

**A FACILE AND DIRECT SYNTHESIS OF ISOQUINOLONE DERIVATIVES  
FROM ALLENES: INTRAMOLECULAR CARBOPALLADATION OF  
ALLENES FOLLOWED BY AMIDATIONS**

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**Abstract**—A new efficient synthesis of isoquinolone skeletons by nucleophilic substitution through intramolecular carbopalladation with the assistance of a catalytic amount of  $\text{Pd}(\text{OAc})_2$  was developed. Palladium-catalyzed cyclization of (*o*-iodobenzamidoalkyl)allene compounds afforded the corresponding isoquinolone derivatives in good yields.

The transition metal-mediated addition of anionic species to carbon-carbon double bonds, activated or not, is now a precedented process of great interest in organic synthesis.<sup>1</sup> In this respect, activated methylenes and methines have been described to add to different kinds of unsaturated systems.<sup>2</sup> Of peculiar mention were the nickel or palladium-catalyzed additions of activated methylenes to conjugated dienes which have often been thought to occur via a  $\pi$ -allylic intermediate.<sup>3-6</sup>

Palladium-catalyzed reactions of allenes with iodobenzene and nucleophiles afforded products by  $\alpha$ ,  $\beta$ -functionalization of the allenes.<sup>7,8</sup> The palladium-catalyzed reactions of allenes with 2-iodobenzylamine or (2-iodobenzyl)malonate effected carbopalladation of the allenes followed by intramolecular nucleophilic substitutions to give cyclized products, isoquinoline or tetraline derivatives. Previously, we reported the stereospecificity of the reactions with chiral allenes<sup>9</sup> and also palladium-catalyzed asymmetric  $\alpha$ ,  $\beta$ -functionalization of allenes with chiral phosphine ligands.<sup>10</sup> Unfortunately, the palladium-catalyzed cyclization reactions of the allene with 2-iodobenzylamine group did not lead into the smooth formation of isoquinoline skeleton (1). However, the similar reactions of allenes with 2-iodobenzamide successfully occurred

in the presence of base to give isoquinolone derivatives.<sup>11</sup>

We wish to communicate herein a novel and facile synthesis of tricyclic isoquinolone compounds by palladium-catalyzed reactions of (2-iodobenzamido)alkylallenyyl compounds using the amide functions as the nucleophiles, which presents a new entry to isoquinolone derivatives (**2**) shown below (Figure 1).

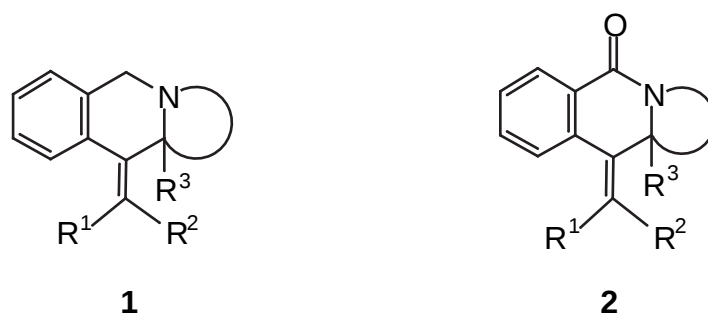
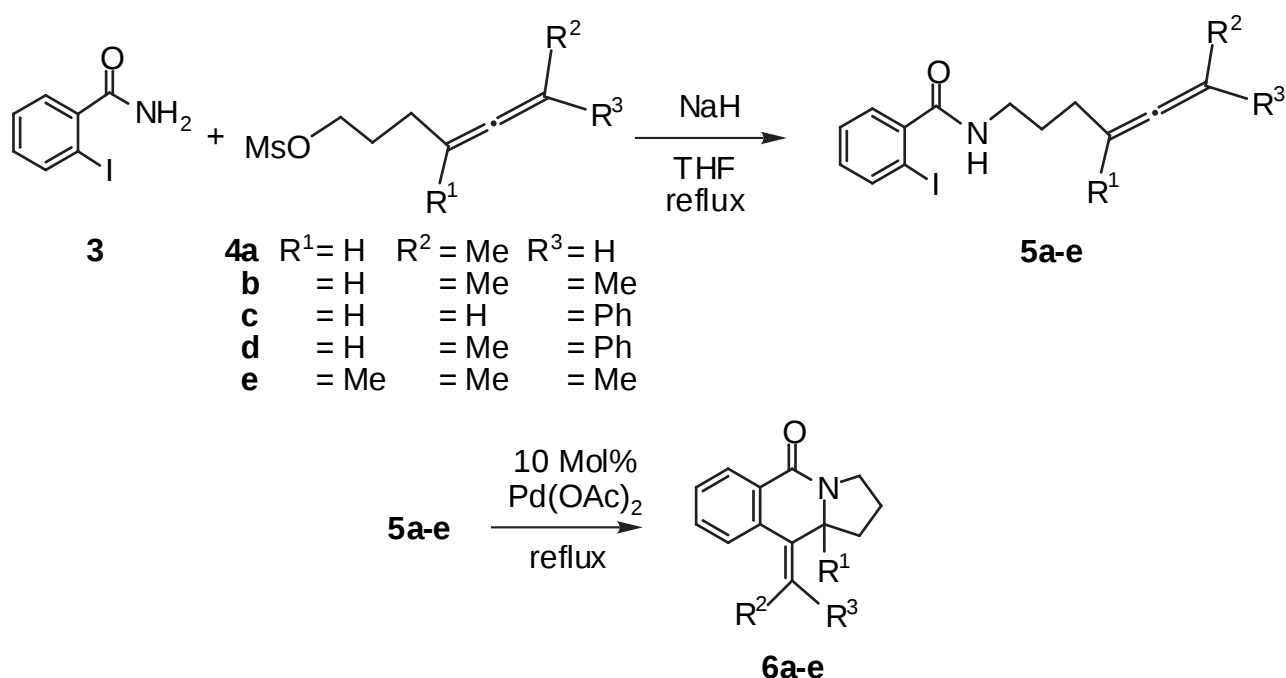


Figure 1

Allenyl substrates were obtained starting from 1,4-butanediol. *N*-Alkylation of 2-iodobenzamide (**3**) with **4a-e** was carried out in THF at reflux using sodium hydride (NaH) as a base to give allenyl substrates (**5a-e**).



Scheme 1

The palladium-catalyzed reactions of allenes (**5a-e**) were carried out at reflux in THF, MeCN, DME or toluene in the presence of a palladium catalyst,  $\text{Pd(dba)}_2$  or  $\text{Pd(OAc)}_2$  (0.1 equiv.), phosphine ligand (0.2 equiv.), and NaH (1.5 equiv.) to furnish cyclized isoquinolone products

(**6a-e**) in good yields. The results are summarized in Table 1.

The reactions of **5a** with Pd(dba)<sub>2</sub>-dppf in refluxing DME resulted in a lower yield (<20 %) of **6a** than those with Pd(OAc)<sub>2</sub>. Use of K<sub>2</sub>CO<sub>3</sub> and Et<sub>3</sub>N as a base instead of NaH in the reaction of **5a** gave **6a** in lower yield (<5 %). The reaction without NaH gave no product. Use of NaH as a base was crucial to achieve the cyclization smoothly. Use of DME as solvent for each reaction of **5a-e** provided higher yields of the products as listed in Table 1.

Table 1. The Palladium-Catalyzed Reactions of Allenes (**5a-e**)<sup>a)</sup>

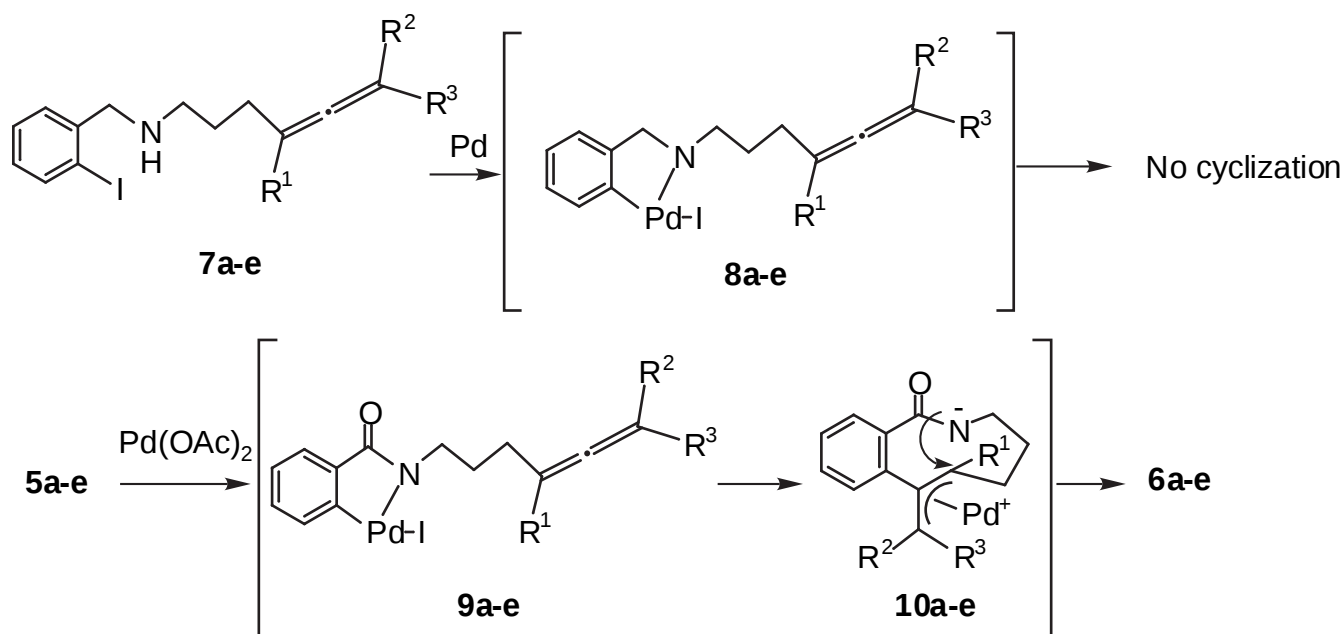
| Entry | Substrate | Ligand           | Solvent            | Product yield (%)<br>(Product) |
|-------|-----------|------------------|--------------------|--------------------------------|
| 1     | <b>5a</b> | PPh <sub>3</sub> | DME                | 23 ( <b>6a</b> )               |
| 2     | <b>5a</b> | dppm             | DME                | 62 ( <b>6a</b> )               |
| 3     | <b>5a</b> | dppe             | DME                | 68 ( <b>6a</b> )               |
| 4     | <b>5a</b> | dpppen           | DME                | 31 ( <b>6a</b> )               |
| 5     | <b>5a</b> | dppf             | DME                | 93 ( <b>6a</b> )               |
| 6     | <b>5a</b> | dppf             | THF                | 0 ( <b>6a</b> )                |
| 7     | <b>5a</b> | dppf             | CH <sub>3</sub> CN | 71 ( <b>6a</b> )               |
| 8     | <b>5a</b> | dppf             | Toluene            | 21 ( <b>6a</b> )               |
| 9     | <b>5b</b> | dppe             | DME                | 74 ( <b>6b</b> )               |
| 10    | <b>5b</b> | dppf             | DME                | 91 ( <b>6b</b> )               |
| 11    | <b>5b</b> | dppf             | CH <sub>3</sub> CN | 63 ( <b>6b</b> )               |
| 12    | <b>5c</b> | dppf             | DME                | 70 ( <b>6c</b> )               |
| 13    | <b>5d</b> | dppf             | DME                | 82 ( <b>6d</b> )               |
| 14    | <b>5e</b> | dppf             | DME                | 99 ( <b>6e</b> )               |

a) The reactions of **5a-e** were carried out at reflux for 48 h in the presence of Pd(OAc)<sub>2</sub> (0.1 equiv.), ligand (0.2 equiv.) and NaH (1.5 equiv.).

The effects of phosphine ligands in the palladium-catalyzed reaction of **5a-e** were examined using PPh<sub>3</sub>, bis(diphenylphosphino)methane (dppm), 1,2-bis(diphenylphosphino)ethane (dppe), 1,5-bis(diphenylphosphino)pentane (dpppen), or 1,1'-bis(diphenylphosphino)ferrocene (dppf). As listed in Table 1, almost quantitative yields of **6a,b** and **e** were obtained with dppf. The palladium-catalyzed reaction of **5a** in refluxing DME provided the corresponding isoquinolone compound in high yield (93 %). The highest yield (99 %) was obtained by the palladium-catalyzed reaction of **5e** on the use of dppf as a ligand.

Conclusively, the highest yields of **6a,b** and **e** were obtained by the reactions of **5 a,b** and **e** using Pd(OAc)<sub>2</sub> (0.1 equiv.) and dppf (0.2 equiv.) at reflux in DME in the presence of NaH (1.5 equiv.).

The reactions are rationalized as follows. The intramolecular carbopalladation at the central carbon of the allenes (**7a-e**) did not provide any isoquinoline skeletons, because of the formation of the stable five membered amino-palladium intermediates (**8a-e**) due to the high basicity of the benzylamine moiety. On the other hand, the palladium-catalyzed reactions of the allenes (**5a-e**) affords the corresponding  $\pi$ -allylpalladium intermediates (**10a-e**) via rather reactive five-membered amide-palladium complexes (**9a-e**), which undergo intramolecular amidation at the allylic sites as expected, giving isoquinolone compounds (**6a-e**).<sup>12</sup>



Scheme 2

Thus, this method is useful for a novel and facile entry to tricyclic isoquinolone derivatives. We are now under way to develop this methodology for construction of other heterocycles and carbocycles.

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