups at the C4 position furnished the corresponding enamine products **3n**−**s** in high yields. Both electron-donating (**3n** and **3o**) and electron-withdrawing (**3p**−**s**) substituents were tolerated in the arylation reaction with a series of substituted arylboronic acids (Table 2).

Although this arylation reaction proceeded with high stereoselectivity, we noted that in several cases (cf. Table 2) mixtures of isomers were obtained upon isolation (9:1 to 5:1 by NMR). The apparent reduction of stereoselectivity likely arose from facile tautomerization of an initial syn product. Rapid isolation of the products was required in order to obtain enamines of high isomeric purity [see the Supporting Information (SI)].

Enamines are endowed with a wealth of reactivity and can serve as versatile precursors for the construction of heterocyclic frameworks.[14] Accordingly, we envisioned that the 2,2-diaryl enamine products **3** could be employed in the synthesis of aryl-substituted indoles via metal-catalyzed cyclization. To this end, we subjected triazole **1b** to the Rh-catalyzed arylation with a series of arylboronic acids, followed by a Cu(I)-catalyzed intramolecular N-arylation of the enamine intermediate (Table 3).

Gratifyingly, triazole **1b** underwent the Rh(II)-catalyzed arylation reaction efficiently, although an increased temperature (50 °C), extended reaction time (12 h), and higher catalyst loading (1.0 mol %) were required. After filtration, the derived enamine products agreeably cyclized into the anticipated *N*-sulfonyl-3-arylindoles **5** when the copper(I)-catalyzed conditions developed by Buchwald and co-workers[15] were employed (Table 3). This cyclization requires a syn orientation

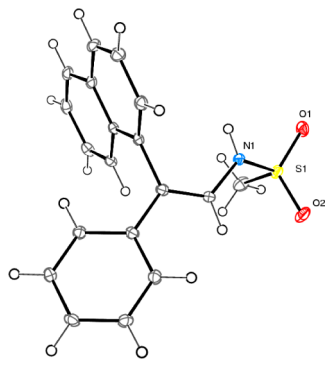


Figure 1. Crystal structure of enamine **3g**.

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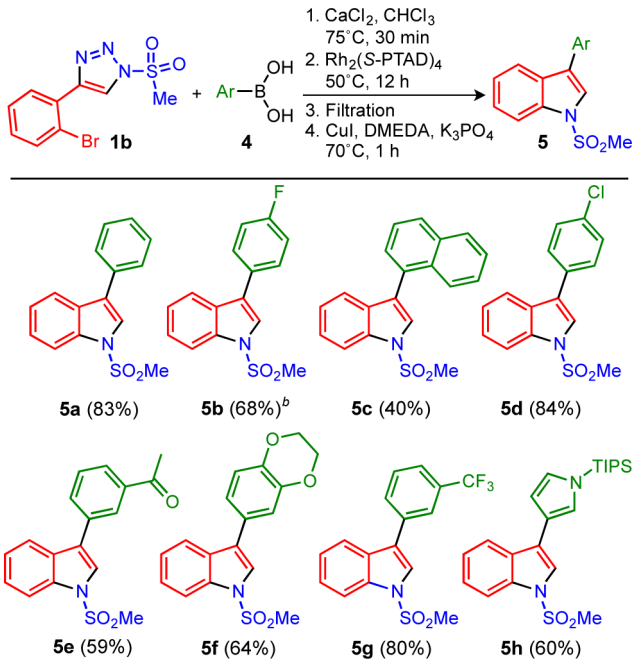
Table 3. Synthesis of 3-Arylindoles via an Arylation/Cyclization Sequence[a]



[a]General reaction conditions: **1b** (1.0 equiv, 0.50 mmol), **4** (1.1 equiv, 0.55 mmol), and $CaCl_2$ (4.0 equiv, 2.0 mmol) in 2.0 mL of dry $CHCl_3$ at 75 °C for 30 min, then Rh_2(*S*-PTAD)$_4$ (1.0 mol %) in 0.5 mL of dry $CHCl_3$, followed by CuI (5.0 mol %), *N*,*N*′-dimethylethylenediamine (10 mol %), and K_3PO_4 (2.0 equiv, 1.0 mmol) in 2.0 mL of dry toluene at 75 °C for 1 h. Values in parentheses are isolated yields from **1b**. [b]$CaCl_2$ was not used; with *p*-fluorophenylboroxine.

of the *o*-bromophenyl substituent and the *N*-sulfonyl amino group, which was readily achieved by a rapid isomerization of the enamine double bond (see above). As demonstrated in Table 3, several arylboronic acids **4** were tolerated in this two-pot synthetic sequence. Thus, halogen-containing indoles **5b** and **5d**, acetyl derivative **5e**, and heteroaryl-substituted indole **5h** were obtained in good yields.

A plausible mechanism for this novel Rh(II)-catalyzed arylation reaction is shown in Figure 2. The ring−chain tautomerization of triazole **1** delivers diazoimine **1′**, which then reacts with the rhodium carboxylate catalyst to form azavinyl carbene complex **2**. We propose that the lone pair of the sulfonylimine nitrogen in **2** reversibly coordinates to the empty $2p_z$ orbital of the boron atom,[16] forming complex **6**. The active arylation species is believed to be a trimeric arylboroxine complex since compounds **3a**, **3m**, and **5b** were obtained from commercially available arylboroxines without the use of $CaCl_2$. The stereochemical outcome of this reaction is likely dictated by the irreversible facial-selective delivery of the aryl group from intermediate **6** to obtain **7**. Finally, dissociation of rhodium and subsequent protonolysis affords the enamine product **3**. The alternative, a concerted arylation mechanism that also accounts for the observed stereochemical outcome, cannot currently be ruled out.

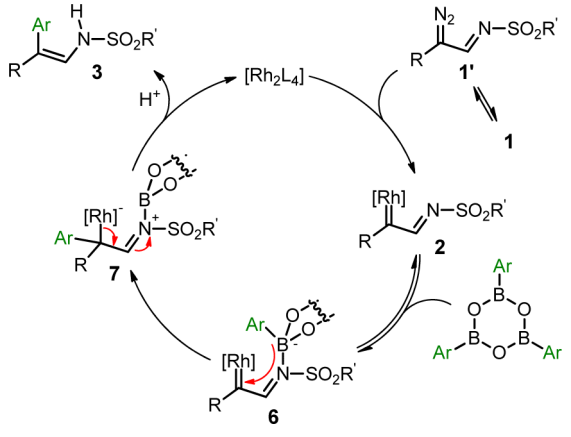


Figure 2. Proposed mechanism for the arylation of **1**.

The mild, efficient, and stereoselective Rh(II)-catalyzed arylation of 1-sulfonyl-1,2,3-triazoles described here provides convenient access to 2,2-diaryl enamines. This sequence of two reliable steps (synthesis of 1-sulfonyl-1,2,3-triazoles followed by their arylation with boronic acids) in effect carboaminates alkynes regio- and stereoselectively, introducing two functional groups into the acetylenic backbone. The synthetic utility of the enamine products was demonstrated by using a copper-catalyzed cyclization to form a range of 3-arylindoles. Further studies of the scope and mechanism of this reaction are underway in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, NMR spectra, and crystallographic data (CIF). 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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(13) The crystal structure of **3g** has been deposited with the Cambridge Crystallographic Data Centre (CCDC 883835). The geometries of all other enamine products **3** were assigned by analogy.
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