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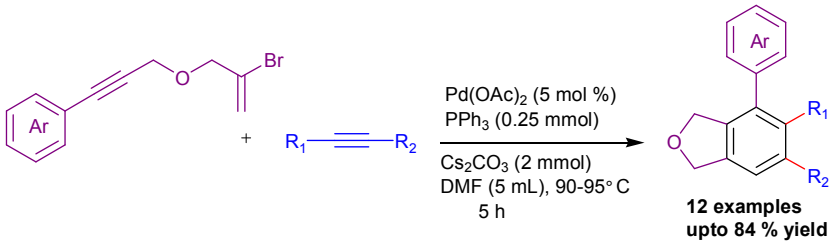
Graphical Abstract

Synthesis of 4,5,6-trisubstituted-1,3-dihydroisobenzofurans by virtue of palladium-catalyzed domino carbopalladation of bromoenynes and internal alkynes

Munmun Ghosh, Raju Singha, Shubhendu Dhara and Jayanta K. Ray*

An efficient hetero-annulation protocol has been developed for the construction of 4,5,6-trisubstituted-1,3-dihydroisobenzofurans *via* palladium-catalyzed domino carbopalladation of bromoenynes and internal alkynes.



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COMMUNICATION

Synthesis of 4,5,6-trisubstituted-1,3-dihydroisobenzofurans by virtue of palladium-catalyzed domino carbopalladation of bromoenynes and internal alkynes

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An efficient hetero-annulation protocol has been developed for the construction of 4,5,6-trisubstituted-1,3-dihydroisobenzofurans *via* palladium-catalyzed domino carbopalladation of bromoenynes and internal alkynes. The reaction followed domino intramolecular Heck cyclization (5-*exo*-*dig*) and termination of the resulting diene with internal alkyne to give highly substituted isobenzofurans in moderate to good yields.

1,3-dihydroisobenzofurans (phthalans) contribute to the family of a considerable number of natural products demonstrating fascinating pharmacological activities including antidepressive, antioxidant, antifungal, antibacterial, antitumor and cardiovascular disease, anti-inflammatory, cytotoxicity against human cancer cell and so on.[1] They are also important in terms of industrial applications[2] and as major building blocks in organic synthesis.[3] Figure 1 represents some selected bioactive phthalans.[1a-g]

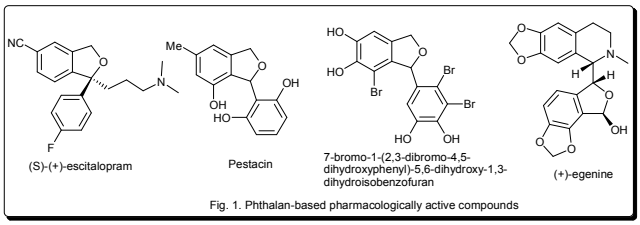


Fig. 1. Phthalan-based pharmacologically active compounds

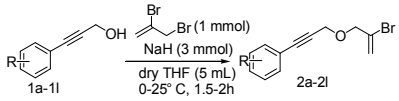
Owing to such versatile pharmacological, industrial as well as synthetic applications, development of efficient and economic methods for the synthesis of phthalans has attracted a number of chemists over the last few decades. A plethora of transition metal catalyzed[4] as well as metal free[5] strategies have been reported for the construction of substituted 1,3-dihydroisobenzofurans.

Cylization of 2-bromo-1,*n*,*m*-enynes and 2-bromo-1,*m*,*n*-dienynes, more particularly, 2-bromo-1,6-enynes *via* sequential cabopalladation leading to the formation of a "living" alkenylpalladium intermediate and consecutive termination of this "living" intermediate *via* further intra- or intermolecular carbopalladation to other double or triple bonds have gained considerable attention of a number of chemists.[6] Following the same strategy, herein we report synthesis of previously unexplored class of highly substituted 1,3-dihydroisobenzofurans from bromoenynes and internal alkynes *via* palladium-catalyzed domino carbopalladation. Although some reports on other metal-catalyzed synthesis of 4,5,7-triphenyl-1,3-dihydroisobenzofurans,[7a-c] 4-methyl-5,6-diphenyl-1,3-dihydroisobenzofurans,[7a] 4,5,6,7-tetraphenyl-1,3-dihydroisobenzofurans[7a,7d] or 4,7-dimethyl-5,6-diphenyl-1,3-dihydroisobenzofurans[7a,7e] are available, no such work has been reported so far for the palladium-catalyzed synthesis of 4,5,6-triphenyl-1,3-dihydroisobenzofurans. Therefore, we targeted to synthesize 4,5,6-triphenyl-1,3-dihydroisobenzofurans using domino carbopalladation (Heck reaction followed by termination) strategy. During the course of the study, we also successfully synthesized 5-hexyl-4,6-diphenyl-1,3-dihydroisobenzofuran along with the other regioisomer.

The Heck precursor [3-(2-Bromo-allyloxy)-prop-1-ynyl]-benzenes (2-bromo-1,6-enynes) **(2a-2l)** were synthesized from the corresponding iodo/bromo-benzenes (1mmol) by Sonogashira coupling with propargyl alcohol (1.2 mmol) using $PdCl_2(PPh_3)_2$ (5 mol %) and CuI (5 mol %) in refluxing Et_3N (6 mL) for 4-5 h (in case of iodides) or 8-10 h (in case of bromides)[8] followed by allylation of the 3-Phenyl-2-propyn alcohols **(1a-1l)** using NaH (3 mmol) and 2,3-dibromopropene (1 mmol) in dry THF (5 mL) (0°C-25°C) for 1.5-2 h (Table 1).[6c,6g]

Table 1

Synthesis of [3-(2-Bromo-allyloxy)-prop-1-ynyl]-benzenes[a] **(2a-2l)**



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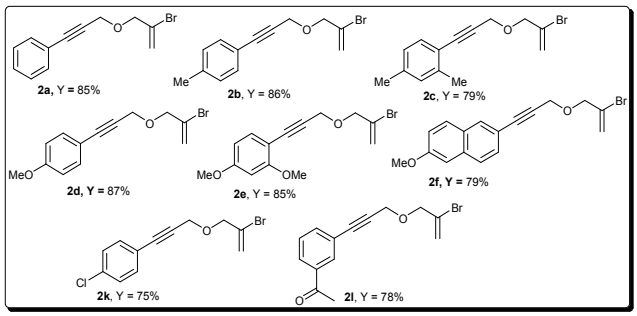
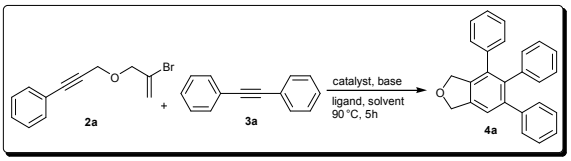


[a] Isolated yields after purification through column chromatography.

Table 2
Optimization studies[a]



Entry	Catalyst	Ligand	Base	Solvent	Temp (°C)	Yield (%)[b]
1	$Pd(OAC)_2$	PPh_3	Et_3N	DMF	90	48
2	$Pd(OAC)_2$	PPh_3	Na_2CO_3	DMF	90	64
3	$Pd(OAC)_2$	PPh_3	K_2CO_3	DMF	90	61
4	**$Pd(OAC)_2$**	**PPh_3**	**Cs_2CO_3**	**DMF**	**90**	**82**
5	$Pd(OAC)_2$	PPh_3	Cs_2CO_3	DMF	70	56
6	$Pd(OAC)_2$	PPh_3	NaOAc	DMF	90	46
7	$Pd(OAC)_2$	PPh_3	$KOBu^t$	DMF	90	55
8	$Pd(OAC)_2$	PPh_3	HCOONa	DMF	90	26
9	$Pd(OAC)_2$	PPh_3	Cs_2CO_3	DMA	90	77
10	$Pd(OAC)_2$	PPh_3	Cs_2CO_3	DMSO	90	72
11	$Pd(OAC)_2$	PPh_3	Cs_2CO_3	1,4-dioxane	90	46
12	$Pd(OAC)_2$	-	Cs_2CO_3	DMF	90	44
13	$Pd(OAC)_2$	PCy_3	Cs_2CO_3	DMF	90	33
14	$Pd(OAC)_2$	BINAP	Cs_2CO_3	DMF	90	40
15	$PdCl_2$	PPh_3	Cs_2CO_3	DMF	90	54
16	$PdCl_2(CH_3CN)_2$	-	Cs_2CO_3	DMF	90	46
17	$Pd(PPh_3)_4$	-	Cs_2CO_3	DMF	90	50
18	$Pd_2(dba)_3$	-	Cs_2CO_3	DMF	90	36

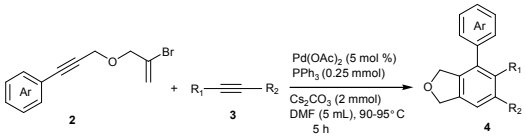
[a] Reagents and conditions: **2a** (1 mmol), diphenylacetylene **3a** (1.5 mmol), Pd catalyst (5 mol %), base (2 mmol), ligand (0.25 mmol) and solvent (5 mL) for 5 h.
[b] Yields refer to the isolated yields after purification through column chromatography.

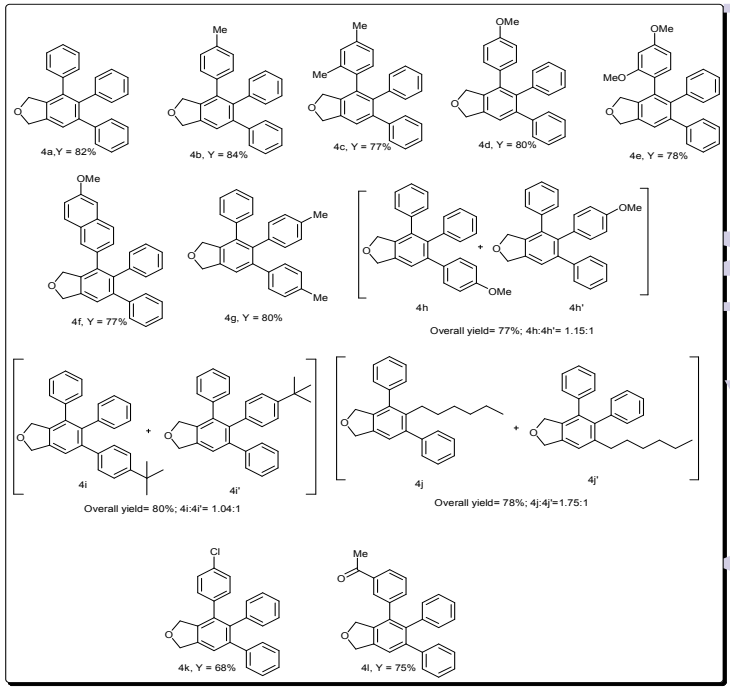
The bromoenyne **2a** was then initially reacted with diphenylacetylene **3a** in presence of Pd $(OAc)_2$ catalyst, Et_3N base and PPh_3 ligand in DMF at 90 °C for 5 h to give 4,5,6-triphenyl-1,3-dihydroisobenzofuran **4a** in 48 % yield. After screening through a number of reaction conditions, the domino carbopalladation reaction was found to be most effective with $Pd(OAc)_2$ (5 mol %), PPh_3 (0.25 mmol), Cs_2CO_3 (2 mmol) when 1 mmol of **2a** was reacted with 1.5 mmol of **3a** in DMF (5 mL) at 90 °C for 5 h resulting in the formation of 82 % of 4,5,6-triphenyl-1,3-dihydroisobenzofuran **4a** as the only isolable product (Table 2, Entry 4).

We next attempted to investigate the general applicability of this methodology and a number of variously functionalised (both electron donating and electron withdrawing) 2-bromo-1,6-enynes **2a-2l** were reacted with symmetrical as well as unsymmetrical internal alkynes **3** under the optimized reaction condition. The results are summarized in **Table 3**.

Table 3

Synthesis of 4,5,6-trisubstituted-1,3-dihydroisobenzofuran [a,b] **(4a-4l)**





[a] Reagents and conditions: all the reactions were carried out under the following conditions: substrates **2** (1 mmol), **3** (1.5 mmol), $Pd(OAc)_2$ (5 mol %), PPh_3 (0.25 mmol), Cs_2CO_3(2 mmol), DMF (5 mL), 90-95 °C, 5 h
[b] Isolated yield (after purification through column chromatography) after 5 h.

The reaction was found to be relatively high yielding in case of electron donating groups present either in **2** or **3** [resulting in **4b-(4j+4j′)**] compared to those with electron withdrawing groups (resulting in **4k** and **4l**). However, when the reaction was carried out with diethyl acetylenedicarboxylate ($R_1 = R_2 = CO_2Et$) and1,1'-(1,2-ethynediyl)bis[4-nitro-benzene] ($R_1 = R_2 = 4\text{-}NO_2\text{-}C_6H_4$), the starting material and/or the product probably could not persist under the applied reaction condition leading to no fruitful result.

With unsymmetrical internal alkynes a regioisomeric mixture was obtained in each case. As indicated by NMR data, **4h** and **4h′** were obtained in a ratio of 1.15:1**(4h:4h′≈1.15:1)**. Similarly, according to NMR data, **4i:4i′≈ 1.04:1** and **4j:4j′≈ 1.75:1**. However, geometry optimization was carried out for **(4h** and **4h′)**, **(4i** and **4i′)** and **(4j** and **4j′)** by using the DFT method at the (U)B3LYP level in the Gaussian 09 program[9] and 6-311G* basis set was used for all the

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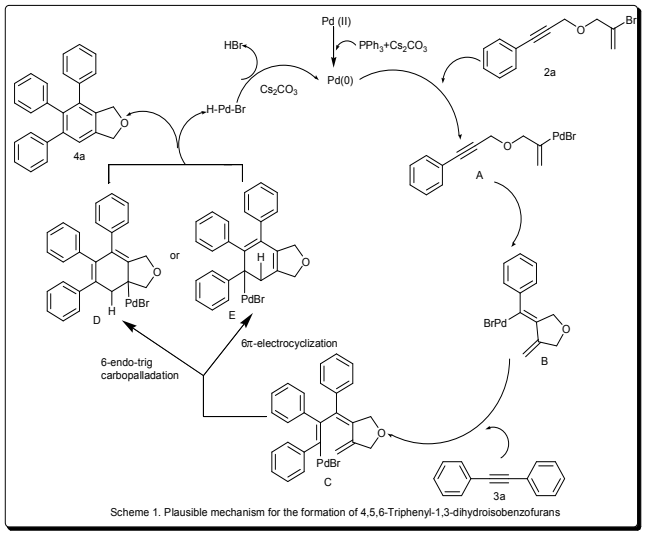
elements. The DFT calculation shows that between **4h** and **4h′**, **4h** is more stable by 0.21 KJ/mol of energy and hence they were obtained in almost equimolar ratio (**4h:4h′≈1.15:1** from NMR data). Between **4i** and **4i′**, **4i** is more stable only by 0.1 KJ/mol and thus they were also obtained in equimolar ratio (**4i:4i′≈1.04:1**from NMR data). Again, between **4j** and **4j′**, **4j** is more stable by 6.67 KJ/mol of energy and hence **4j** was obtained as the major product (**4j:4j′≈1.75:1**from NMR data). Thus the DFT calculation supports the results obtained experimentally. The results thus obtained also stand consistent with the regiochemical consequences reported by Negishi *et al.* in 1993.[6c]

To explain mechanistically, it would be rationalized that Pd(II) is initially reduced by PPh_3 to Pd(0) which enters the catalytic cycle by oxidative addition to the sp^2-C-Br bond of the bromoenyne **2a** leading to the formation of the alkenylpalladium intermediate **A**. This intermediate then undergoes intramolecular carbopalladation to the triple bond forming a "living" alkenylpalladium intermediate **B**. Carbopalladation of diphenylactylene **3a** to **B** furnishes intermediate **C** which is then converted to the desired product **4a** either *via* **D** (6-endo-trig carbopalladation) or *via* **E** (6π-electrocyclization)followed by β-dehydropalladation sequence.[6b,10]



Scheme 1. Plausible mechanism for the formation of 4,5,6-Triphenyl-1,3-dihydroisobenzofurans

Conclusions

In summary, we have developed an easy access to highly substituted 1,3-dihydroisobenzofurans using domino carbopalladation of bromoenynes and internal alkynes. Our methodology is advantageous with respect to good yield and substrate versatility. Moreover, the starting materials are readily accessible. Hope this methodology may find successful application in the construction of phthalan-containing natural products and also help in materials, pharmaceutical as well as in industrial research.

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