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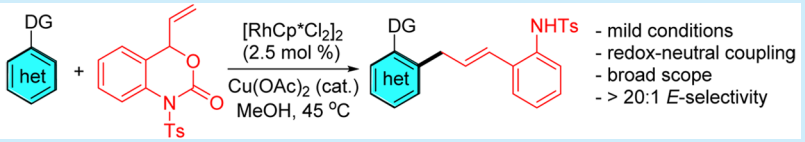
Rhodium(III)-Catalyzed Regio- and Stereoselective C−H Allylation of Arenes with Vinyl Benzoxazinanones

Zisong Qi, Lingheng Kong, and Xingwei Li*

Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, China

Supporting Information



ABSTRACT: Vinyl benzoxazinanone was applied as an electrophilic allylating reagent for a series of arenes under redox-neutral Rh(III) catalysis. This reaction occurs in high efficiency under mild conditions to afford allylarenes bearing a sulfonamide functionality in exclusively *E*-selectivity. This allylation system combines C−H activation of arenes and scission of an unstrained six-membered ring.

The allylarene motif is widely found in various natural products and biologically active compounds. In addition, the rich chemistry of the allyl group allows chemical transformations to expediently construct complex structures.[1] Therefore, introduction of an allyl unit into arenes has gained increasing attention for many years, and numerous efficient methodologies have been developed. Traditional routes such as the Friedel−Crafts-type allylation[2] and metal-catalyzed cross-coupling[1e,3] of aromatic electrophiles or organometallic reagents with allylic electrophiles are well-known, but they suffer from limited substrate scope, poor selectivity, and multistep reactions.

Recently, transition-metal-catalyzed C−H functionalization was recognized as a powerful strategy in organic synthesis.[4] In this context, the past decade has witnessed the rapid development of transition-metal-catalyzed C−H allylation of arenes. The allylation of electron-deficient polyfluoroarenes with allylic electrophiles was developed in the presence of palladium[5] or copper[6] catalysts. However, a stoichiometric amount of base or a high temperature was necessary. Various methods of transition-metal-catalyzed, directing-group-assisted C−H allylation have also been intensively explored using different allylating agents.[7] For example, rhodium(III)-catalyzed direct C−H allylation using allenes as an allyl source was reported by Cramer[7d] and Ma.[7n] Glorius recently developed an elegant allylation system between arenes and allylic carbonates via a rhodium(III)-catalyzed C−H activation pathway.[7c] Allylic alcohols,[7f,k,l,8] allyl ethers,[7b] vinyl oxiranes,[9] vinylcyclopropanes,[10] and 4-vinyl-1,3-dioxolan-2-ones[11] have also been applied as allylating agents in the presence of iron, cobalt, ruthenium, or rhodium catalysts. Very recently, the Ackermann group disclosed iron-[12] and manganese-catalyzed[13] C−H allylation of aromatics using allylic halides and allylic carbonates. Ackermann et al. also reported cobalt-catalyzed allylation reactions between arenes and vinylcyclopropanes, which occurred with high *Z*-selectivity.[14] Shibata and Tanaka reported the oxidative sp^2 C−H allylation with aliphatic alkenes using an electron-deficient (η^5-cyclopentadienyl)-rhodium(III) complex as a catalyst.[15] Despite these significant advances, C−H allylation of arenes remains largely underexplored, and the allylating agents are generally limited to allyl phosphates, allyl carbonates, allyl halides, and allenes. Furthermore, previous allylation systems mostly delivered limited molecular complexity, which introduced either no other functional groups or simple alcohols, with moderate to low *E*/*Z*-selectivity in many cases. We reasoned that vinyl benzoxazinanones[16] may function as an efficient and a novel electrophilic allyl source. However, challenges remain because opening of an unstrained six-membered ring generally requires driving forces.[11a,17] In addition, compatibility with C−H activation of arenes may pose potential issues because side reactions of vinyl benzoxazinanones, such as homocoupling, will limit their applications. Herein, we report rhodium(III)-catalyzed direct C−H allylation of arenes with >20:1 *E*-selectivity.

We initiated our studies with the coupling between *N*-(2-pyrimidinyl)-indole (**1a**) and vinyl benzoxazinanone (**2a**) using $[RhCp^*Cl_2]_2$ as a catalyst in MeOH at 80 °C. While no product was detected in the presence of CsOAc or $AgSbF_6$ additive (Table 1, entries 1 and 2), switching to $Cu(OAc)_2$ as an additive afforded product **3aa** in 83% yield with >20:1 *E*-selectivity on the basis of ^1H NMR analysis (entry 3). Further screening of the solvent revealed that 1,4-dioxane, DCE, and THF were all inferior to MeOH (entries 4−6). The catalyst loading could be lowered to 2.5 mol % with no loss of efficiency (entries 7 and 8), and the temperature could even be lowered to 45 °C, under which conditions **3aa** was isolated in 89% yield. However, further decreasing of reaction temperature to room temperature diminished the coupling efficiency (entry 9). In a control experiment, no reaction occurred when the rhodium catalyst was omitted (entry 10). Thus, the following conditions were

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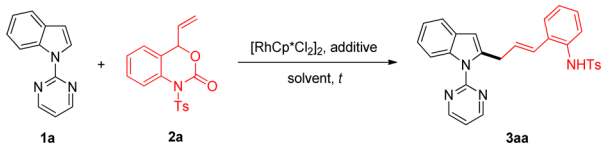
Table 1. Examination of Reaction Parameters[a]



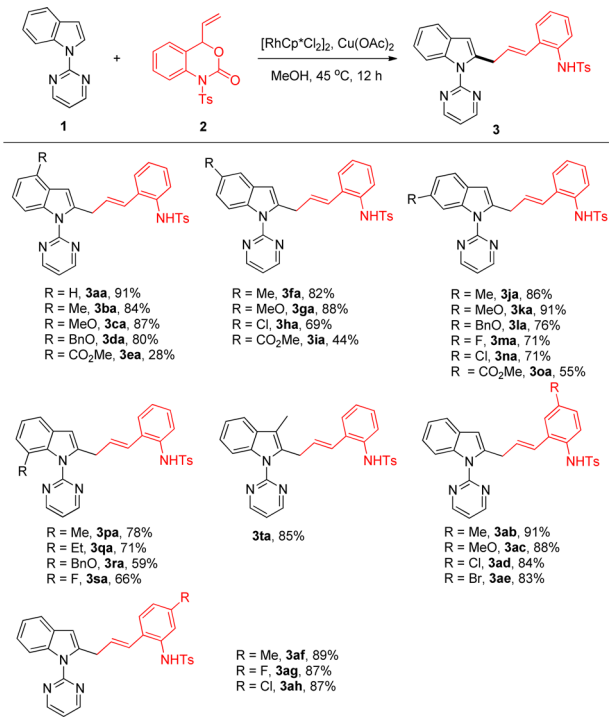
entry	additive	solvent	t (°C)	yield (%)[b]
1	CsOAc	MeOH	80	nd
2[c]	$AgSbF_6$	MeOH	80	nd
3	$Cu(OAc)_2$	MeOH	80	83
4	$Cu(OAc)_2$	1,4-dioxane	80	65
5	$Cu(OAc)_2$	DCE	80	59
6	$Cu(OAc)_2$	THF	80	49
7[d]	$Cu(OAc)_2$	MeOH	60	88
8[d]	**$Cu(OAc)_2$**	**MeOH**	**45**	**89**
9	$Cu(OAc)_2$	MeOH	25	24
10[e]	$Cu(OAc)_2$	MeOH	45	nd

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), $[RhCp^*Cl_2]_2$ (4.0 mol %), additive (30 mol %), solvent (1 mL) at the indicated temperature under N_2 for 12 h. [b]Isolated yields. [c]$AgSbF_6$ (16 mol %). [d]$[RhCp^*Cl_2]_2$ (2.5 mol %). [e]No $[RhCp^*Cl_2]_2$ was used.

eventually determined for subsequent studies: $[RhCp^*Cl_2]_2$ (2.5 mol %) and $Cu(OAc)_2$ (30 mol %) in MeOH at 45 °C for 12 h.

With the optimized conditions in hand, we next investigated the scope of *N*-(2-pyrimidinyl)-indoles **1** in the coupling with vinyl benzoxazinanone **2a** to evaluate the generality of the transformation (Scheme 1). With electron-donating groups at the C4-, C5-, and C6-positions of indoles, the coupling afforded the corresponding allylated products in good to high yields

Scheme 1. Scope of *N*-(2-Pyrimidinyl)-indoles and Vinyl Benzoxazinanones[a]

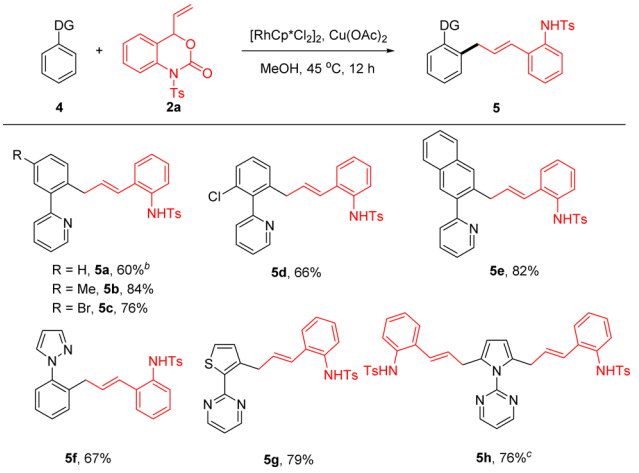


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $Cu(OAc)_2$ (30 mol %), MeOH (2 mL), at 45 °C for 12 h, isolated yields.

(**3aa**–**da**, **3fa**–**ga**, and **3ja**–**la**). Compared with the electron-donating-group-functionalized arenes, relatively low yields were isolated for those bearing electron-withdrawing groups at the C4-, C5-, and C6-positions (**3ea**, **3ha**–**ia**, and **3ma**–**oa**). Thus, the reaction efficiency seems to be related to the electronic effect of the substituent at such positions. Moreover, C7-substituted indoles are also applicable as in the isolation of products **3pa**–**sa** in 59–78% yields. Notably, the introduction of substituent at the 3-position of the indole ring had minimal influence, giving the desired product **3ta** in 85% yield. To further evaluate the generality of this system, the scope with respect to the substituents in the vinyl benzoxazinanones was next explored. Vinyl benzoxazinanones bearing methyl, methoxy, and halo groups (**2b**–**h**) at different positions proved viable, and the reactions proceeded smoothly to furnish the corresponding products **3ab**–**ah** in 83–91% yields. In all cases, >20:1 *E*-selectivity was consistently secured.

The arene substrate is not limited to a *N*-(2-pyrimidinyl)-indole (Scheme 2). It was found that simple 2-phenypyridine

Scheme 2. Scope of Other Arenes[a]



[a]Reaction conditions: **4** (0.2 mmol), **2a** (0.24 mmol), $[RhCp^*Cl_2]_2$ (2.5 mol %), $Cu(OAc)_2$ (30 mol %), MeOH (2 mL), at 45 °C for 12 h, isolated yields. [b]MeOH/1,4-dioxane (1 mL/1 mL) as a mixed solvent. [c]2.5 equiv of **2a** was used.

(**4a**) also coupled with **2a** under the modified conditions, from which product **5a** was isolated in 60% yield using MeOH/1,4-dioxane (1/1) as a mixed solvent. 2-Phenylpyridines bearing methyl, bromo, or chloro groups all underwent smooth coupling with **2a** to afford the desired monoallylated products **5b**–**d** in 66–84% yields. 2-(2-Naphthalenyl)-pyridine and *N*-phenyl-pyrazole were also amenable to the reaction conditions, furnishing **5e** and **5f** in 82 and 67% yield, respectively. Furthermore, the arene substrate was extended to a thiophene (**4g**) and a pyrrole (**4h**), affording the corresponding products (**5g**,**h**). We noted that **4h** coupled with 2.5 equiv of **2a** to produce diallylated product **5h** in 76% yield. We also observed a coupling between the N-unprotected vinyl benzoxazinanone and 2-phenylpyridine, which occurred in diselectivity. However, no analytically pure product could be isolated.

To briefly demonstrate the synthetic utility of the allylated product, product **3aa** was heated in DMF in the presence of Ag_2CO_3 (eq 1).[18] The oxidative C–N cyclization led to construction of another indole ring, and diindolylmethane **6** was isolated in good yield.

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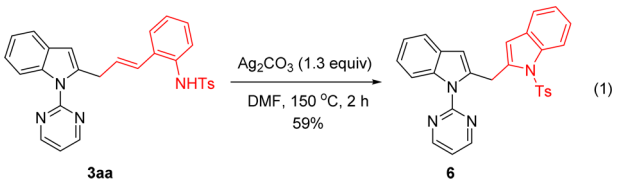
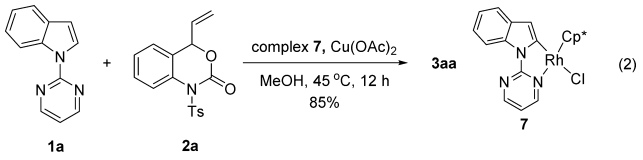
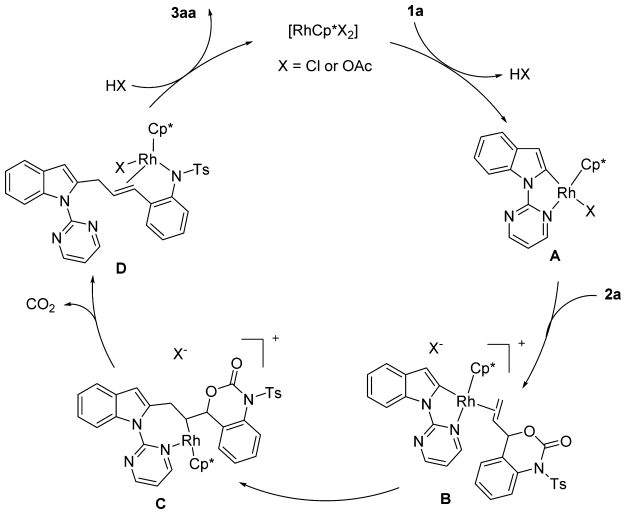


In order to probe the reaction mechanism, a cyclometalated rhodium(III) complex **7** was synthesized according to a literature report.[19] Complex **7** was designated as a catalyst for the coupling **1a** with **2a** under otherwise the same conditions, from which product **3aa** was isolated in 85% yield (eq 2). This high and comparable reactivity indicated that the reaction likely proceeded via a C−H activation mechanism.



Based on literature precedents and our observations,[11] a plausible mechanism is proposed in Scheme 3. Coordination of

Scheme 3. Proposed Mechanism



1a to the catalyst and subsequent C−H activation generates a rhodacyclic intermediate **A**. Substitution of the X (X = Cl or OAc) ligand of **A** by the incoming olefin unit in **2a** then gives a cationic olefin intermediate **B**. Subsequent migratory insertion of the Rh−aryl bond into the olefin generates a Rh(III) alkyl species **C**. Subsequent β-oxygen elimination of **C** followed by β-elimination of CO_2 provides a rhodium sulfonamide intermediate **D**, protonolysis of which by HX furnishes the final product together with the regeneration of the active catalyst. In this catalytic cycle, the employment of a polar MeOH solvent likely facilitates the ionization of the X ligand and stabilizes the resulting cationic intermediates. The role of $Cu(OAc)_2$ is probably two-fold. It offers an acetate ligand that is exchangeable with the chloride ligand in the initial catalyst to facilitate the C−H activation process. In addition, the Lewis acidic copper(II) might bind to the carbonyl in **B** to promote migratory insertion.

In conclusion, we have developed a rhodium(III)-catalyzed C−H activation−allylation of a series of functionalized arenes including indoles, benzenes, thiophene, and pyrrole using vinyl benzoxazinanones as an allylating reagent. This reaction proceeded in exclusively *E*-selectivity under mild, redox-neutral conditions with CO_2 as the only co-product. This system represents a combination of C−H activation and scission of an unstrained six-membered ring. The allylated product can be applied to the construction of an indole. Future studies on C−H activation and coupling with other unstrained rings are underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02146.

Experimental procedures, characterization of the products, and copies of the ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: xwli@dicp.ac.cn.

Notes

The authors declare no competing financial interest.

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