## **ORGANOMETALLICS**

# Palladium-Catalyzed Dearomative Arylvinylation Reaction of Indoles with *N*-Arylsulfonylhydrazones

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**S** Supporting Information

**ABSTRACT:** A Pd-catalyzed dearomative arylvinylation reaction of indoles with *N*-arylsulfonylhydrazones as coupling partners is developed, which proceeds via a domino sequence involving dearomative carbopalladation, Pd-carbene migratory insertion, and regioselective  $\beta$ -hydride elimination. A range of 3vinylindolines bearing vicinal quaternary and tertiary carbon stereocenters is achieved in moderate yields. The enantiose-



lective reaction was established by using a chiral BINOL-based phosphoramidite ligand, which led to the arylvinylation products in good enantiomeric ratios and excellent diastereoselectivities.

iazo compounds or N-arylsulfonylhydrazones are important coupling partners, used as carbene precursors in palladium-catalyzed cross-coupling reactions since the important contributions made by the groups of Van Vranken, Barluenga, and Wang.<sup>1–3</sup> Through a sequential palladiumcarbene migratory insertion followed by  $\beta$ -hydride elimination, a series of coupling reactions between diazo compounds or Narylsulfonylhydrazones with benzyl/allyl halides,<sup>4</sup> aryl halides,<sup>5</sup> and terminal alkynes<sup>6</sup> has been developed and offers powerful approaches to olefin derivatives. Furthermore, Gu, Wang, and Jiang<sup>9</sup> realized efficient domino coupling reactions of aryl halides and olefins with diazo compounds or N-arylsulfonylhydrazones, leading to olefin difunctionalization via carbopalladation followed by the coupling of alkyl-Pd species with the carbene intermediate (Scheme 1a). Despite these significant advances, no asymmetric variant of such domino coupling reactions has been developed to achieve enantioselective olefin difunctionalization. Moreover, it is highly desirable to utilize

### Scheme 1. Pd-Catalyzed Arylvinylation Reactions of Alkenes and Indoles



these domino reactions for synthesizing structurally complex molecules.

The recent transition-metal-catalyzed catalytic asymmetric dearomatization (CADA) of aromatic compounds represents an important strategy to access optically active alicyclic compounds.<sup>10</sup> In this context, Lautens, Liang, and our group have developed a number of domino dearomative Heck/ anionic capture sequences on the basis of a dearomative Heck reaction.<sup>11,12</sup> Various 2,3-disubstituted indoline derivatives were achieved by the dearomative difunctionalization of indoles, which included Heck/cyanation,<sup>13</sup> Heck/Suzuki,<sup>14</sup> Heck/Sonogashira,<sup>15</sup> and Heck/borylation<sup>16</sup> domino coupling reactions. Nevertheless, the enantiocontrol of such reactions still remains difficult and further development of dearomative difunctionalization reaction is in high demand. Inspired by previous success in the coupling reaction with a carbene intermediate, we conceived that a dearomative arylvinylation reaction of indoles might be realized via a Heck arylation followed by coupling of the generated alkyl-Pd species with Narylsulfonylhydrazones. Herein, we present the primary results. The reaction efficiently furnished a range of 2,3-disubstituted indolines, in which  $\beta$ -hydride elimination of the resulting organopalladium intermediate regioselectively occurred to form a 3-vinylated carbon stereocenter. Additionally, an enantioselective domino reaction has been established, leading to the arylvinylation products in good enantiomeric ratios and

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excellent diastereoselectivities by using a BINOL-based phosphoramidite chiral ligand (Scheme 1b).

We commenced our research by using *N*-o-iodobenzoyl indole 1a and *N*-tosylhydrazone 2a (PMP = 4-methoxyphenyl) as the model substrates. Optimization of the reaction conditions is summarized in Table 1. An initial test led to

Table 1. Optimization of the Reaction Conditions<sup>a</sup>

		PMP		
	Ph	NNHTs Poor	(OAc) <sub>2</sub> /L	Ph
Ŷ	+ PM	P Me Solve	ent. 100 °C	
	°	2a	,	$\mathbf{Y}$
1a, X = I; 1a', X = Br 3a				
entry	L	base	solvent	yield <sup>b</sup> /%
1	dppf	K <sub>2</sub> CO <sub>3</sub>	MeCN	26
2	dppf	K <sub>2</sub> CO <sub>3</sub>	toluene	25
3	dppf	K <sub>2</sub> CO <sub>3</sub>	THF	27
4	dppf	K <sub>2</sub> CO <sub>3</sub>	1,4-dioxane	42
5	dppf	K <sub>2</sub> CO <sub>3</sub>	DMF	30
6	dppf	KO <sup>t</sup> Bu	1,4-dioxane	ND
7	dppf	$Cs_2CO_3$	1,4-dioxane	43
8	dppf	K <sub>3</sub> PO <sub>4</sub>	1,4-dioxane	46
9	XantPhos	K <sub>3</sub> PO <sub>4</sub>	1,4-dioxane	36
10	dppe	K <sub>3</sub> PO <sub>4</sub>	1,4-dioxane	33
11	dppb	K <sub>3</sub> PO <sub>4</sub>	1,4-dioxane	40
12	PPh <sub>3</sub>	K <sub>3</sub> PO <sub>4</sub>	1,4-dioxane	37
13	<sup>t</sup> Bu <sub>3</sub> P·HBF <sub>4</sub>	K <sub>3</sub> PO <sub>4</sub>	1,4-dioxane	18
14	RuPhos	K <sub>3</sub> PO <sub>4</sub>	1,4-dioxane	28
15	dppf	K <sub>3</sub> PO <sub>4</sub>	1,4-dioxane	36
16 <sup>c</sup>	dppf	K <sub>3</sub> PO <sub>4</sub>	1,4-dioxane	39
17 <sup>d</sup>	dppf	K <sub>3</sub> PO <sub>4</sub>	1,4-dioxane	34
18 <sup>e</sup>	dppf	K <sub>3</sub> PO <sub>4</sub>	1,4-dioxane	19
19 <sup>f</sup>	dppf	K <sub>3</sub> PO <sub>4</sub>	1,4-dioxane	63 (61)

<sup>*a*</sup>Reaction conditions unless stated otherwise: **1a** (0.2 mmol), **2a** (0.3 mmol), Pd(OAc)<sub>2</sub> (5 mol %), L (6 mol % for diphosphine ligand, 10 mol % for monophosphine ligand), and base (3.0 equiv) in 2.0 mL solvent at 100 °C for 2 h; X = Br for entry 15 and X = I for others. <sup>*b*</sup>NMR yields using CH<sub>2</sub>Br<sub>2</sub> as internal standard; the isolated yield is given in parentheses. <sup>*c*</sup>2.0 equiv of H<sub>2</sub>O was added. <sup>*d*</sup>100 mg of 4 Å molecular sieves was added. <sup>*e*</sup>**1a** (0.3 mmol), **2a** (0.2 mmol). <sup>*f*</sup>Pd(OAc)<sub>2</sub> (10 mol %), dppf (12 mol %).

the target product 3a as a single isomer in 26% NMR yield in the presence of 5 mol % of  $Pd(OAc)_2$ , 6 mol % of dppf, and 3.0 equiv of  $K_2CO_3$  in MeCN at 100 °C for 2 h (Table 1, entry 1). Solvent examination showed that an improved yield (42%)of 3a was detected in 1,4-dioxane, while lower yields were achieved in toluene, THF, and DMF (Table 1, entries 2-5). Changing the base to Cs<sub>2</sub>CO<sub>3</sub> or K<sub>3</sub>PO<sub>4</sub> resulted in a slightly improved yield, but in the case of KO<sup>t</sup>Bu no product was detected (Table 1, entries 6-8). Other ligands were then investigated to improve the reactivity; however, all of the tested phosphine ligands, including diphosphines (XantPhos, dppe, dppb) and monophosphines (PPh<sub>3</sub>, P<sup>t</sup>Bu<sub>3</sub> and RuPhos), failed to improve the yields (Table 1, entries 9-14). As a comparison, a lower yield was obtained for the reaction of the bromo substrate 1a' (Table 1, entry 15). The addition of 2.0 equiv of water or 4 Å molecular sieves to the reaction mixture was ineffective in improving the yield (Table 1, entries 16 and 17). In addition, the product yield dropped to 19% on modifying the equivalent ratio of 1a to 2a to 1.5:1.0 (Table 1,

entry 18). Finally, the isolated yield was improved to 61% by increasing the catalyst loading (Table 1, entry 19).

Under the conditions established above, we explored the substrate scope of this domino dearomative arylvinylation reaction of indoles with *N*-tosylhydrazones. As shown in Scheme 2, a series of indoles 1 and *N*-tosylhydrazones 2 were

Scheme 2. Substrate Scope and Synthetic Transformations<sup>a</sup>



<sup>*a*</sup>Reaction conditions unless stated otherwise: 1 (0.2 mmol), 2 (0.3 mmol), Pd(OAc)<sub>2</sub> (10 mol %), dppf (12 mol %), and  $K_3PO_4$  (0.6 mmol) in 1,4-dioxane (2.0 mL) at 100 °C for 2 h; isolated yield; dr >20:1. <sup>*b*</sup>Reaction conditions: **3a** (0.2 mmol), LiAlH<sub>4</sub> (5 equiv) in THF at 90 °C for 5 h. <sup>c</sup>Reaction conditions: (i) **3a** (0.2 mmol) under an atmosphere of O<sub>3</sub> in DCM/MeOH (1/1 v/v) at -78 °C for 0.5 h; (ii) PPh<sub>3</sub> (4 equiv), 3 h at room temperature.

examined in the reaction. Substituent groups, including Me, MeO, F, and Cl, attached on the benzene ring of the 2iodobenzoyl moiety were compatible with the reaction, which led to the desired products 3b-g in 43-61% yields. Steric effects were not observed, as a satisfactory yield was obtained for product 3g bearing a methyl group ortho to the iodine atom. The substituent effect on the indole ring was then examined. Indoles bearing different aryl groups at C2 reacted smoothly with N-tosylhydrazone 2a to give products 3h-l in 46-63% yields. A methyl group at C2 of the indole ring was also tested, and products 3m,p-s were obtained in moderate yields. In addition, substituents F and Me at C5 of indole were also compatible, which yielded products 3n,o in 45% and 57% yields, respectively. A variety of acetophenone-derived Ntosylhydrazones 2 were then investigated in reactions with indole 1a, affording the corresponding indolines 3t-y in 50-67% yields under the standard conditions. Synthetic transformations of product 3a were then conducted. Reduction of 3a with LiAlH<sub>4</sub> in THF gave amine 4 in 89% yield. Oxidative cleavage of the C=C bond of 3a led to ketone 5 in 72% yield with ozone  $(O_3)$  as an oxidant.

An enantioselective variant of the above domino dearomative arylvinylation reaction was then studied (Scheme 3). Through an extensive examination of chiral ligands (see the

#### Scheme 3. Enantioselective Variant<sup>a</sup>



<sup>a</sup>Reaction conditions: 1 (0.2 mmol), 6 (0.3 mmol), Pd(OAc)<sub>2</sub> (10 mol %), (R)-L1 (24 mol %), and  $K_3PO_4$  (3.0 equiv) in 1,4-dioxane (2.0 mL) at 80 °C for 12 h; isolated yield; dr >20:1; ee values were determined by chiral HPLC analysis.

Supporting Information for ligand tests), the BINOL-based phosphoramidite L1 proved to be a promising chiral ligand in this dearomative arylvinylation reaction, which furnished optically active 3a in 54% yield with 72% ee at 100 °C. Other ligands, including TADOL-based chiral phosphoramidites, PHOX, and BINAP, resulted in lower enantioselectivities. Gratifyingly, the use of (2,4,6-triisopropylphenyl)sulfonylhydrazone 6a instead of 2a as a coupling partner improved the product yield to 64% and the ee to 79% at 80 °C. Therefore, a few other substrates were investigated, which produced the corresponding indolines 3d,h,n,o,t in comparable ee values with yields ranging from 50% to 68%. The ee value of 3a was improved to 98% by a recrystallization in 64% yield, and a single crystal was then obtained in pentane/CH<sub>2</sub>Cl<sub>2</sub>. The absolute configuration of 3a was determined to be 10S,11S by the X-ray diffraction analysis (see the Supporting Information and CCDC 1912078).

In summary, we have developed a palladium-catalyzed dearomative arylvinylation of indoles by employing *N*-arylsulfonylhydrazones as coupling partners. This sequential coupling reaction proceeded via the intramolecular dearomative carbopalladation of indole, palladium-carbene migratory insertion, and subsequent regioselective  $\beta$ -hydride elimination. A variety of 3-vinylated indolines bearing vicinal quaternary and tertiary carbon centers was achieved in moderate yields. The enantioselective variant was explored, giving the products in good enantiomeric ratios with a BINOL-based chiral phosphoramidite ligand.

#### ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organo-met.9b00112.

Experimental details and characterization data of the products (PDF)

#### Accession Codes

CCDC 1912078 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data\_request/cif, or by emailing data\_request@ccdc.cam.ac.uk, or by contacting The Cam-

bridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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#### Notes

The authors declare no competing financial interest.

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