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## Nondirected C-H Alkenylation of Arenes with Alkenes under Rhodium Catalysis

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1 A nondirected dehydrogenative direct alkenylation of 2 simple aromatic compounds with alkenes under rhodium 3 catalysis is described. The site-selectivity is dominantly 4 dictated by the steric bulkiness around the targeting C–H 5 bond. The reaction efficiency was largely contingent on the 6 identity of copper(II) carboxylate as oxidant, and 7 considerable improvement of the productivity was achieved 8 by the addition of a sulfate salt.

9	Keywords:	alkenylation,	aromatic	compounds,
0	rhodium cata	alvst		

11 Vinylarenes and their derivatives are fundamental 12 motifs in natural products as well as various manufactured 13 chemicals, and thus, tremendous efforts have gone into 14 developing new synthetic methods for preparing them. The palladium-catalyzed coupling reaction of aryl halides with 15 alkenes, which is well-known as the Mizoroki-Heck 16 reaction,<sup>1,2</sup> has often been applied for the construction of 17 18 vinylarene scaffolds. Meanwhile, significant research 19 interests have been focused on the aromatic C-H 20 alkenylation protocols under oxidative conditions because 21 of their atom/step economic nature and operational 22 simplicity. After the leading work reported by Fujiwara and 23 Moritani,<sup>3,4</sup> various catalytic systems using palladium and other transition metals have been developed for the direct 24 25 alkenvlation of aromatic compounds. The efficient site-26 selective C-H coupling reactions developed to date 27 commonly rely on chelation assistance with directing groups on aromatic substrates.<sup>5</sup> Besides, for the direct reactions on 28 simple arenes without the aid of any directing functions, the 29 30 main challenges have been associated with (i) reducing the 31 amount of the aromatic substrates with a reasonable catalyst 32 loading and (ii) achieving the site-selectivity of the coupling.6 33

34 The nondirected C-H alkenylation reactions have 35 traditionally been explored using Pd catalysts. Recently, substantial progress has been achieved by employing well-36 designed ligand systems,<sup>7</sup> where arenes may be employed as 37 limiting substrates.<sup>7e</sup> Despite the remarkable success, a 38 39 major drawback of the Pd catalysis is the low site-selectivity 40 of the coupling because both steric and electronic factors are responsible for the selectivity. In contrast, the product distribution in the Rh catalysis<sup>8,9</sup> is largely dictated by steric 41 42 factors so that the reaction outcome is rather predictable. As 43 a seminal example, Glorious reported a Cp\*Rh(III)-44 45 catalyzed dehydrogenative alkenylation of solvent arenes (Figure 1a).<sup>9a</sup> Recently, Yu group described the reaction of 46 47 arenes as limiting reagents with the combination of PCy<sub>3</sub> 48 ligand and Cu(TFA)<sub>2</sub>/V<sub>2</sub>O<sub>5</sub> oxidant system; however, the role of these additives was not fully established (Figure 49

1b).<sup>9d</sup> In this context, further development of efficient 50 51 catalytic systems and better understanding of the reaction 52 mechanism are in high demand for the Rh catalysis. As part 53 of our continuous work in this field,<sup>10</sup> we report a new Rhcatalyzed dehydrogenative alkenylation that is enhanced by 54 55 the addition of a sulfate salt together with a copper 56 carboxylate oxidant (Figure 1c). Characteristic feature of 57 the reaction is described herein.



59 **Figure 1.** Rh-catalyzed dehydrogenative alkenylation.

61 We first examined the direct alkenylation using 62 naphthalene (1a, 0.5 mmol) and cyclohexyl acrylate (2a, 0.1 63 mmol) as model substrates in the presence of 64  $[RhCl(C_2H_2)_2]_2$  (2.5 mol%) and a number of oxidants (0.2 65 mmol) (Table 1). The use of metal acetate oxidants such as Cu(OAc)<sub>2</sub> and AgOAc did not provide any coupling 66 products (entries 1 and 2). On the other hand, the formation 67 of a small amount of product 3aa was detected with 68 Cu(OPiv)2, and a significant improvement was achieved by 69 70 using  $Cu(eh)_2$  (eh = 2-ethylhexanoate)<sup>11</sup> to afford a 33% 71 yield of 3aa (entries 3 and 4). We also examined another 72 copper carboxylate bearing a long alkyl chain, Cu(str)<sub>2</sub> (str 73 = stearate), but it was ineffective for the present reaction 74 (entry 5). It should be noted that Rh(II) carboxylate 75 complexes such as [Rh<sub>2</sub>(OAc)<sub>4</sub>] and [Rh<sub>2</sub>(OPiv)<sub>4</sub>] in 76 combination with  $Cu(eh)_2$  were totally inactive even at an 77 elevated temperature of 160 °C (entries 6 and 7). We 78 surmise that the 2-ethylhexanoate anion improves the 79 solubility of metal complexes present in the non-polar 80 medium, and at the same time, prevents the formation of 81 catalytically inactive Rh(II) dimeric species.

Afterward, cyclohexane was found to work remarkably
well as the solvent to produce **3aa** in 59% yield (entry 8).
To enhance the productivity further, we tested the effect of
several additives (0.2 mmol) on the present catalytic system.

Interestingly, addition of KH<sub>2</sub>PO<sub>4</sub> and Ag<sub>2</sub>SO<sub>4</sub> enhanced the 1 2 reaction to give 3aa in 69% and 79% yields, respectively 3 (entries 9 and 10). To exclude the possibility that the 4 Ag<sub>2</sub>SO<sub>4</sub> acts as an extra oxidant, we conducted some control 5 experiments. Addition of Ag(eh) significantly retarded the 6 reaction and the yield was reduced to 34% (entry 11), 7 whereas a bit of improvement was found with a doubled 8 amount of Cu(eh)<sub>2</sub> (entry 11). Furthermore, replacement of 9 Cu(eh)<sub>2</sub> with Ag(eh) resulted in the negligible outcome 10 (entry 13). From these observations, we concluded that the counter anion  $[SO_4]^2$  as well as  $[H_2PO_4]^-$  apparently has 11 some influence in the catalytic cycle (see below). Indeed, 12 other sulfate salts involving Na<sub>2</sub>SO<sub>4</sub> and K<sub>2</sub>SO<sub>4</sub> improved 13 14 the yield of **3aa**, while they were less effective than  $Ag_2SO_4$ (entries 14 and 15). 15 After investigating various 16 parameters,<sup>12</sup> the conditions in entry 10 were found to be optimal and employed for the following experiments. 17 18 Analysis of the isolated product **3aa** (entry 10, 76%) by <sup>1</sup>H 19 NMR indicated that it formed as the single  $\beta/E$  isomer as 20 shown. 21

## 22 **Table 1**. Optimization study<sup>*a*</sup>

23

			solvent		
	1a	2a	140 °C, 12 h	3aa	
	entry	oxidant	additive	solvent	yield <sup>b</sup>
1	1	Cu(OAc) <sub>2</sub>	-	octane	n.d.
	2	AgOAc	_	octane	n.d.
	3	Cu(OPiv) <sub>2</sub>	_	octane	<5%
	4	Cu(eh) <sub>2</sub>	_	octane	33%
	5	Cu(str) <sub>2</sub>	_	octane	n.d.
	6 <sup><i>c</i></sup>	Cu(eh) <sub>2</sub>	_	octane	n.d.
	$7^d$	Cu(eh) <sub>2</sub>	_	octane	n.d.
	8	Cu(eh) <sub>2</sub>	_	cyclohexane	59%
	9	Cu(eh) <sub>2</sub>	$KH_2PO_4$	cyclohexane	69%
	10	Cu(eh) <sub>2</sub>	Ag <sub>2</sub> SO <sub>4</sub>	cyclohexane	79%
	11	Cu(eh) <sub>2</sub>	Ag(eh)	cyclohexane	34%
	$12^{e}$	Cu(eh) <sub>2</sub>	-	cyclohexane	69%
	13	Ag(eh)	-	cyclohexane	<5%
	14	Cu(eh) <sub>2</sub>	$Na_2SO_4$	cyclohexane	64%
	15	Cu(eh) <sub>2</sub>	$K_2SO_4$	cyclohexane	74%

[RhCl(C2H2)2]2

CO2CV

56

(2.5 mol%) oxidant / additive

24 <sup>*a*</sup> Reaction conditions: **1** (0.5 mmol), **2** (0.1 mmol), 25 [RhCl( $C_2H_4$ )<sub>2</sub>]<sub>2</sub> (2.5 mol %), oxidant (0.2 mmol), and 26 additive (0.2 mmol) in cyclohexane (0.5 mL) at 140 °C for 27 12 h. <sup>*b*</sup> Determined by GC analysis. <sup>*c*</sup> [Rh<sub>2</sub>(OAc)<sub>4</sub>] is used 28 as catalyst at 160 °C. <sup>*d*</sup> [Rh<sub>2</sub>(OPiv)<sub>4</sub>] is used as catalyst at 29 160 °C. <sup>*e*</sup> Cu(eh)<sub>2</sub> (0.4 mmol) was used.

30

31 We next examined the electronic and steric 32 effects of aromatic substrates on the reaction outcome,

and the results are showcased in Scheme 1. The reaction 33 34 of toluene (1b) with 2a gave 3ba in 62% isolated yield 35 with a *para/meta* ratio of 3:7. Di-substituted benzene 36 derivatives 1c-1e were selectively converted into 3ca-37 **3ea** in good yields where the reaction took place at the sterically more accessible positions. It is of interest to 38 39 compare with the fact that haloarenes such as 1d and 1e 40 usually suffer from low yields and poor selectivity under Pd catalysis.<sup>6,7</sup> Moreover, 4-phenyltoluene (1f) afforded 41 3fa in 53% yield with a *para/meta* ratio of 1:2 ratio, 42 keeping the *p*-tolyl moiety untouched. 43 This clearly 44 indicates that the selectivity of the present protocol is mainly influenced by steric environment rather than 45 46 electronic effect. The current reaction conditions were 47 suitable for the selective β-functionalization of 48 naphthalene derivatives as expected. 49



51 Scheme 1. Substrate scope of the direct alkenylation. 52 Reaction conditions: 1 (1.25 mmol), 2 (0.25 mmol), 53 [RhCl(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub>]<sub>2</sub> (2.5 mol %), Cu(eh)<sub>2</sub> (0.5 mmol), and 54 Ag<sub>2</sub>SO<sub>4</sub> (0.5 mmol), in cyclohexane (3.0 mL) at 140 °C 55 for 24 h. Isolated yields are shown.

2,3-Dimethylnaphthalene (1g) and 2,3-bis(ethoxycarbonyl)-1 2 naphthalene (1h) respectively produced the corresponding alkenylated products 3ga and 3hb in 76% and 62% yields. 3 4 With the mono-substituted naphthalenes 1i and 1j, the 5 corresponding mixtures of *β*-alkenylated products were 6 obtained. Importantly, no reaction at the neighbouring 7 positions of the carbonyl functionalities in **1h**, **1j**, and  $1k^{13}$ 8 was observed, despite directed C-H coupling would be feasible with ester and ketone directing groups.<sup>5,14</sup> 9,10-9 10 Dibromoanthracene (11) was also applicable to give the  $\beta$ alkenylated product 5la. Additionally, we were interested in 11 checking the reactivity of electronically biased heterocyclic 12 13 compounds. High yields were obtained with complete C2 14 selectivity when benzo[b]thiophene (1m), benzo[b]furan 15 (1n), and thieno [3,2-b] thiophene (1o) were employed under 16 the optimized reaction conditions. On the other hand, 17 dibenzo[b,d]furan (1p) provided the mixture of two isomers 18 with 70% isolated yield where the C2 and C3 were 19 preferably alkenylated.

20 Subsequently, the reaction of some polycyclic aromatic 21 hydrocarbons with various alkenes were tested (Scheme 2). 22 Treatment of naphthalene with a series of acrylate esters 2a-23 2d afforded 3aa-3ad with synthetically appreciable 24 chemical yields. The reaction of 1a with 2a could be 25 conducted in 1.0 mmol scale without any difficulty (eq. 1). 26 In addition, styrene (2e) and other Michael acceptors 2f-2h 27 were well-tolerated. However, no productive result was 28 obtained with an aliphatic alkene, 1-octene (not shown). 29 Pyrene (1r) was exclusively transformed into the 30 corresponding C2-alkenylated products 3ra, 3rb, and 3rd in 31 good yields. Such unique selectivity towards the C2 32 position of pyrene again advocates that the current 33 methodology is driven by steric factor. Likewise, 34 phenanthrene (1q) gave 3qa as a mixture of the C2- and C3-35 alkenylated isomers in 60% yield, and the most olefinic K-36 region<sup>15</sup> remained intact. 37



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39 Scheme 2. Alkenylation using various alkene coupling 40 partners. Reaction conditions: 1 (1.25 mmol), 2 (0.25 41 mmol), [RhCl( $C_2H_4$ )<sub>2</sub>]<sub>2</sub> (2.5 mol%), Cu(eh)<sub>2</sub> (0.5 mmol), 42 and Ag<sub>2</sub>SO<sub>4</sub> (0.5 mmol) in cyclohexane (3.0 mL) at 43 140 °C for 24 h. Isolated yields are shown.



45 After the exploration of substrate scope in the present 46 protocol, we turned our attention to the possible mechanism 47 of the current catalytic system. A significant difference of 48 3aa yield between the independent reactions of 1a with 2b 49 (31%) and  $1a-d_8$  with 2b (14%) was observed after 1 h (eqs. 50 2 and 3). This may imply that the aromatic C-H bond 51 cleavage step is involved in the rate-limiting stage, while the 52 accurate kinetic constants could not be determined due to 53 the presence of initial incubation time (see below).<sup>9a</sup> To 54 provide some information concerning the oxidation state of 55 the catalytically active Rh species, we examined the direct 56 alkenylation of 1a with 2a using a stoichiometric amount of 57 either  $[RhCl(C_2H_2)_2]_2$  or RhCl<sub>3</sub> in the presence of K(eh) (potassium 2-ethylhexanoate) and  $\hat{A}g_2SO_4$  (eq. 58 4). 59 Interestingly, **3aa** was not formed at all with  $[RhCl(C_2H_2)_2]_2$ . 60 whereas RhCl<sub>3</sub> allowed to give the product in 24% yield. 61 According to these observations, we concluded that the C-H 62 activation is only initiated by a Rh(III) species with the aid 63 of 2-ethylhexanoate anion as the internal base.



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67 In order to gain additional insight into the role of 68 Ag<sub>2</sub>SO<sub>4</sub> in the catalytic system, we monitored the reaction 69 progress in detail (Figure 2). In the presence of Ag<sub>2</sub>SO<sub>4</sub>, 70 there was an induction period and a considerable rate 71 acceleration was observed after 30 min. This period is not for the initial generation of the catalytically active Rh 72 73 complex, because the use of pre-heated mixture, 74 [RhCl(C<sub>2</sub>H<sub>2</sub>)<sub>2</sub>]<sub>2</sub>, Cu(eh)<sub>2</sub>, and Ag<sub>2</sub>SO<sub>4</sub> at 120 °C for 30 min 75 in cyclohexane before the addition of 1a and 2a, exhibited a 76 similar time course at the initial stage. Additionally, a 77 considerable rate acceleration was observed when Ag<sub>2</sub>SO<sub>4</sub> 78 was introduced to the reaction mixture after 1 h. From these 79 observations, Ag<sub>2</sub>SO<sub>4</sub> does not likely participate in the 80 initial C-H activation stage of the reaction, but it might assist the reoxidation of Rh(I) species to generate the 81 catalytically active Rh(III) complex.<sup>9d,11,16</sup> While the detail 82 83 is not clear at this stage, the additive would help the electron 84 transfer from Rh(I) to Cu(II) by ligation. We are still 85 working to find more the specific role of the additive and 86 the proper reaction mechanism.



 $\frac{1}{2}$ Figure 2. Time course of the direct alkenylation of 3 naphthalene (1a) with alkene 2a: (i)  $\circ$  standard condition, (ii) • without Ag<sub>2</sub>SO<sub>4</sub>, (iii)  $\blacksquare$  [RhCl(C<sub>2</sub>H<sub>2</sub>)<sub>2</sub>]<sub>2</sub>, Cu(eh)<sub>2</sub>, and 4 Ag<sub>2</sub>SO<sub>4</sub> were pre-heated at 120 °C for 30 min, (iv) ▲ 5 Ag<sub>2</sub>SO<sub>4</sub> was added at 60 min. 6

7 8 In summary, we have found that the combination of Cu(eh)<sub>2</sub> and Ag<sub>2</sub>SO<sub>4</sub> is an effective oxidant system for the 9 Rh-catalyzed nondirected C-H alkenylation of aromatic 10 compounds without using any precious phosphine and 11 cyclopentadienyl ligands. The reaction system exhibits 12 relatively broad scope for the preparation of alkenylated 13 14 arenes in good yields. Control experiments suggested the 15 occurrence of Rh(III) species in the C-H activation stage, 16 and that the ethylhexanoate and sulfate could jointly 17 suppress the catalyst deactivation. 18

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- http://dx.doi.org/10.1246/cl.\*\*\*\*\*. 25

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