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# COMMUNICATION

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## Palladium-Catalyzed [5+1] Annulation of 2-(1-Arylvinyl) Anilines and α-Diazocarbonyl Compounds toward Multifunctionalized Quinolines

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Abstract: A palladium-catalyzed [5+1] annulation of 2-(1-arylvinyl) anilines and  $\alpha$ -diazocarbonyl compounds has been developed, affording a series of multi-functionalized quinolines in moderate to good yields. This procedure proceeded with the sequential insertion of N-H bond to the palladium carbene, intramolecular Heck reaction and decarboxylation steps. In this reaction, alkyl 2diazophenylacetates served as C1 building block, which represents a key compliment to diazo chemistry.

**keywords:** palladium-catalyzed; annulation; αdiazocarbonyl compounds; 2,4-aryl quinolines

α-Diazocarbonyl compounds have been extensively considered metal as carbene precursors in [n+2] cyclizative annulation toward heterocyclic compounds, where they served as C2 subunits (Scheme 1, eq 1).<sup>[1]</sup> Meanwhile,  $\alpha$ diazocarbonyl compounds were widely applicable in the insertion reaction to X-H (X = OR, SR, NHR,  $SiH_2R$ ) bonds (Scheme 1, eq 3).<sup>[2]</sup> We believe the further transformation of metal species after the insertion of metal carbenes to X-H bonds would be beneficial to construct the final products with diversities (Scheme 1, eq 4).<sup>[3]</sup>

With this regard, herein, we wish to report a [5+1] procedure proceeding with the sequential insertion of N-H bonds to the palladium carbenes derived from  $\alpha$ -diazocarbonyl compounds,<sup>[4]</sup> intramolecular Heck reaction and decarboxylation steps toward multi-functionalized quinolones (Scheme 1, eq 2). Notably, during this transformation,  $\alpha$ -diazocarbonyl compounds served as C1 subunits in the cyclization rather than C2 building blocks, which represents a key compliment to diazo chemistry.<sup>[5]</sup> The annulated product 2,4-disubstituted quinoline is one of the ubiquitous structural motifs with important biological

activities and potential pharmaceutical applications.<sup>[6]</sup> Besides the traditional methods to access such frameworks,<sup>[7]</sup> the development of new transformation starting from new reaction partners remains an active research area.

**Scheme 1.** Some Typical Reactions Involving α-Diazocarbonyl Compounds.



Initially, we test the reaction of 2-(1phenylvinyl)aniline **1a** (0.2 mmol), ethyl 2-diazo-2phenylacetate **2a** (0.4 mmol) in the presence of PdCl<sub>2</sub> (10 mol%), DTBP or K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (0.4 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.6 mmol) in diglyme under N<sub>2</sub> at 150 °C. However, only trace of the desired product was detected (Table 1, entries 1 and 2). Screening other oxidants revealed that O<sub>2</sub> gave the best result (35%, Table 1, entry 3). Replacing diglyme with DMSO or DMF increased the yield to 62% and 65%, respectively (Table 1, entries 4 and 5).To our delight, the reaction efficiency increased to 68% by using DMAc as the solvent (Table 1, entry 6). Other palladium salts such as  $Pd(OAc)_2$  (48%) and  $Pd_2(dba)_3$  (43%) were inferior to  $PdCl_2$  (Table 1, entries 7 and 8). Among the bases tested, such as KO'Bu (< 5%), DBU (10%), and Et<sub>3</sub>N (< 5%) were all inferior to K<sub>2</sub>CO<sub>3</sub> (Table 1, entries 9-11). The reaction efficiency decreased under lower temperature (Table 1, entry 12). Finally, the blank reaction revealed that the reaction did not work without PdCl<sub>2</sub>, O<sub>2</sub> or K<sub>2</sub>CO<sub>3</sub> (Table 1, entry 8, 11-12).

**Table 1.** Screening the optimized reaction condition.<sup>[a]</sup>

Ph

NH <sub>2</sub>	Ph +	N <sub>2</sub> COOEt	condi	tions <b>&gt;</b>	N Ph
1a		2a			3a
Entry	Pd	Oxidant	Base	Solvent	Yield(%) <sup>[a]</sup>
1	PdCl <sub>2</sub>	DTBP	$K_2CO_3$	diglyme	< 5
2	PdCl <sub>2</sub>	$K_2S_2O_8$	$K_2CO_3$	diglyme	< 5
3	PdCl <sub>2</sub>	$O_2$	$K_2CO_3$	diglyme	35
4	PdCl <sub>2</sub>	$O_2$	$K_2CO_3$	DMSO	62
5	PdCl <sub>2</sub>	$O_2$	$K_2CO_3$	DMF	65
6	PdCl <sub>2</sub>	$O_2$	$K_2CO_3$	DMAc	68
7	Pd(OAc) <sub>2</sub>	$O_2$	$K_2CO_3$	DMAc	48
8	Pd <sub>2</sub> dba <sub>3</sub>	$O_2$	$K_2CO_3$	DMAc	43
9	PdCl <sub>2</sub>	$O_2$	KO'Bu	DMAc	< 5
10	PdCl <sub>2</sub>	$O_2$	DBU	DMAc	10
11	PdCl <sub>2</sub>	$O_2$	Et <sub>3</sub> N	DMAc	< 5
12	PdCl <sub>2</sub>	$O_2$	$K_2CO_3$	DMAc	58 <sup>[c]</sup> , 65 <sup>[d]</sup>
13	PdCl <sub>2</sub>	$O_2$	K <sub>2</sub> CO <sub>3</sub>	DMAc	0 <sup>[e]</sup>

<sup>[a]</sup> Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), [Pd] (10 mol%), base (0.6 mmol), solvent (3.0 mL), O<sub>2</sub> (1 atm), at 150 °C for 24 h <sup>[b]</sup> Isolated yield. <sup>[c]</sup> 120 °C. <sup>[d]</sup> 140 °C. <sup>[e]</sup> In the absence of either PdCl<sub>2</sub>, O<sub>2</sub>, or K<sub>2</sub>CO<sub>3</sub>. DMSO = dimethylsulfoxide. DMF = N,N-dimethylforamide. DMAc = dimethylacetamide. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

With the optimized reaction conditions in hand, the scope and limitation of 2-(1-arylvinyl) anilines were studied (Table 2). First, substrates with substitutions on the aniline moiety were tested. Generally, the reaction efficiency was not sensitive to the electronic property of the groups on the anilines as substrates bearing both electron-donating (3b-3d, 63-73%) and electron-withdrawing groups (3e-3f, 62%-68%) all worked well to deliver the desired products in moderate to good yields. The substrates possessing substitutents at ortho- and meta- positions also worked well, leading to corresponding 2,4diarylquinoline derivatives in 53% (3g) and 64% (3h) yields. To our delight, 2-(1-phenylvinyl)naphthalen-1amine also ran smoothly under the standard conditions to afford the desired products 3s in 62% yield. Secondly, substrates with substituted aryl on the alkene moiety were also tested. Substrates with electron-donating groups on the aryl attached in the vinyl (3k, 3l, 3n and 3o, 48-72%) showed similar reactivity with those analogues possessing electronwithdrawing groups (30 and 3m, 52% and 54%). Moreover, the steric hindrance did not hamper the reaction, as **3n** and **3p** were isolated in 72% and 52% vields, respectively. Notably, 2-(1methylethenyl)aniline took part in the reaction, providing 3t in 48% yield. Moreover, this procedure was not limited to terminal alkene, and 2 - [(1E) - 1 - 1]phenyl-1-propen-1-yl]benzenamine took part in this transformation, providing 3-methyl-2,4diphenylquinoline 3r in 78% yield.





<sup>[a]</sup> Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), PdCl<sub>2</sub> (0.02 mmol, 3.4 mg),  $K_2CO_3$  (0.6 mmol, 82.9 mg), DMAc (3.0 mL), O<sub>2</sub> (1 atm), at 150 °C for 24 h, in a sealed Schlenk tube.

Next, the scope and limitation of  $\alpha$ -diazocarbonyl compounds were also investigated. As shown in Scheme 2, the substrates bearing both electron-donating and electron-withdrawing groups all worked well to deliver the desired products in moderate to good yields (**3u-3x**, 61%-68%). Notably, the hindrance in aryl in  $\alpha$ -diazocarbonl compounds had almost no effect on the reaction efficiency (**3x**, 58%). Moreover, methyl- (67%), ethyl- (68%) and benzyl-

(67%) 2-diazophenylacetates provided comparable yields.

Scheme 2. Scope of α-diazocarbonyl compounds [a]



<sup>[a]</sup> Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), PdCl<sub>2</sub> (0.02 mmol, 3.4 mg),  $K_2CO_3$  (0.6 mmol, 82.9 mg), DMAc (3.0 mL),  $O_2$  (1 atm), at 150 °C for 24 h, in a sealed Schlenk tube.

The practicability of this transformation was further increased as 3a was isolated in an acceptable 67% yield in a 1 mmol scale reaction.

Some control experiments were conducted to get insights into this transformation. The potential intermediates **B** and **E** were detected under the standard procedure (Scheme 3, eq 1) and all could transform into the final product in comparable yields (Scheme 3, eqs 2 and 3). Although the isolation of **G** failed, intermediate **G** was detected by GC-MS too.



Scheme 3. Preliminary mechanism study.

Based on these experimental results, a proposed mechanism was outlined in Scheme 4. First, in the presence of Pd(II), after the extrusion of N<sub>2</sub>, palladium carbene **A** is formed. Then, the insertion of N-H to palladium carbene **A** produces intermediate **B**, along with PdCl<sub>2</sub>. Second, in the presence of base and PdCl<sub>2</sub>, after the  $\alpha$ -deprotonation of intermediate **B**  produces the Pd(II) species **C**. After that, an intramolecular Heck reaction takes place leading to intermediate **D**. Then the procedure proceeds with  $\beta$ -H elimination leading to intermediate **E**, along with HPdCl species, which enter the catalytic cycle by sequential reductive elimination to Pd(0) and oxidation by O<sub>2</sub>.<sup>[8]</sup> Third, the hydrolization of **E** produces intermediate **F**, which loses CO<sub>2</sub> toward intermediate **G**. Finally, the aromatization of **E** affords the final product **3**.

PdCL





Pď

PdC1

EtO<sub>2</sub>O

[0]

CO,

G

EtO<sub>2</sub>O

In conclusion, we have developed a palladiumcatalyzed annulation of 2-(1-arylvinyl) anilines with commercially available  $\alpha$ -diazocarbonyl compounds, affording a series of multi-functionalized quinolones in moderate to good yields. This procedure proceeds with the sequential insertion of N-H bonds to the palladium carbenes, intramolecular Heck reaction and decarboxylation steps.  $\alpha$ -Diazocarbonyl compounds served as C1 building blocks for the construction of multi-functionalized quinolones, representing a key compliment to the diazo chemistry.

### **Experimental Section**

**Experimental Details** 

#### Synthesis of Multi-functionalized Quinolines

Under oxygen, a 20 mL Schlenk tube equipped with a stir bar was charged with 2-(1-substituted vinyl) anilines (0.2 mmol), aryldiazo esters (0.4 mmol), PdCl<sub>2</sub> (0.02 mmol), K<sub>2</sub>CO<sub>3</sub> (0.6 mmol), DMAc (3 mL). The tube was sealed with a Teflon lined cap. The reaction mixture was stirred at 150 °C for 24 h in oil bath. After the completion of the reaction, the solvent was concentrated in vacuum and the residue was purified by flash column chromatography on silica gel with petroleum ether-EtOAc (V1/V2 = 50:1) as the eluent to give the desired product.

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