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Rhodium Catalyzed Direct Arylation of α-Diazoimines

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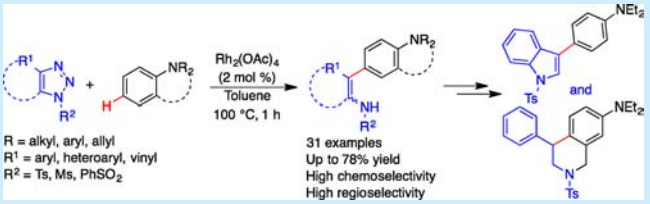
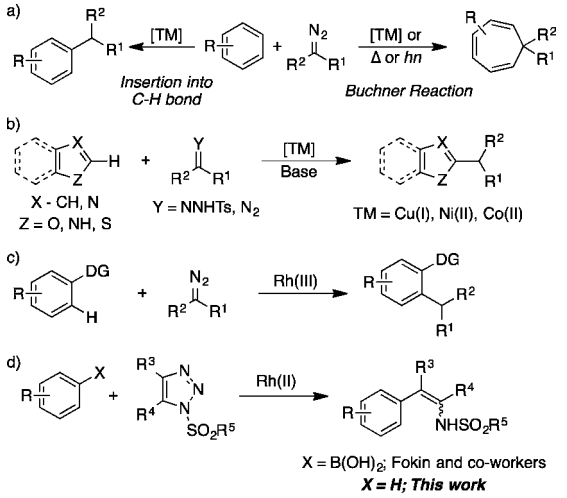
Supporting Information

ABSTRACT: An efficient rhodium catalyzed direct arylation of α-diazoimines, generated from readily accessible 1,2,3-triazole, has been accomplished for the synthesis of 2,2-diaryl enamides. The reaction involves the chemo- and regioselective insertion of rhodium azavinyl carbene into aromatic C(sp^2)−H bonds. Utility of the developed methodology was demonstrated in the synthesis of indole and tetrahydroisoquinoline frameworks.



Transition metal catalyzed insertion of carbenes into various C−H bonds is one of the most widely practiced methods in organic synthesis.[1] These reactions generally show high selectivity for the intramolecular reaction with either a C(sp^3)−H or C(sp^2)−H bond, for the formation of small membered rings.[2] But, the intermolecular reaction of transition metal carbenes with C−H bonds is rather nonselective. Particularly, the reaction of metal carbenes with arenes affords the cycloheptatriene, well-known as the Buchner reaction,[3] instead of the possible C(sp^2)−H insertion (Scheme 1a).[4]

Scheme 1. Transition Metal Catalyzed Reaction of Diazo Compounds and Arenes



Recently, Wang et al.[5] disclosed the Cu-catalyzed insertion of metal carbene generated from *N*-tosylhydrazones to the acidic C−H of 1,3-azoles. A similar reaction was later demonstrated employing either a Ni- or Co-based catalyst (Scheme 1b).[6] Rh-catalyzed directing group assisted activation of the *ortho* C−H bond of arene followed by insertion of the diazo compound was reported by Yu et al.[7] and Li et al.[8] (Scheme 1c). Subsequently, the groups of Rovis,[9] Glorius,[10] Cui,[11] and Wang[12] have demonstrated the study of diazo compounds in the Rh-catalyzed functionalization of various directing group assisted C−H bonds. These reactions are majorly limited to C(sp^2)−H bonds of specific substrates, such as acidic heterocyclic or chelation assisted C−H bonds. Thus, the generally direct intermolecular insertion of transition metal carbenes into C−H bonds of simple arenes is highly warranted.

Use of 1,2,3-triazole as a source of α-diazoimines, which is difficult to access through traditional routes,[13] and its functionalization to various nitrogen-based building blocks and heterocycles, has gained reasonable attention in recent years.[14] Recently, we disclosed the Rh-catalyzed denitrogenative [2,3]-sigmatropic rearrangement of azavinylcarbene derived from 1,2,3-triazole with allyl aryl(alkyl) sulfides.[15] Based on our interest in the C−H functionalization of arenes[16] and unique reactivity of 1,2,3-triazole, we herein reveal the new Rh-catalyzed direct arylation of α-diazoimines generated from *N*-sulfonyl-1,2,3-triazole with arenes (Scheme 1d).

At the beginning of our studies, we examined the rhodium acetate (2 mol %) catalyzed reaction of 1,2,3-triazoles (1 equiv) **1a** with various arenes (4 equiv) in chloroform at 70 °C. Although a number of arenes such as xylene, mesitylene, and anisole did not show a promising result,[17] *N*,*N*-diethylaniline **2a** gave a detectable amount of product (21% yield) along with the hydrated product, α-aminoketone. Analysis of the isolated product proved the formation of enamide **4aa**[18] as a mixture of *Z*/*E* isomers in a 1.6:1 ratio, instead of expected imine **3**, which may also arise from imine **3** through imine−enamine tautomerism (Scheme 2). The formation of product **4aa** was further confirmed through hydrogenation over Pd/C to amide, where amide **5** was isolated in 94% yield as the sole product.

The synthesis of a similar enamide was reported by Fokin and co-workers from 1,2,3-triazoles employing arylboronic acid, a prefunctionalized arene, as a coupling partner (Scheme 1d),[19] but the present reaction utilizes the simple arene as a coupling

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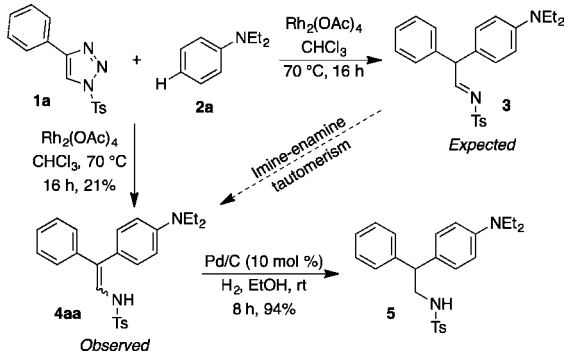
Scheme 2. Rh-Catalyzed Arylation of Triazole 1a with *N,N*-Diethylaniline 2a

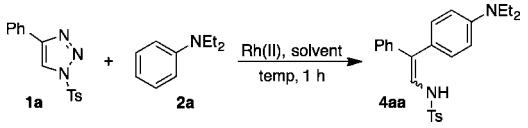


partner and forms the enamide through C−H insertion. Interestingly, excellent selectivity is observed for the functionalization of *para* C−H bonds, which is not accessible through the chelation assisted strategy, over possible other C−H bonds in arenes and the known α-C(sp^3)−H functionalization of alkylamines.[20]

Encouraged by the result, various other critical parameters were investigated to improve the yield of **4aa**. As shown in Table 1, increasing the temperature to 90 °C as well as changing the solvent to 1,2-dichloroethane (DCE) showed a positive influence on the outcome of reaction and **4aa** was isolated in 52% yield in 1 h (Table 1, entry 2). A similar trend was observed with toluene at 100 °C, where the formation of **4aa** was observed in 71% yield (Table 1, entry 3). No arylated product derived from toluene was observed. However, a further change in either the temperature or solvent did not show any improvement (Table 1, entries 4 and 5). Screening other Rh-catalysts revealed $Rh_2(Oct)_4$ furnished **4aa** in comparable yield (70%), but other bulky catalysts, $Rh_2(TBSP)_4$ and $Rh_2(DOSP)_4$, gave **4aa** in 34% and 49% yield, respectively (Table 1, entries 7−9). Similarly, decreasing the equivalents of arene to 2 decreased the yield of **4aa** (Table 1, entry 6).

Increasing the scale of the reaction by 10-fold furnished **4aa** in 70% yield, which is highly important in the synthetic application (Table 1, entry 3). From the optimization studies, the following conditions were chosen for studying the generality of the present methodology: 1 equiv of 1,2,3-triazole **1a**, 4 equiv of arene **2a**, 2 mol % of $Rh_2(Oct)_4$, toluene, 100 °C, 1 h.

Table 1. Rh-Catalyzed Arylation of Triazole 1a with 2a: Optimization[a]

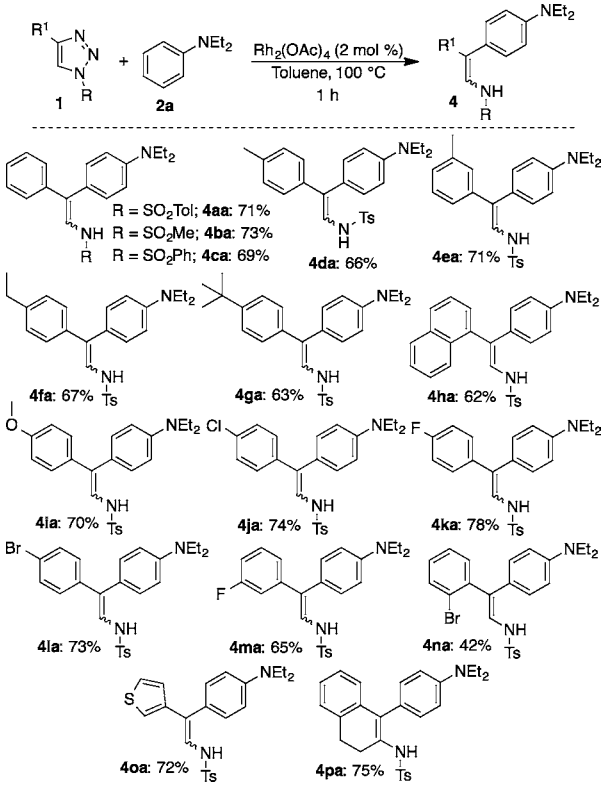


entry	Rh(II)-catalyst	solvent	temp (°C)	yield (%)[b]
1	$Rh_2(OAc)_4$	$CHCl_3$	70	21[c]
2	$Rh_2(OAc)_4$	DCE	90	52
3	$Rh_2(OAc)_4$	toluene	100	71 (70)[d]
4	$Rh_2(OAc)_4$	toluene	120	69
5	$Rh_2(OAc)_4$	C_6H_5Cl	120	46
6[e]	$Rh_2(OAc)_4$	toluene	100	45
7	$Rh_2(Oct)_4$	toluene	100	70
8	$Rh_2(TBSP)_4$	toluene	100	34
9	$Rh_2(DOSP)_4$	toluene	100	49

[a]Triazole **1a** (0.17 mmol, 1 equiv), arene **2a** (0.66 mmol, 4 equiv), Rh(II)-catalyst (2 mol %), solvent (1 mL), temp, 1 h. [b]Isolated yields, *Z*/*E* ratio ∼1.6:1. [c]16 h. [d]1.7 mmol of **1a** was used. [e]2 equiv of **2a**.

After identifying the optimized conditions, the generality of the present method was investigated with functionally different triazoles and arenes. As can be seen in Scheme 3, various substituted triazoles were subjected under the Rh-catalyzed arylation conditions with **2a** to afford the enamides **4** as a mixture of isomers in a variable ratio (see Supporting Information). Changing the sulfonyl moiety of triazole to mesyl or benzenesulfonyl gave the corresponding enamide **4ba** and **4ca** in comparable yield. Alkyl (methyl, ethyl, *tert*-butyl) substituted aryl containing triazole underwent smooth arylation to furnish the enamides (**4da**−**4ga**) in good yield. Sterically hindered *ortho* substituted enamides (**4ha** and **4na**) were synthesized in moderate to good yield. Interestingly, electron-rich anisyl substituted triazole also afforded the enamide **4ia** in 70% yield. Synthetically useful halogen substituted aryl containing enamides (**4ja**−**4na**) were also synthesized in good yield. In addition, thiophene, a sulfur-containing heterocyclic substituted triazole, also tolerated the optimized conditions and afforded the enamide **4oa** in 72% yield. Tetrasubstituted enamide **4pa** was achieved in 75% yield from the corresponding 4,5-disubstituted triazole and **2a**.

Scheme 3. Rh-Catalyzed Arylation of Triazoles 1 with 2a



The Rh-catalyzed arylation of vinyl substituted triazole **1q** and diethylaniline **2a** under the optimized conditions furnished **6**, as a single product (Scheme 4). The formation of **6** can be explained through the rearrangement of formed enamide to the conjugatively more stable azadiene.

Subsequently, the scope of arenes in the Rh-catalyzed arylation of triazole **1a** was examined (Scheme 5). Symmetrically substituted aniline derivatives on reaction with **1a** gave the

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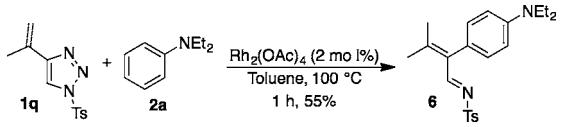
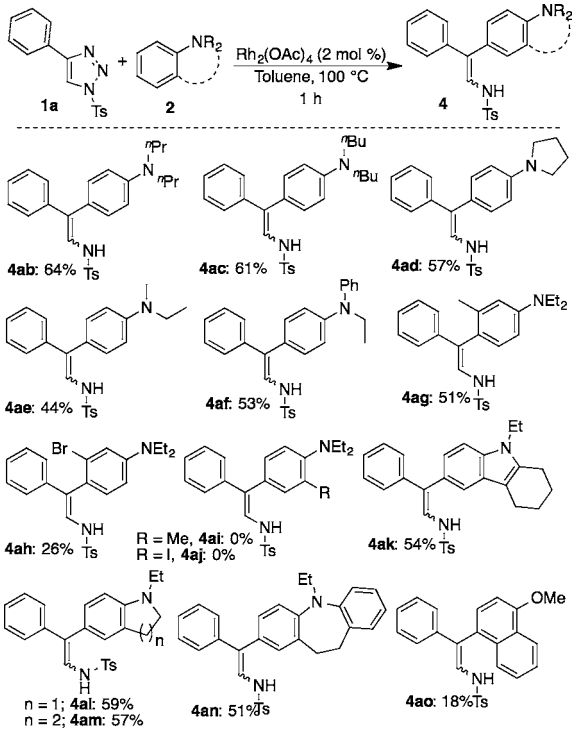
Scheme 4. Rh-Catalyzed Arylation of Triazoles 1q with 2a



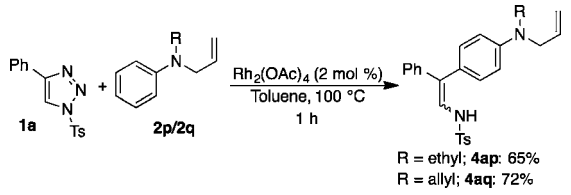
Scheme 5. Rh-Catalyzed Arylation of Triazole 1a with Arenes 2



corresponding enamides **4ab**, **4ac**, and **4ad** in 64%, 61%, and 51% yield, respectively. Unsymmetrically substituted nitrogen in aniline also afforded the enamides **4ae** and **4af** in good yield. Furthermore, *meta*-methyl and bromo substituted aniline derivatives furnished the corresponding enamides **4ag** and **4ah** in moderate to good yield. But, the *ortho*-substituted aniline derivatives did not afford the expected enamides (**4ai** and **4aj**). Interestingly, the reaction of *N*-based heterocyclic arene (indole, indoline, tetrahydroquinoline, and dibenzoazepine), which contains the *ortho*-substitution in the fused form, with **1a** giving the corresponding enamides (**4ak**−**4an**) in good yield. Furthermore, enamide **4ao** was achieved from the arylation of **1a** with a naphthalene derivative.

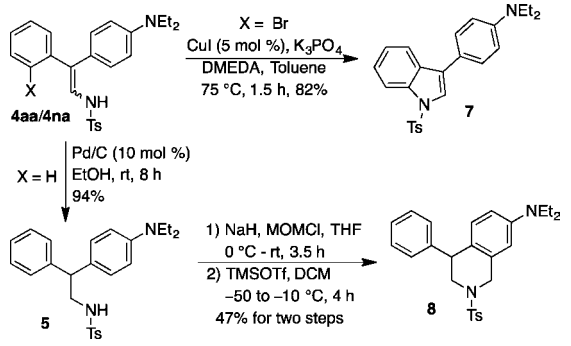
After establishing the scope of the developed methodology, the chemoselectivity of the Rh-catalyzed arylation reaction was investigated employing allyl substituted aniline derivatives, which is prone to other possible reactions such as cyclopropanation, [2,3]-sigmatropic rearrangement, and α-C−H insertion reactions. To our delight, the reaction of **1a** under the Rh-catalyzed arylation conditions with **2p** and **2q** selectively afforded the C(sp^2)−H inserted product, enamides **4ap** and **4aq** in excellent yield, respectively (Scheme 6). The structure of **4aq** was unambiguously confirmed by X-ray analysis (see Supporting Information).[21] This demonstrates that the present method is highly selective for the arene C−H insertion over other possible reactions.

Scheme 6. Chemoselective Rh-Catalyzed Arylation of 1a



Enamides are present as key subunits in various natural products and pharmaceutically important molecules[22] and are vital intermediates in organic synthesis having diverse synthetic utilities.[23] With the ready accessibility of various enamides established, next, the synthetic application was demonstrated through the synthesis of a pharmaceutically important *N*-based heterocyclic system such as 3-arylindole and 4-arylisoquinolines (Scheme 7). 3-Arylindole **7** was achieved from the Cu-catalyzed

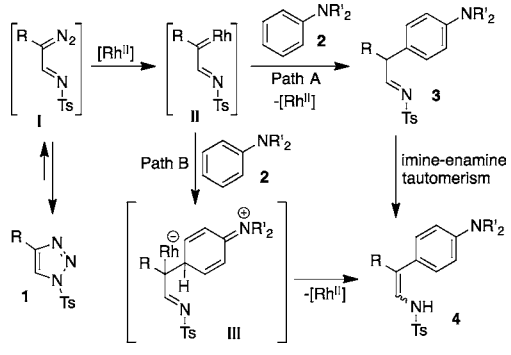
Scheme 7. Synthetic Utility of Enamide 4



C−N cross-coupling[24] of the *ortho* brominated enamide **4na**. Consequently, hydrogenation of enamide **4aa** over palladium on carbon afforded the 2,2-diarylethylamide **5** in excellent yield. Protection of NH as a MOM group followed by TMSOTf mediated cyclization through an iminium ion furnished the 4-arylisoquinoline **8** in 47% overall yield.

A plausible mechanism for the direct arylation of triazole **1** with arene **2** to enamide **4** is shown in Scheme 8. The catalytic

Scheme 8. Plausible Mechanism



cycle starts with the formation of reactive rhodium carbenoid **II** from α-diazoimine **I** with the extrusion of nitrogen, which in turn is derived from triazole **1** via ring−chain isomerism. The formation of product **4** from **II** with an arene can be realized by two pathways. The concerted direct insertion of **II** into a C−H bond of arene would lead to the formation of **3**, which upon tautomerization affords the enamide **4** (Path A). Alternatively,

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the addition of **2** to an electrophilic metal carbene center with the assistance of a nitrogen lone pair would furnish the zwitterion **III**. The direct formation of **4** from **III** can be achieved by loss of a proton and rearomatization (Path B). Among them, path B can be a preferable pathway: (1) formation of **III** is favored with electron-rich arenes (aniline derivatives) over the neutral (toluene) and moderately electron-rich arene (anisole derivative), and (2) since involvement of a nitrogen lone pair is important to increase the nucleophilicity of the arene and formation of **III**, electrophilic substitution occurs at the *para* instead of the *ortho* position, and *ortho*-substituted (methyl and iodo) aniline derivatives were not successful under the present optimized conditions (Scheme 5). Similarly, attempts toward the functionalization of an *ortho* C−H bond with *para*-substituted *N*,*N*-diethyl-*p*-methylanilines were also unsuccessful. With the plausible mechanism, the present method complements and possesses an advantage over traditional acid mediated electrophilic aromatic alkylation/acylation, where electron-rich aniline derivatives are shown to be the least reactive.

In conclusion, we developed an efficient strategy for the direct arylation of azavinyl carbenes, derived from 1,2,3-triazole with various arenes. This strategy involves chemo- and regioselective arene C(sp^2)−H insertion and offers electronically and sterically different substituted enamides, which are of high synthetic importance. Furthermore, the utility of enamides was demonstrated through the synthesis of *N*-based heterocycles, such as indole and isoquinolines.

■ ASSOCIATED CONTENT

Supporting Information

Experimental methods, characterizations data, and ^{1}H and ^{13}C NMR spectra of isolated compounds. 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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(21) CCDC 979169 (**4aq**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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