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Pd(0)-catalyzed intramolecular Heck reaction: a versatile route for the synthesis of dibenzoazocinone derivatives

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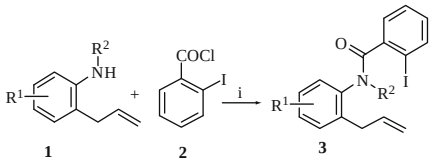
ABSTRACT

Two efficacious synthetic methodologies for the construction of medium-sized nitrogen heterocycles dibenzoazocinones have been developed. The phosphine-assisted protocol afforded better yields of the dibenzoazocinones (73–82%).

The advancement of new efficient synthetic protocols for the basic skeletons of various heterocyclic compounds is a challenging task. Usually, synthesis of bicyclic or tricyclic fused-heterocycles containing nitrogen attached to an aromatic ring (including benzazepine, benzoxazine, benzoxazepine, benzthiazine, and benzthiazepine) is crucial, since these often form the core structures of medicines or clinical candidates.[1] However, there are only few synthetic methods available to prepare eight-membered dibenzoazocinone derivatives. Construction of the basic skeletons is relatively difficult and usually requires lengthy synthetic procedures when conventional methods are employed, such as lactamization and reduction.[2–4] It is well known that a number of important features make reactions involving palladium catalysts and reagents particularly useful and versatile among the transition metals used in organic synthesis. In general, palladium catalysts offer wide scope for the C–C bond formation. The importance of the C–C bond formation in organic synthesis needs no explanation. No other transition metal can offer such versatility of the C–C bond formation as palladium. Moreover, the motivation is that this type of azocine architecture is found in several nitrogen-based natural products of biological interest.[5]

The examples of 8-*endo*-trig cyclizations are rare. However, in certain instances it appears possible that the corresponding eight-membered ring-containing products may also form competitively.[6] For example, Rigby demonstrated[7] that for one substrate class, 7- and 8-*endo*-trig cyclizations occur in preference to their *exo*-counterparts under Jeffery-type conditions.[8] Jeffery's two-phase ligandless conditions involve the addition of more than equimolar amounts of tetraalkylammonium salts as a phase transfer catalyst and solid base without ligands. A large amount of rate enhancement has been observed using Jeffery's conditions. This regiochemical outcome is reversed under more standard conditions. Similarly, Gibson et al. showed[9] that dehydroamino acid-derived substrates, in which the intermediate palladium species resulting from *exo*-carbopalladation are unable to undergo β-hydride elimination, generate reasonable to good yields of the products resulting from *endo*-cyclization. At first sight, these reports appear surprising since, based on a combination of entropic and thermodynamic considerations, the formation of 'medium' ring-containing heterocycles (8–10-membered) remains a synthetic challenge.[10,11]

To this end, we have synthesized different types of Heck precursors for the investigation of intramolecular Heck reactions which



1 2 3

3a, $R^1 = R^2 = H$ **3d**, R^1 = 4-Me, R^2 = Ts
3b, R^1 = H, R^2 = Ts **3e**, R^1 = 4-OMe, R^2 = Ts
3c, R^1 = 2-F, R^2 = Ts **3f**, R^1 = 2-Me, R^2 = Ts

Scheme 1. Reagents and conditions: (i) CH_2Cl_2, DMF–Et_3N, DMAP, 0 °C to rt, 8 h.

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are depicted in Scheme 1. Different *C*-allylanilines **1a–f** were prepared by BF_3-catalyzed aza-Claisen rearrangement in good yields.[12] The reaction of acyl chloride **2** (prepared from 2-iodobenzoic acid with the oxalyl chloride in CH_2Cl_2 in presence of a catalytic amount of DMF) with 2-allylanilines **1a–f** in CH_2Cl_2–Et_3N in presence of a catalytic amount of DMAP at 0 °C to rt for 8 h afforded the amides **3a–f** (Scheme 1).

The first set of experiments was carried out with **3a** as the model substrate under ligand-free conditions. Substrate **3a** was initially allowed to react in dry DMF at 90 °C in the presence of palladium acetate as catalyst, potassium acetate as base, and tetrabutylammonium bromide as phase transfer catalyst[13] in dry DMF under nitrogen atmosphere. No reaction occurred under these conditions and the starting material was recovered unchanged. We then repeated this reaction under phosphine-assisted standard Heck reaction conditions which also ended with no reaction. The reason for the failure may be due to the fact that the palladium catalyst loses its catalytic activity by the formation of the following types of chelate-complexes[14,15] between the palladium metal and the amide carbonyl oxygen atom (Fig. 1).

Therefore, we conducted the Heck reaction with the substrate **3b** under two different reaction conditions. Substrate **3b** was allowed to react with phosphine-free Jeffery's two-phase protocol, that is, $Pd(OAc)_2$/KOAc/TBAB/DMF/90 °C/N_2 conditions and pleasingly the cyclized product **6a** was obtained in 59% yield. When the reaction was performed with the same substrate **3b** using $Pd(OAc)_2$ as catalyst, NaOAc as base, and Ph_3P as ligand in dry DMA at 90 °C for 3.5 h the corresponding *exo*-Heck product **7a** was obtained as the sole product in 82% yield (without TBAB as phase transfer catalyst).[13] Generally, Heck reactions are carried out in the presence of a solid–liquid phase transfer catalyst, namely, TBAB, TBAC, and TBAHS. But, we successfully accomplished the Heck reaction in the absence of any phase transfer catalyst (Scheme 2).

Here it is important to note that substrates containing an unactivated allylic moiety usually undergo intramolecular Heck cyclization to give a mixture of *exo*- and *endo*-Heck products.[16] However, the substrates possessing an activated Michael type of olefinic fragment[9a,17] usually undergo Heck cyclization to afford the corresponding *endo*-Heck, as the sole product. However, the phosphine-free method A is more important than method B.

Between the two eight-membered dibenzoazocinones **6a** and **7a**, compound **7a** possesses *exo*-methylene function in the azocine ring suitable for further functionalization. We therefore, studied the Heck reaction of the substrate **3c** by the application of the aforesaid protocols (phosphine-free and phosphine-assisted). Expectedly, in this case also the azocinones **6b** and **7b** were obtained.

From the results it is clear that the Jeffery's two-phase protocol would be applicable for the construction of the *endo*-cyclic product and the other protocol (phosphine-assisted method B) will be applicable for the synthesis of the exo-cyclic product. Due to further application potential of the exo-cyclic product, we excluded the first method and continued with our newly developed method B.

To find out the optimization conditions of our phosphine-assisted protocol, a series of experiments were conducted where

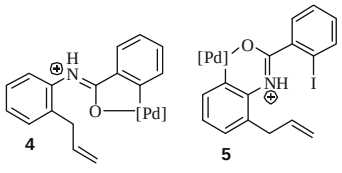
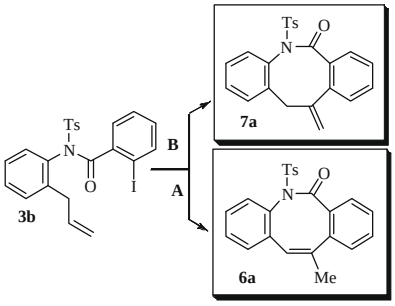
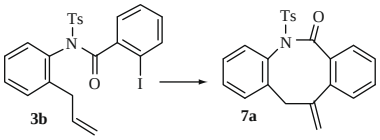


Figure 1. Chelate-complexes.



Scheme 2. Heck reactions of **3b** under phosphine-free and phosphine-assisted conditions: (A) 10 mol % Pd(OAc)2, 2.75 equiv KOAc, 1.2 equiv TBAB, DMF, N2, 59%; (B) 10 mol % Pd(OAc)2, 20 mol % PPh_3, 1.2 equiv NaOAc, DMA, N_2, 82%.

Table 1
Optimization of the Heck reaction[a]



Entries	Catalyst	Solvent	Base	Yields[b] (%)
1	$Pd(OAc)_2$	DMF	KOAc	65
2	$Pd(OAc)_2$	DMA	KOAc	72
3[c]	$Pd(OAc)_2$	DMA	NaOAc	82
4	$Pd(PPh3)_2Cl_2$	DMF	KOAc	24
5	$PdCl_2$	DMF	KOAc	NR[d]
6	$Pd(OAc)_2$	Toluene	KOAc	NR[d]
7	$Pd(OAc)_2$	Et_3N	KOAc	NR[d]
8	$Pd(OAc)_2$	THF	KOAc	32
9	$Pd(OAc)_2$	Dioxane	KOAc	NR[d]
10	$Pd(OAc)_2$	CH_3CN	Et_3N	23
11	$Pd(OAc)_2$	DMF	Ag_2CO_3	NR[d]
12	$Pd(OAc)_2$	DMF	K_2CO_3	NR[d]
13	$Pd(PPh_3)_2Cl_2$	DMA	NaOAc	25
14	$PdCl_2$	DMA	NaOAc	30

[a] All reactions were carried out using 20 mol % PPh_3.
[b] Isolated yield.
[c] Optimized reaction condition.
[d] No reaction.

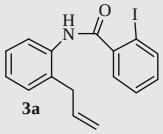
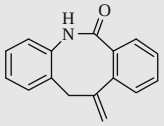
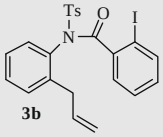
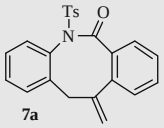
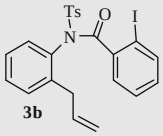
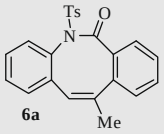
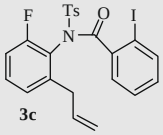
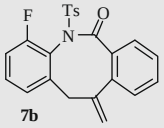
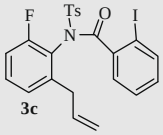
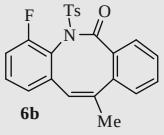
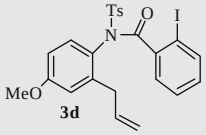
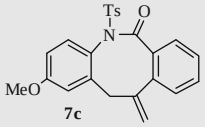
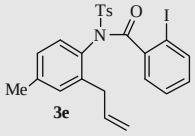
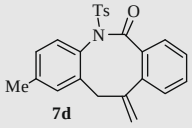
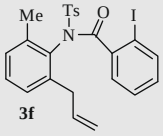
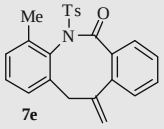
sequential changes were made to the catalyst, base, and solvent (Table 1).

The use of $Pd(PPh_3)_2Cl_2$ as the catalyst was also found to be effective but the yield of the Heck product **7a** was low (24%). We have studied the effect of the base employed and NaOAc was found to be most effective whereas Ag_2CO_3, K_2CO_3, and Et_3N were not suitable. An examination of the influence of various solvents such as DMF, DMA, MeCN, dioxane, toluene, and THF suggested that DMA is the best choice and therefore, the optimized conditions are: 10 mol % $Pd(OAc)_2$/20 mol % PPh_3/1.2 equiv NaOAc/10 mL DMA/90 °C/N_2.

After achieving the optimized conditions, other substrates **3c–f** were similarly treated under the optimized reaction conditions to afford the corresponding *exo*-Heck-cyclized products dibenzoazocinone derivatives **7b–e** in 73–82% yields. The results are summarized in Table 2.

The formation of the products may easily be explained by considering two different modes of the intramolecular Heck reaction. During the course of the intramolecular cyclization by the application of the phosphine-free and phosphine-assisted conditions two different products **6** and **7** are formed. The formation of the product **7** may be explained via the 8-*exo*-trig mode of cyclization and it is quite reasonable due to the less steric demanding environment

Table 2
Synthesis of dibenzoazocinones by Heck reaction

Entry	Starting	Product	Conditions	Yields (%)
1	 **3a**		Method A Method B	0 0
2	 **3b**	 **7a**	Method B	82
3	 **3b**	 **6a**	Method A	59
4	 **3c**	 **7b**	Method B	73
5	 **3c**	 **6b**	Method A	49
6	 **3d**	 **7c**	Method B	82
7	 **3e**	 **7d**	Method B	76
8	 **3f**	 **7e**	Method B	79

and this is also the kinetically-controlled product. But, in case of the product **6**, it is quite difficult to say whether it is actually *endo*-Heck product via 8-*endo*-trig mode of cyclization or *exo*-Heck thermodynamically-controlled double-bond-isomerized product. For the 8-*endo*-trig pathway to operate, the allylic double bond of the substrate **6** would have to be isomerized to afford the *endo*-Heck precursors and under basic conditions this type of migration may be possible.[18] To get more insight into the mechanism we have subjected product **7a** to the reaction under conditions of method A. However, no reaction occurred. As the *exo*-cyclic product **7a** is not convertible to **6a** under the conditions of method A the question of double bond isomerization after the occurrence of *exo*-trig mode of cyclization is ruled out. Therefore, the formation of product **6a** should have occurred with prior double bond isomerization in **3** followed by 8-*endo*-trig mode of cyclization.

In conclusion, we have developed two distinct regioselective synthetic protocols for the construction of the dibenzoazocinone derivatives possessing diversity relevant to drug design and drug discovery. The developed protocols are simple, general, and high yielding.

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