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A Simple and Efficient Synthesis of 2,3-Diarylnaphthofurans using Sequential Hydroarylation/Heck Oxyarylation

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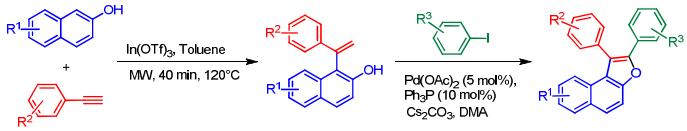
ABSTRACT



An efficient and simnple strategy has been developed for the synthesis of 2,3-diarylnaphthofurans using sequential hydroarylation of naphthols and alkynes in the presence of $In(OTf)_3$ under microwave irradiation followed by one-pot Heck-oxyarylation of generated 1-substituted-α-hydroxy styrenes.

Benzofurans and naphthofurans are important classes of heterocyclic compounds that are present as key structural motifs in many natural products, as well as in synthetic pharmaceutical compounds.[1, 2] Biological significance of these motifs have been clearly exemplified by natural products and synthetic compounds, such as Furomollugin,[3] Viniferifuran,[4] Anigopreissin A[5] and 7-methoxy-2-nitronaphtho[2,1-b]furan (R7000)[6] (Figure 1). Naphthofuran is a powerful paradigm in the development and design of potentially active compounds for anticancer,[1] regulators of the nuclear receptor HNF4α,[7] and imaging agents for β-amyloid plaques in the brain.[8]

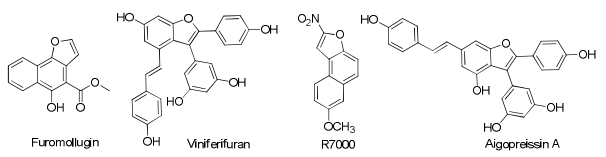


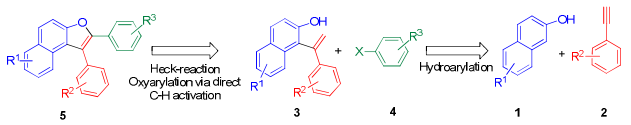
Figure 1. Structure of bioactive benzofuran and naphthofurans

Considerable attention has been directed toward the synthesis of compounds with benzofuran and naphthofuran framework because of their remarkable biological activities.[9-16] Acardi *et al.* described the first palladium-catalyzed intramolecular cyclization of arylsubstituted alkynes possessing a hydroxyl group at *ortho*-position to the triple bond for the synthesis of 2,3-diarylbenzofuran.[17] Since then transition metal catalyzed coupling/ cyclization of suitably functionalized alkynes as starting materials has been focus for the synthesis of 2,3-diarylbenzofurans and 2,3-diarylnaphthofurans.[18-21] A number of methods have been developed for synthesis of 2,3-diarylbenzofurans but synthetic routes for naphthofurans are limited,[11, 14] and synthesis of diversified naphthofurans still presents major challenge in organic synthesis.

Encouraged by the illustrated biological and synthetic interest in 1,2-diarylnaphtho[2,1-b]furans and prompted by the recent results for metal catalyzed C–H activation reactions, we envisaged a novel synthetic pathway to 2,3-diarylnaphthofurans starting from 2-naphthols (**1**), aryl alkynes (**2**), and haloarenes (**4**). It was expected that

hydroarylation of **2** with **1** in the presence of Lewis acids will generate α-hydroxy styrenes (**3**).[22-27] Heck-oxyarylation of **3** with **4** will afford desired 2,3-diarylnaphthofurans (Scheme 1). We report herein a simple and efficient method for the synthesis of 2,3-diarynaphthofurans by sequential hydroarylation/Heck-oxyarylation. To the best of our knowledge, this is the first report of the synthesis of diversified diarylnaphthofurans using sequential diarylation rections.

Scheme 1. Retrosynthetic analysis of 1,2-diarylnaphthofurans



In our initial investigation, 2-naphthol (**1a**), phenylacetylene (**2a**) and iodobenzene (**4a**) were used as substrates to form 2,3-diphenylnaphthofuran (**5a**) using $Yb(OTf)_3$ as a catalyst for hydroarylation and $Pd(OAc)_2$ for *in situ* Heck-oxyarylation. This strategy was unsuccessful since hydroarylation did not happen under these conditions. Thus, first the reaction conditions for hydroarylation of **2a** with **1a** to give 1-(1-phenylvinyl)naphthalen-2-ol (**3a**) were optimized using different Lewis acid catalysts (Table 1). Among different metal triflates screened, $Cu(OTf)_2$, $Sc(OTf)_3$, and $Bi(OTf)_3$ afforded **3a** in good to moderate yields (30-81%, Table 1, entries 7-9). In the case of $Cu(OTf)_2$ homocoupled product of **2a** was also obtained in 30% yield along with **3a**. An excellent yield of **3a** (91%) was obtained by the use of $In(OTf)_3$ (10 mol %) under microwave irradiation in toluene (Table 1, entry 10).

Table 1. Optimization of Hydroarylation Conditions for **3a**.

Entry	Catalyst	Mol (%)	Time (min)	Solvent	Yield[a] (%)
1	$Yb(OTf)_3$	10	40	Toluene	-[b,c]
2	$Y(OTf)_3$	10	40	Toluene	Trace
3	$Ce(OTf)_3$	10	40	Toluene	-[b]
4	$Ln(OTf)_3$	10	40	Toluene	Trace
5	$Gd(OTf)_3$	10	40	Toluene	10
6	$Zn(OTf)_2$	10	40	Toluene	Trace
7	$Cu(OTf)_2$	10	40	Toluene	30
8	$Sc(OTf)_3$	10	40	Toluene	81
9	$Bi(OTf)_3$	10	40	Toluene	59
10	**$In(OTf)_3$**	**10**	**40**	**Toluene**	**91 (76)**[c]
11	$In(OTf)_3$	10	20	Toluene	66
12	$In(OTf)_3$	5	40	Toluene	61
13	$In(OTf)_3$	10	20	ACN	79
14	$In(OTf)_3$	10	20	THF	71

[a]Isolated yield after MW irradiation for 40 min at 120 °C; [b]No product was formed; [c]Thermal heating at reflux condition for 10 h.

It is noteworthy to mention that when the hydroxyl group of naphthol was converted to methoxy and acetoxy, hydroarylation did not occur to give the corresponding 1-substituted-α-hydroxy styrene. It is expected that the hydroarylation reaction proceeds through the mechanism as proposed in literature.[23,28]

Following the optimized reaction conditions for the hydroarylation, **1a** and 7-methoxynaphthol (**1b**) were hydroarylated with different 4-substituted phenylacetylenes (**2a-c**) in the presence of $In(OTf)_3$ to give the corresponding 1-substituted-α-hydroxy styrenes (**3a-f**) in high yields (85-95%, Table 2).

The structures of **3a-f** were confirmed by NMR and high-resolution mass spectrometry (HRMS) (Supporting information). Vinylic CH_2 protons for **3a** resonated at δ 6.35 and 5.53 with a splitting constant of 1.5 Hz, and the phenolic proton resonated at δ 5.61 as a singlet in the ^1H NMR spectra. In the ^{13}C NMR, a total of 16 carbons appeared, which is as expected for the structure of **3a**, and a peak at 247.1126 for $[M + H]^+$ ion in HRMS spectra further confirmed the structure of **3a**.

Table 2. Synthesis of 1-Vinylnaphthols.[a]

Entry	R^1	R^2	Product	Time (min)	Yield (%)[b]
1	H	H	**3a**	40	91
2	H	4-CH_3	**3b**	40	92
3	H	4-OCH_3	**3c**	30	95
4	7-OCH_3	H	**3d**	35	86
5	7-OCH_3	4-CH_3	**3e**	35	85
6	7-OCH_3	4-OCH_3	**3f**	30	86

[a]Reaction conditions: **1** (1.39 mmol), **2** (1.66 mmol), $In(OTf)_3$ (78 mg, 10 mol %), toluene (2 mL) MW at 120 °C, 30 psi; [b]Isolated yield.

Next, the reaction conditions were standardized for a one-pot sequential palladium-catalyzed cross-coupling reaction and oxyarylation (Heck-oxyarylation) of 1-substituted-α-hydroxy styrenes (**3**) with haloarenes (**4**) to afford the desired 2,3-disubstituted naphthofurans. The model reaction performed with **3a** using iodobenzene (**4a**) in the presence of $Pd(OAc)_2$ (5 mol %) and potassium carbonate (2 equiv) in *N,N*-dimethylacetamide (DMA) resulted in an 18% yield of 1,2-diphenylnaphtho[2,1-b]furan (**5a**) after 14 h at 140 °C. When triphenylphosphine (PPh_3) was used as a ligand in the above reaction, in contrast to our earlier result, **5a** was obtained in 50% yield. Further optimization of the reaction condition using different palladium catalysts, ligands, bases, and solvents (Table 3) led to improvement in the yield of **5a**. The highest yield of **5a** (72%, entry 2) was obtained by using $Pd(OAc)_2$ (5 mol %) in the presence of PPh_3 and Cs_2CO_3 in DMA. The yield of **5a** was moderate to good (27-64%) with other palladium catalysts such as $PdCl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(dba)_2$ and $Pd(dppf)Cl_2$ (Table 3, entry 2-4, 18).

Table 3. Optimization of Heck-oxyarylation Condition for **5a**.[a]

Entry	Catalyst	Ligand	Base	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	-	Cs_2CO_3	DMA	18
2	**$Pd(OAc)_2$**	**PPh_3**	**Cs_2CO_3**	**DMA**	**72**
3	$PdCl_2$	PPh_3	Cs_2CO_3	DMA	27
4	$Pd(PPh_3)_2Cl_2$	PPh_3	Cs_2CO_3	DMA	59
5	$Pd(dba)_2$	PPh_3	Cs_2CO_3	DMA	64
6	$Pd(OAc)_2$	PPh_3	KOH	DMA	15
7	$Pd(OAc)_2$	PPh_3	Et_3N	DMA	Trace
8	$Pd(OAc)_2$	PPh_3	K_2CO_3	DMA	50
9	$Pd(OAc)_2$	PPh_3	tBuOK	DMA	64
10	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	DMF	48
11	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	Toluene	35
12	$Pd(OAc)_2$	Phen[c]	Cs_2CO_3	DMA	50
13	$Pd(OAc)_2$	biPy[d]	Cs_2CO_3	DMA	30
14	$Pd(OAc)_2$	$(Tol)_3P$	Cs_2CO_3	DMA	55
15	$Pd(OAc)_2$	TFP[e]	Cs_2CO_3	DMA	62
16	$Pd(OAc)_2$	TCP[f]	Cs_2CO_3	DMA	55
17	$Pd(OAc)_2$	DMEDA[g]	Cs_2CO_3	DMA	52
18	$Pd(dppf)Cl_2$[h]	PPh_3	Cs_2CO_3	DMA	20

[a]Reaction conditions: Catalyst (5 mol %), Ligand (10 mol %), Base (2 equiv), Solvent (5 mL), 140 °C, 14 h; [b]Isolated yield; [c]Phen = 1,10-phenanthroline; [d]biPy = 2,2'-bipyridine; [e]TFP = Tri(2-furyl)phosphine; [f]TCP = Tricyclohexylphosphine; [g]DMEDA = *N*,*N*-Dimethylethyl-enediamine (5 mmol %); $C_{35}H_{30}Cl_4FeP_2Pd$ = [1,1′-*Bis*(diphenyl-phosphino)ferrocene]dichloropalladium(II), complex with DCM.

The synthetic merit of the method was demonstrated by varying the substrates for the reaction (Table 4). Various haloarenes and α-hydroxy styrenes containing electron donating or withdrawing groups could be used for this reaction satisfactorily. For example, 1-(1-(4-methoxyphenyl)vinyl)-naphthalen-2-ol (**3c**) reacted with **4a** to give **5b** in 68% yield (Table 4, entry 2) and 7-methoxy-1-(1-(4-methoxyphenyl)vinyl)-naphthalen-2-ol (**3f**) reacted with **4a** to afford **5k** in 65% (Table 4, entry 11). Reaction of **3a** with 4-nitroiodobenzene afforded corresponding naphthofuran **5i** in 51% yield (Table 4, entry 9). The structures of all the synthesized 2,3-diarylnaphthofurans (**5a-n**) were established by IR, NMR (^{1}H and ^{13}C) and mass spectrometry data (Supporting Information). In the ^{1}H NMR of **5a**, the peak for the vinylic methylene protons and the phenolic proton of **3a** disappeared, and only the signal for the aromatic protons were observed. Similarly, in the IR spectrum no peak was observed for the phenolic OH group.

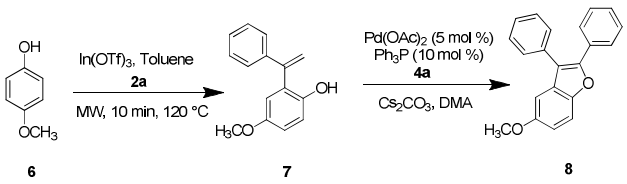
The sequential hydroarylation/Heck-oxyarylation was not limited to naphthol derivatives and was also applied to the synthesis of 2,3-diarylbenzofurans from electron rich phenols. Indeed, this catalytic system also proved viable with 4-methoxyphenol (**6**). Reaction of **6** with **2a** using $In(OTf)_3$ under microwave irradiation for 10 min gave the corresponding α-hydroxystyrene (4-methoxy-2-(1-phenylvinyl)-phenol, **7**) in 68% yield. The structure of **7** was elucidated by IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. In the IR, a peak for the phenolic OH group appeared in the region of 3417-3525 cm^{-1}. In the ^{1}H NMR, peak for the vinylic and phenolic protons appeared at 5.41 and 5.85 ppm as doublets and at 4.79 ppm as a singlet, respectively. Reaction of **7** with **4a** in the presence of $Pd(OAc)_2$ (5 mol %), PPh_3 and Cs_2CO_3 gave 5-methoxy-2,3-diphenylbenzofuran (**8**) in 75% yield (Scheme 1).

Table 4. Synthesis of 2,3-Diarylnaphthofurans.[a]

Entry	R^1	R^2	R^3	Prod.	Time (h)	Yield[b] (%)
1	H	H	H	**5a**	14	72
2	H	4-OCH_3	H	**5b**	12	68
3	H	4-CH_3	H	**5c**	14	57
4	H	H	4-OCH_3	**5d**	12	72
5	H	H	4-CH_3	**5e**	14	53
6	H	4-CH_3	4-CH_3	**5f**	14	50
7	H	4-OCH_3	4-CH_3	**5g**	11	52
8	H	H	2-CH_3	**5h**	14	51
9	H	H	4-NO_2	**5i**	14	41
10	H	H	2,3-C_4H_4	**5j**	14	36
11	7-OCH_3	4-OCH_3	H	**5k**	10	65
12	7-OCH_3	4-OCH_3	4-CH_3	**5l**	10	62
13	7-OCH_3	H	4-CH_3	**5m**	11	56
14	7-OCH_3	4-CH_3	4-CH_3	**5n**	11	39

[a]Reaction condition: **3** (0.81 mmol), **4** (0.975 mmol), $Pd(OAc)_2$ (0.04 mmol), Ph_3P (0.081 mmol), Cs_2CO_3 (1.63 mmol), DMA (5 mL), 140 °C, 14 h. [b]Isolated yield.

Scheme 1. Synthesis of 5-methoxy-2,3-diphenylbenzofuran



The structure of **8** was unambiguously elucidated by spectroscopic analysis. The ^{1}H NMR spectrum showed only one singlet in the aliphatic region at 3.80 ppm for the OCH_3 group, and the integration for the aromatic region was in accordance with the required 13 aromatic protons of **8**. The presence of a peak at 55.98 ppm of OCH_3 group along with other 16 carbons peaks in ^{13}C NMR and molecular ion peak at 323.1065 for $[M + Na]^+$ ion in HRMS, confirmed the structure of **8**. The structure of **8** was further independently confirmed by an X-ray crystal structure (CCDC 923801) (Figure 2). The two aryl rings generate steric strain, and they are oriented in different planes.

Based on the structure of the product obtained and literature reports,[29, 30] the mechanism of the reaction is tentatively proposed as shown in Scheme 2. It is expected that initially **3** reacts with Ar-Pd-I to form an oxygen-coordinated Pd(II)-aryl complex (**9**) which on insertion of alkene gives a five membered oxygen- coordinated

palladium(II) complex (**10**). This intermediate on β-hydride elimination gives an intermediate with $OPd^{(II)}H$ (**11**). Intramolecular addition of the alkene of **11** to $OPd^{(II)}H$ gives the six membered oxygen-coordinated Pd(II) complex (**12**). Reductive elimination of **12** gives tetrahydrofuran derivative (**13**). Subsequent oxidation of **13** results in the formation of naphthofuran (**5**)/benzofuran (**8**).

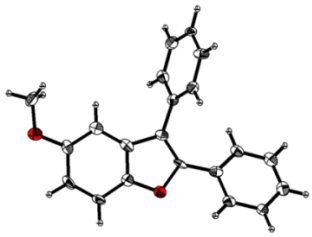
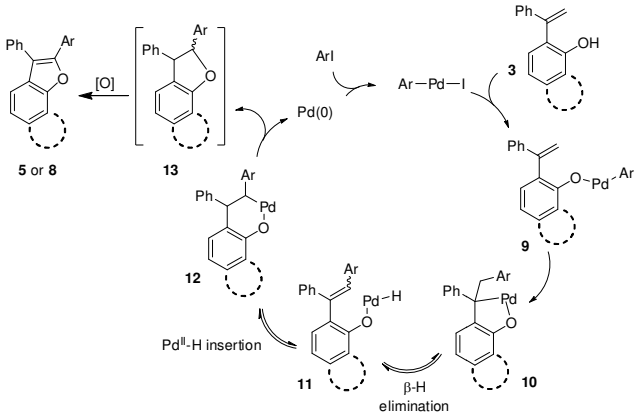


Figure 2. ORTEP diagram of **8**

Scheme 3. Tentative proposed mechanism for the Heck oxyarylation.



For clarity the ligands for Pd are omitted.

In conclusion, 2,3-diarylnaphthofurans were synthesized in an efficient and general synthetic strategy in good to high yield from easily available naphthols, alkynes, and iodoarenes. An interesting feature of the method is that it accommodates functional groups amenable to further manipulation and with a rapid increase in molecular complexity. Further studies are ongoing in our laboratory to expand the synthetic utility of this versatile catalytic system.

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Supporting Information Available: Experimental procedure, characterization data and copies of the ^{1}H and ^{13}C NMR of the synthesized compounds **4a-h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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