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Silver-catalyzed synthesis of 4-substituted benzofurans *via* a cascade oxidative coupling-annulation protocol†

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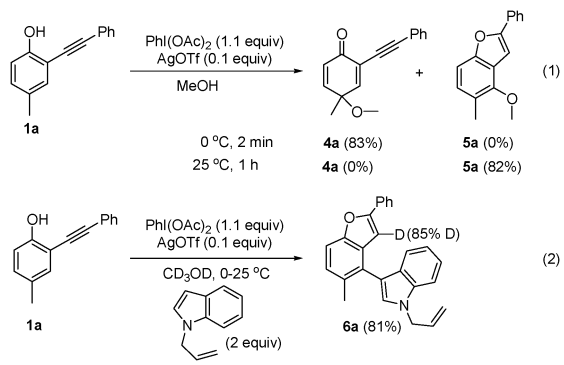
A facile synthesis of 4-indole benzofurans from the one-pot reaction of 4-alkyl-2-ynylphenols and indoles *via* a hypervalent iodine-induced oxidative dearomatization, a silver-catalyzed cascade Michael addition-annulation, and an aromatization is reported.

The widespread availability and inherent functionality of phenols make them attractive pharmaceutical and fine chemicals. The selective conversion of simple phenols into useful complex molecules is an important area in organic synthesis. Hypervalent organoiodine induced oxidative dearomatization of phenols leads to a variety of synthetically useful compounds.[1,2] The oxidation of *ortho*- and *para*-substituted phenols in the presence of an appropriate internal or external nucleophile gives rise to cyclohexadienones,[3] which have been widely used as the important intermediates in the synthesis of natural and unnatural biologically active compounds.[4] While much has been learned about the intramolecular reactions of the resulting cyclohexadienones to construct a range of cyclohex-2-enone derivatives,[5] the synthesis of aromatic complex molecules from the dearomatization of phenols has been achieved in only a few instances.[6] On the other hand, substituted benzofurans are widely found in natural products and have considerable medicinal potential.[7] Transition metal-catalyzed annulation of *o*-hydroxylarylacetylenes is one of the most efficient methods to access benzofurans.[8] However, limited methods exist to selectively introduce a desired functional group at the 4-position of benzofurans.[9] Here, we report an efficient method to access 4-substituted benzofurans from 4-alkyl-2-ynylphenols *via* a dearomatization strategy.

4-Alkyl-2-ynylphenols are conveniently prepared from 4-alkylphenols *via* iodination and a subsequent Sonogashira coupling reaction. Because arylindoles appear as the basic skeletons in a wide range of biochemical, biological and medicinal compounds, indoles were chosen as the nucleophiles.

First, we selected 4-methyl-2-(2-phenylethynyl)phenol **1a** and indole **2a** as the standard substrates to search for potential catalysts and suitable reaction conditions‡. The mixture of substrate **1a** and catalyst in methanol was treated with $PhI(OAc)_2$ (1.1 equiv.) at 0 °C. After 2 min, indole **2a** was added, and the reaction mixture was warmed to 25 °C. No desired product was formed in the presence of $PdCl_2$, $Pd(OAc)_2$, or CuI (Table 1, entries 1–3). When $Cu(OTf)_2$ was used, the desired product **3aa** was obtained in 4% yield. Increasing the reaction temperature to 50 °C improved the yield to 48% (Table 1, entries 4 and 5). When $Cu(OTf)_2$ was replaced by AgOTf, product **3aa** was isolated in 63% yield. Interestingly, by decreasing the reaction temperature to 25 °C, the yield was improved to 80%. When $AuCl_3$ was used instead of AgOTf under the same conditions, the reaction afforded product **3aa** in 54% yield (Table 1, entries 6–8). When the reaction with AgOTf was carried out at 0 °C, only a trace amount of product **3aa** was formed even after 3 days (Table 1, entry 9). Decreasing the amount of AgOTf dramatically reduced the product yield (Table 1, entry 11). The adding order of reactants had an influence on the reaction. When AgOTf was added together with indole after the oxidation, the yield of product **3aa** decreased to 68%. When substrate **1a**, AgOTf, and indole were premixed in methanol before $PhI(OAc)_2$ was added, the reaction only afforded product **3aa** in 11% yield. When other alcohols were used as the solvent, lower yields were obtained.

Under the optimized reaction conditions, various indoles were used to react with 4-methyl-2-(2-phenylethynyl)phenol, and representative results are listed in Table 2. We found that both free (*NH*)-indole and *N*-alkyl indoles were suitable reaction partners, but *N*-acetyl indole was unreactive under the present conditions (Table 2, entries 1–5). Indoles bearing electron-withdrawing substituents delivered the corresponding



Scheme 1

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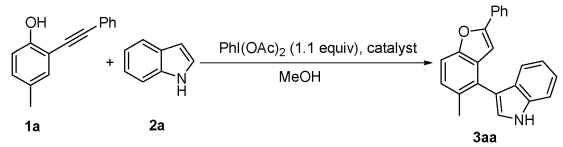
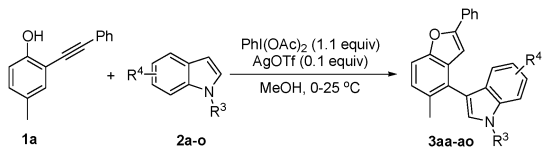
Table 1 Evaluation of reaction conditions



Entry	Catalyst (equiv.)	T (°C)	Time (h)	Yield (%)[a]
1	$PdCl_2$ (0.1)	0–25	12	0
2	$Pd(OAc)_2$ (0.1)	0–25	12	0
3	CuI (0.1)	0–25	12	0
4	$Cu(OTf)_2$ (0.1)	0–25	12	4
5	$Cu(OTf)_2$ (0.1)	0–50	24	48
6	AgOTf (0.1)	0–50	8	63
7	AgOTf (0.1)	0–25	8	80
8	$AuCl_3$ (0.1)	0–25	3	54
9	AgOTf (0.1)	0	72	trace
10	AgOTf (0.2)	0–25	8	81
11	AgOTf (0.05)	0–25	24	19

[a] Isolated yield based on substrate **1a**.

Table 2 Reactions of 4-methyl-2-(2-phenylethynyl)phenol **1a** with indoles **2a–o**



Entry	**2**	R^3	R^4	**3**	Yield (%)[a]
1	**2a**	H	H	**3aa**	80
2	**2b**	Me	H	**3ab**	85
3	**2c**	$PhCH_2$	H	**3ac**	75
4	**2d**	$H_2C=CHCH_2$	H	**3ad**	82
5	**2e**	MeCO	H	**3ae**	0
6	**2f**	H	5-F	**3af**	64
7	**2g**	H	5-Cl	**3ag**	46
8	**2h**	H	5-Br	**3ah**	53
9	**2i**	H	5-Me	**3ai**	0
10	**2j**	H	5-MeO	**3aj**	0
11	**2k**	$H_2C=CHCH_2$	5-Me	**3ak**	78
12	**2l**	$H_2C=CHCH_2$	5-MeO	**3al**	65
13	**2m**	$H_2C=CHCH_2$	6-MeO	**3am**	61
14	**2n**	$H_2C=CHCH_2$	5-F	**3an**	55
15	**2o**	$H_2C=CHCH_2$	5-Cl	**3ao**	40

[a] Isolated yield based on substrate **1a**.

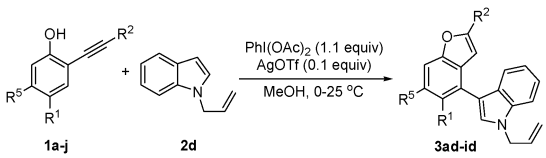
products, albeit in lower yields (Table 2, entries 6–8). The reactions of indoles with electron-donating groups did not yield the desired products, and the formation of metallic silver was observed (Table 2, entries 9 and 10). To avoid the reduction of AgOTf, indoles with electron-donating groups were protected with the allylic group. The resultant *N*-allylic indoles were smoothly converted to the corresponding products (Table 2, entries 11–13). The same protection for indoles bearing electron-withdrawing substituents did not improve the product yields (Table 2, entries 14 and 15).

The scope of the one-pot reaction was further tested with a range of 4-alkyl-2-ynylphenols. When a straight-chain alkyl group was placed at the 4-position of substrate **1**, the reaction proceeded smoothly (Table 3, entries 1–3). When 4-*tert*-butyl and 4-phenyl-2-(2-phenylethynyl)phenol **1d** and **1e** were used as the substrates, the reactions were complex and the desired products were not detected (Table 3, entries 4 and 5). 4,5-Dimethyl-2-(2-phenylethynyl)phenol **1f** also showed a good reactivity (Table 3, entry 6). When the phenylethynyl group at the 2-position was replaced by the hex-1-ynyl group, a complicated reaction was observed, and no corresponding product **3gd** was obtained (Table 3, entry 7). When the R^2 group was changed to the *tert*-butyl group, the reaction gave rise to the corresponding product **3hd** in 80% yield (Table 3, entry 8). When 2-ethynyl-4-methylphenol **1i** was employed, 1.1 equiv. of AgOTf was required to finish the reaction, and product **3id** was formed in 60% yield. Meanwhile, product **3id** was also isolated in 74% yield from the reaction of 4-methyl-2-(2-(trimethylsilyl)-ethynyl)phenol **1j** under the present conditions (Table 3, entries 9 and 10).

When the reaction of substrate **1a**, AgOTf, and $PhI(OAc)_2$ in methanol was quenched at 0 °C after 2 min, 4-methoxy-4-methyl-2-(2-phenylethynyl)cyclohexa-2,5-dienone **4a** was isolated in 83% yield. When the reaction was warmed to 25 °C, a cyclization and coupling product with methanol **5a** was generated in 82% yield after 1 h (Scheme 1, eqn (1)). A control experiment in the fully deuterated methanol provided the corresponding product with 85% deuterium incorporation into the benzofuran (Scheme 1, eqn (2)). Additionally, the reactions using other nucleophiles such as $TsNH_2$, $CH_2(COOEt)_2$, and $HPO(OEt)_2$ did not afford the corresponding products.

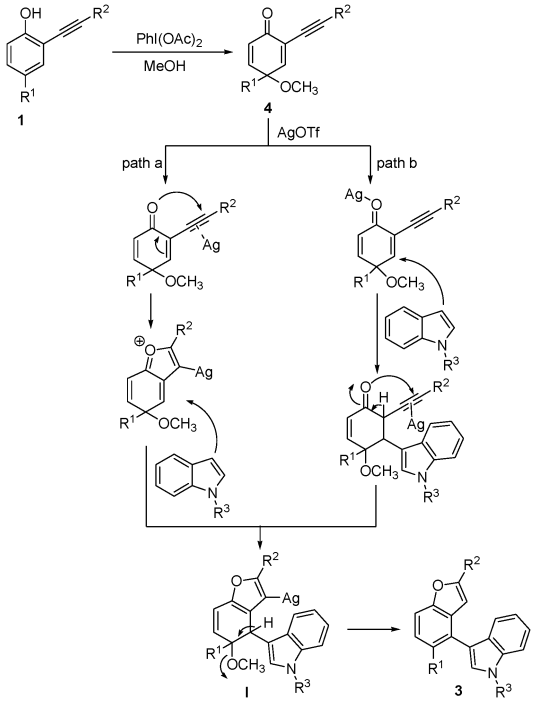
A tentative mechanism is shown in Scheme 2. The first step is the oxidative dearomatization of 4-alkyl-2-ynylphenol **1** by iodobenzene diacetate in methanol to generate 4-alkyl-4-methoxy-2-ynylcyclohexa-2,5-dienone **4**. At least two reaction pathways are plausible for the subsequent silver-catalyzed cyclization and addition of the resulting compound **4**.[10] In path a, AgOTf activates the acetylene group to promote the intramolecular nucleophilic attack of the carbonyl oxygen on the triple bond. The annulation yields an oxonium ion, which is ready to undergo the intermolecular nucleophilic attack by indole to form intermediate **I**. In path b, AgOTf first facilitates the

Table 3 Reactions of 4-alkyl-2-ynylphenols **1a–j** with *N*-allylic indole **2d**



Entry	**1**	R^1	R^5	R^2	**3**	Yield (%)[a]
1	**1a**	Me	H	Ph	**3ad**	82
2	**1b**	*n*-Bu	H	Ph	**3bd**	78
3	**1c**	$EtOOCCH_2$	H	Ph	**3cd**	68
4	**1d**	*t*-Bu	H	Ph	**3dd**	0
5	**1e**	Ph	H	Ph	**3ed**	0
6	**1f**	Me	Me	Ph	**3fd**	70
7	**1g**	Me	H	*n*-Bu	**3gd**	0
8	**1h**	Me	H	*t*-Bu	**3hd**	80
9	**1i**	Me	H	H	**3id**	60[b]
10	**1j**	Me	H	TMS	**3id**	74

[a] Isolated yield based on substrate **1**. [b] 1.1 Equivalent of AgOTf was used.



Scheme 2 Hypothesized reaction pathway.

1,4-addition with indole, then induces the cyclization of the generated Michael adduct to provide intermediate **I**. After aromatization and protonation of the carbon-silver bond, 4-indole benzofuran **3** is obtained and the silver catalyst is regenerated.

In conclusion, we have developed an efficient method to prepare 4-indole benzofurans from 4-alkyl-2-ynylphenols and indoles *via* a hypervalent iodine-induced oxidative dearomatization, a silver-catalyzed cascade Michael addition-cyclization, and an aromatization. The method provides an attractive and useful route to introduce functional groups at the 4-position of benzofurans. The current direction for future research is aimed at extending the scope and potential synthesis applications, as well as investigation on the reaction mechanism.

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Notes and references

‡ Representative experimental procedure: The mixture of 4-alkyl-2-ynylphenol **1** (0.5 mmol) with AgOTf (13 mg, 0.05 mmol) in MeOH (2 mL) was treated with $PhI(OAc)_2$ (177 mg, 0.55 mmol) at 0 °C. After 2 min, indole **2** (1 mmol) was added. The reaction mixture was warmed up and allowed to stir at 25 °C. Upon completion by TLC, the reaction was quenched with saturated $NaHCO_3$, and extracted by ethyl acetate (100 mL × 3). The organic layer was dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to give the corresponding product **3**.

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