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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 $Pd(OAc)_2$ 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.[1] In this respect, activated methylenes and methines have been described to add to different kinds of unsaturated systems.[2] 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 π-allylic intermediate.[3-6]

Palladium-catalyzed reactions of allenes with iodobenzene and nucleophiles afforded products by α, β -functionalization of the allenes.[7,8] 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[9] and also palladium-catalyzed asymmetric α, β -functionalization of allenes with chiral phosphine ligands.[10] Unfortunately, the palladium-catalyzed cyclization reactions of the allene with 2-iodobenzylamine group did not lead into the smooth formation of isoquinoline skeletone (**1**). However, the similar reactions of allenes with 2-iodobenzamide successfully occurred

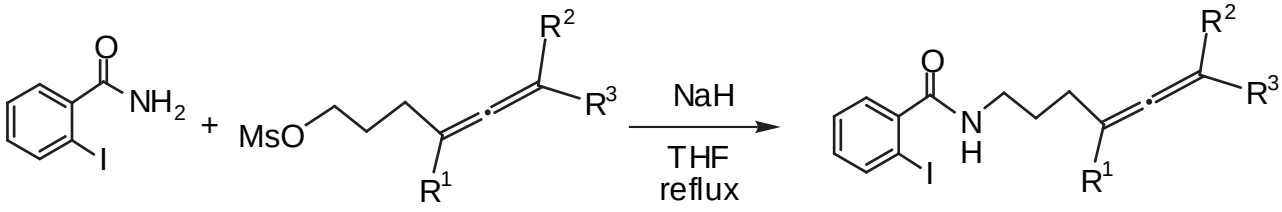
in the presence of base to give isoquinolone derivatives.[11]

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

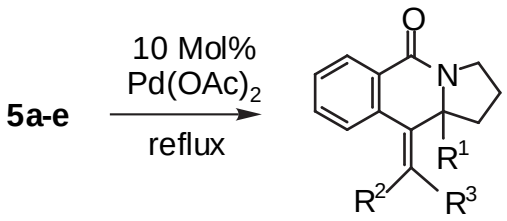
1 **2**

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**).



3 **4a** R^1= H R^2 = Me R^3 = H; **b** = H = Me = Me; **c** = H = H = Ph; **d** = H = Me = Ph; **e** = Me = Me = Me **5a-e**



6a-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, $Pd(dba)_2$ or $Pd(OAc)_2$ (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 $Pd(dba)_2$-dppf in refluxing DME resulted in a lower yield (<20 %) of **6a** than those with $Pd(OAc)_2$. Use of K_2CO_3 and Et_3N 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**)[a)]

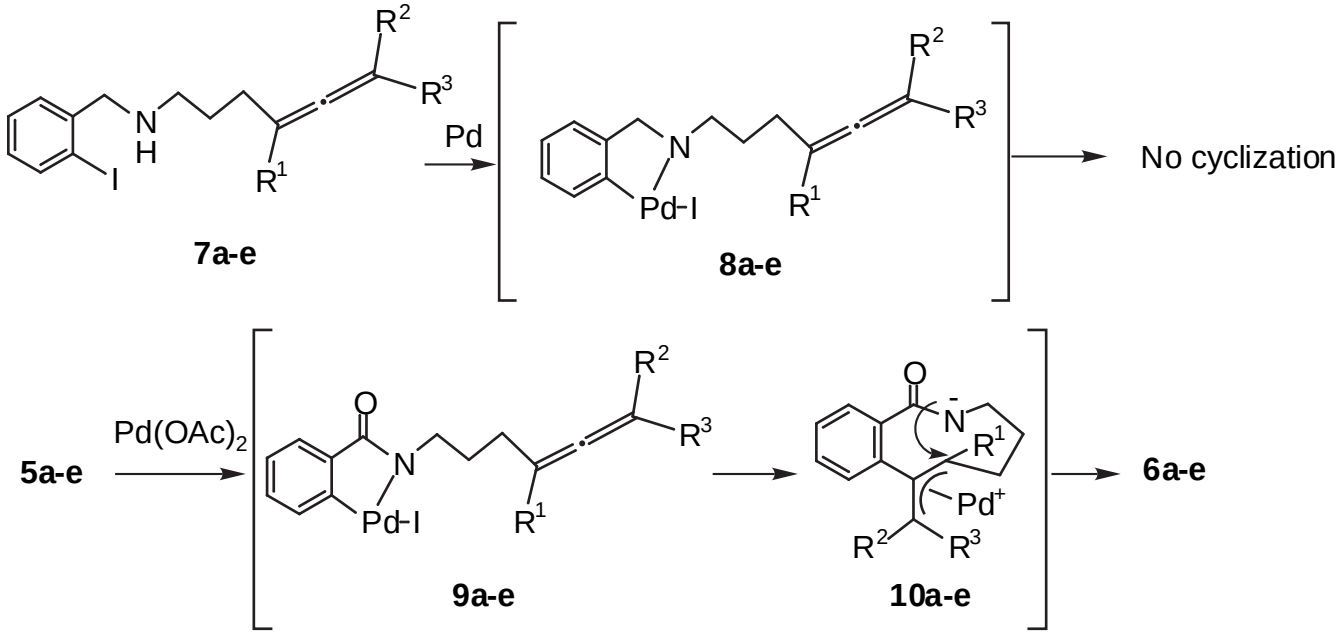
Entry	Substrare	Ligand	Solvent	Product yield (%) (Product)
1	**5a**	PPh_3	DME	23 (**6a**)
2	**5a**	dppm	DME	62 (**6a**)
3	**5a**	dppe	DME	68 (**6a**)
4	**5a**	dpppen	DME	31 (**6a**)
5	**5a**	dppf	DME	93 (**6a**)
6	**5a**	dppf	THF	0 (**6a**)
7	**5a**	dppf	CH_3CN	71 (**6a**)
8	**5a**	dppf	Toluene	21 (**6a**)
9	**5b**	dppe	DME	74 (**6b**)
10	**5b**	dppf	DME	91 (**6b**)
11	**5b**	dppf	CH_3CN	63 (**6b**)
12	**5c**	dppf	DME	70 (**6c**)
13	**5d**	dppf	DME	82 (**6d**)
14	**5e**	dppf	DME	99 (**6e**)

a) The reactions of **5a-e** were carried out at reflux for 48 h in the presence of $Pd(OAc)_2$ (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_3, 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 $Pd(OAc)_2$ (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, becouse 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 π-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**).[12]



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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