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Direct Propargylation of *ortho*-Quinone Methides with Alkynyl Zinc Reagents: An Application to the One-Pot Synthesis of 2,3-Disubstituted Benzofurans

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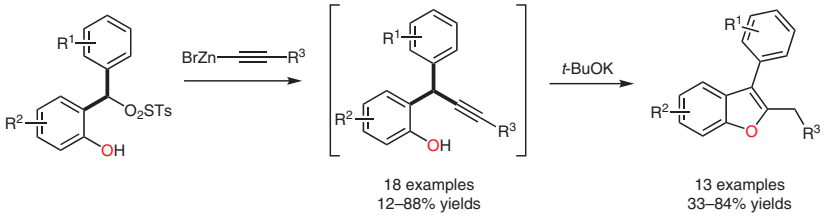

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Abstract A transition-metal-free propargylation of *ortho*-quinone methides (*o*-QMs) with alkynyl zinc reagents was achieved. A conjugate alkynylation of an *o*-QM and subsequent cyclization sequence in the presence of KO*t*-Bu for the synthesis of 2,3-disubstituted benzofurans in one pot was developed. This efficient strategy exhibits good functional-group compatibility and gives moderate to good yields. The present reaction might serve as an attractive method for the synthesis of polysubstituted benzofurans.

Key words propargylation, *ortho*-quinone methides, alkynyl zinc reagents, benzofurans

The 1-benzofuran moiety is a common structural motif, found in natural products, pharmaceuticals, and agrochemicals.[1] In particular, 2,3-disubstituted 1-benzofurans are widely distributed in natural products and bioactive structures.[2] For example, phenolic compound **A** (Figure 1), isolated from the stems of the tree *Dalbergia cochinchinensis*, is an antiandrogenic agents acting against testosterone.[3] The benzofuran compound **B** is considered to be a human MT1 and MT2 melatonin receptor ligand on the basis of its affinity activity.[4] The 2-benzyl-3-biphenyl-4-ylbenzofuran derivatives **C** exhibit potent protein tyrosine phosphatase inhibitory activity and also good oral antihyperglycemic activity.[5]

Among the methods available for C–C bond formation, one of the most versatile and reliable is the conjugate addition of organometallics to α,β-enones, particularly the conjugate addition of terminal alkynes to α,β-unsaturated carbonyl compounds,[6] because of the synthetic utility of the resulting β-alkynyl carbonyls.[7] As highly reactive α,β-unsaturated carbonyl species, *ortho*-quinone methides (*o*-QMs) have been widely used in organic synthesis, materials chemistry, fine-chemical syntheses, and pharmaceutical

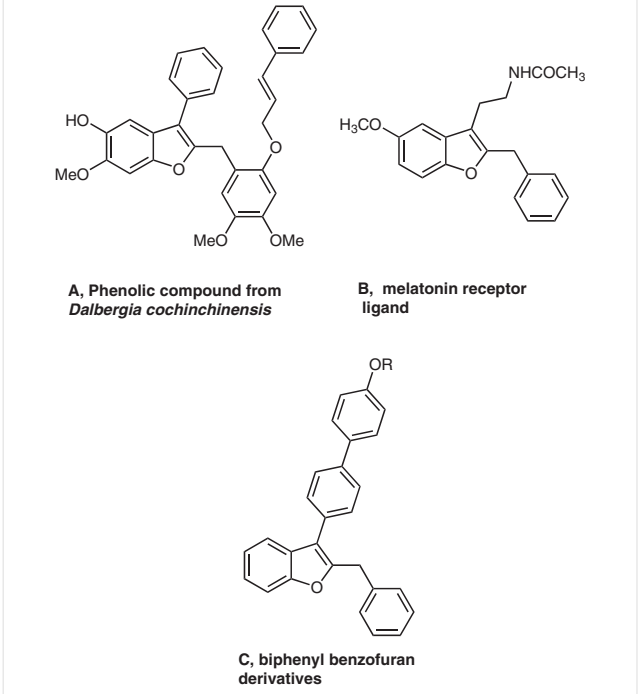

Figure 1 Bioactive 2,3-disubstituted 1-benzofurans

production.[8] The conjugate addition of nucleophilic reagents to *o*-QMs systems would be very desirable in organic synthesis and drug discovery.[9] Because organic zinc reagents are among the most useful organometallic compounds in organic synthesis, we previously reported a transition-metal-free synthesis of unsymmetrical and highly functionalized triarylmethanes through arylation of *o*-QMs, generated in situ from diarylmethyl *p*-tolyl sulfones, with arylzinc reagents (Scheme 1, upper).[10] In attempts to install an alkynyl group on the substrates, we examined the direct

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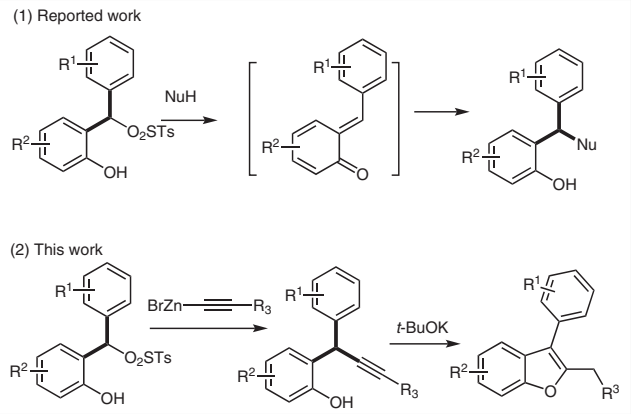
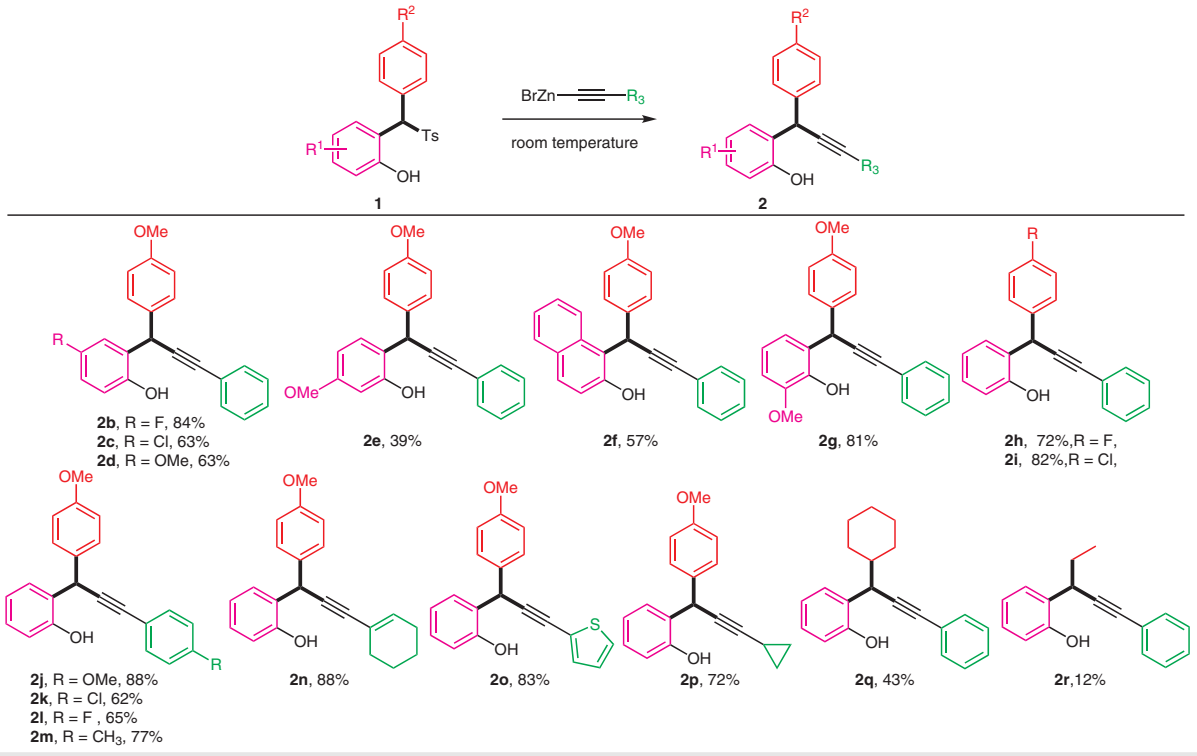
conjugate alkynylation of *o*-QMs and a subsequent cyclization for the synthesis of 2,3-disubstituted benzofurans in the presence of KO*t*-Bu in one pot (Scheme 1, lower).



Scheme 1 The conjugate addition of nucleophilic reagents to *o*-QMs systems

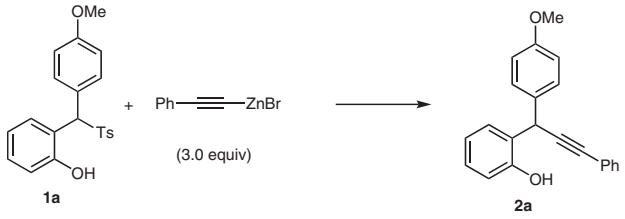
Experimentally, we began our investigation by examining the reaction of 2-[(4-methoxyphenyl)(tosyl)methyl]phenol (**1a**), synthesized by a modified version of the reported method, with three equivalents of bromo(phenylethynyl)zinc, prepared in situ from ethynylbenzene, butyllithium, and zinc bromide, and our key results are summarized in Table 1. We first carried out the reaction by using CuCl (5 mol%) as catalyst in tetrahydrofuran (THF) at 60 °C for 12 hours, and we obtained the desired propargylation product **2a** in 53% isolated yield (Table 1, entry 1). Through control experiments, we found that both CuBr and CuI effectively promoted the reaction at 60 °C, giving the desired product **2a** in yields of 73 and 74%, respectively (entries 2 and 3). Gratifyingly, when the reaction was carried out at room temperature for 12 h in the presence of CuI (5 mol%), the yield improved to 80% (entry 4). When $CoCl_2$ was used as a catalyst, the yield decreased to 31% at room temperature (entry 5). When $FeCl_3$ or $Fe(acac)_3$ was used as catalyst, the desired product **2a** was obtained after 12 hours in yields of 86 and 73%, respectively (entries 6 and 7). When the reaction was carried out without any catalyst at 60 °C for 12 hours, the desired product **2a** was obtained in 55% yield (entry 9) but, to our delight, when the reaction was carried out without any catalyst at room temperature for 24 hours, the yield increased to 82% (entry 8).

Having established the optimal reaction conditions, we next evaluated the generality of our propargylation reaction (Scheme 2). A series of substituted 2-(tosylmethyl)phenols were first investigated. The reaction proved to be broadly applicable; both the *ortho*- and *para*-substituted phenols were reactive with good conversions, giving **2b–d**



Scheme 2 Scope of the propargylation. *Reagents and conditions*: **1** (0.5 mmol), bromo(alkynyl)zinc (3.0 mmol; generated from the corresponding alkyne, BuLi, and $ZnBr_2$) under N_2, rt, 12–24 h.

Table 1 Optimization of the Reaction Conditions[a]

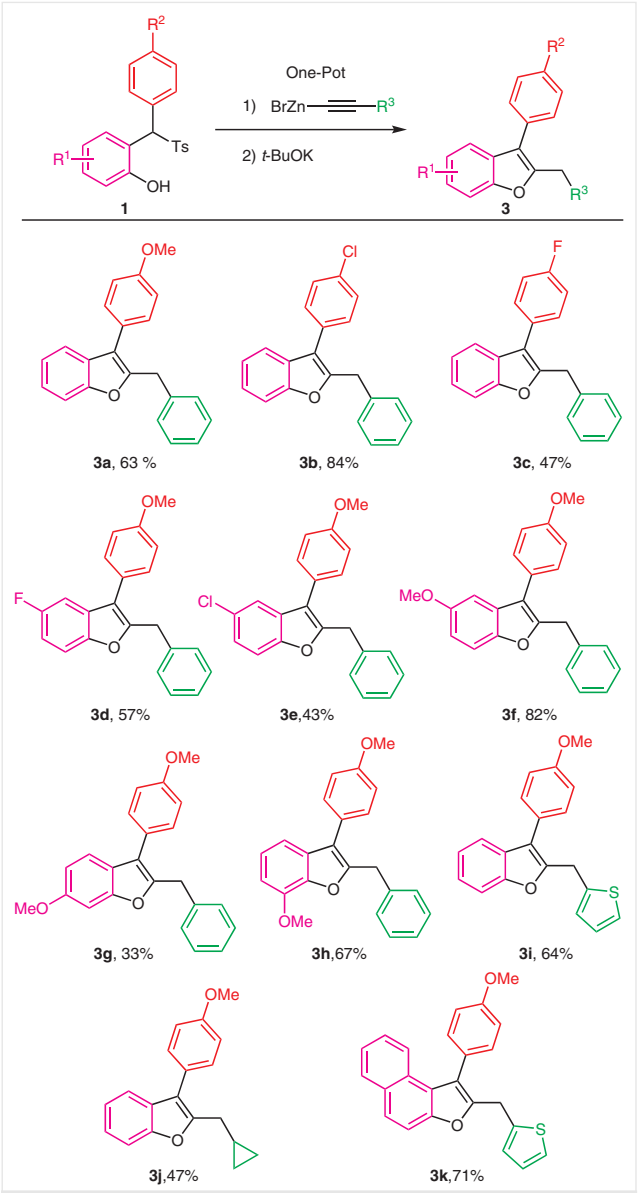


Entry	Cat.	Temp	Time (h)	Yield[b] (%)
1	CuCl	60 °C	12	53
2	CuBr	60 °C	12	73
3	CuI	60 °C	12	74
4	CuI	rt	24	80
5	$CoCl_2$	rt	24	31
6	$FeCl_3$	rt	24	86
7	$Fe(acac)_3$	rt	24	73
8	–[c]	rt	24	82
9	–[c]	60 °C	12	55

[a] Reaction conditions: **1a** (0.5 mmol), bromo(phenylethynyl)zinc (3.0 mmol; generated from ethynylbenzene, BuLi, and $ZnBr_2$), catalyst (5 mol%), THF, under N_2.
[b] Isolated yield.
[c] No catalyst.

and **2g** in isolated yields of up to 84%. Substitution at the *meta*-position led to decreased reactivity and a poor yield of **2e**. In the case of a 2-hydroxynaphth-1-yl substrate, the conjugated propargylation product **2f** was obtained in 57% yield. Substitution of the phenyl ring increased the reactivity, leading to high yields of **2h** and **2i** from the corresponding fluoro- and chloro-substituted substrates. As expected, substitution of the terminal phenyl group of the alkyne acting as a nucleophile toward their corresponding zinc reagent did not affect the conversion rate to products **2j–m**. However, decreased yields of **2q** and **2r** were obtained when the aromatic ring was replaced by an alkyl group, possibly because the resulting *o*-QM intermediate is less reactive. Deprotonation of the arylmethyl *p*-tolyl sulfone to the respective styrene is very likely to be a major side-reaction pathway.

On the basis of reports in the literature regarding the synthesis of substituted benzofurans from (hydroxyphenyl)propargylic alcohols,[11] we surmised that 2,3-disubstituted benzofurans might be accessible from our reaction products in a one-pot operation. After consumption of the starting material **1a** in THF (TLC monitoring), KO*t*-Bu was added, and the desired 2-benzyl-3-(4-methoxyphenyl)benzofuran (**3a**) was obtained in 44% yield at room temperature, through *exo-dig* cycloisomerization.[12] When the *exo-dig* cycloisomerization was carried out in 1,4-dioxane at room temperature, the yield of product **3a** increased to 63% (Scheme 3). With success in the formation of 2-benzyl-3-

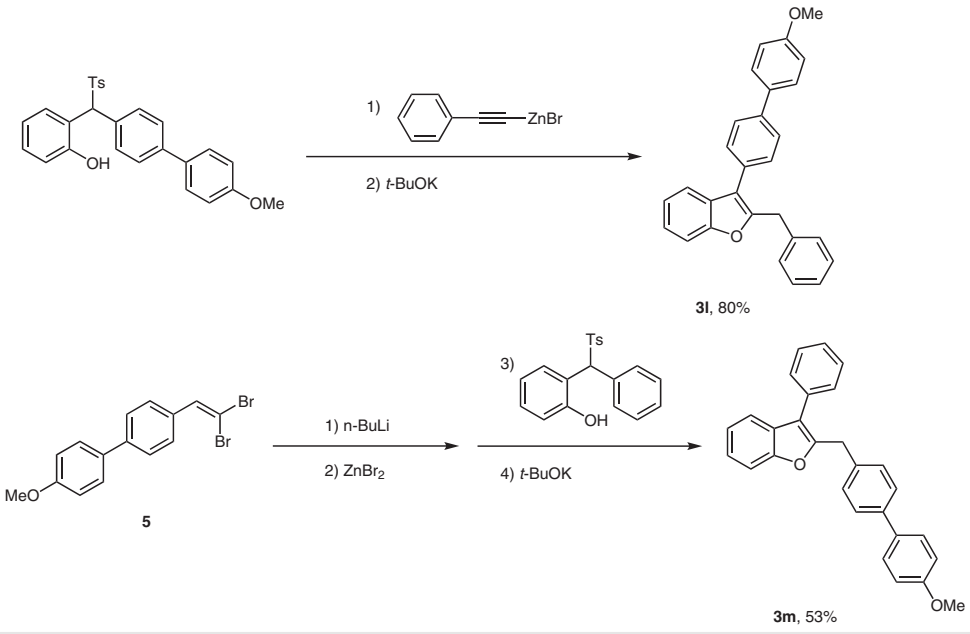


Scheme 3 Scope of the synthesis of 2,3-disubstituted benzofurans by a one-pot process. *Reagents and conditions*: **1** (0.5 mmol), bromo(alkynyl)zinc (3.0 mmol; generated from the corresponding alkyne, BuLi, and $ZnBr_2$), under N_2, rt, 12–24 h.

(4-methoxyphenyl)benzofuran (**3a**) by a one-pot protocol, we examined the scope and generality of the method, and our results are summarized in Scheme 3.[13] When the propargylphenol had an electron-donating substituent (*p*-OMe) or a weakly electron-withdraw substituent (*p*-Cl) on the aryl group, the reaction proceeded cleanly to afford **3a** and **3b**, respectively, in yields of 63 and 84%. However, when an electron-withdrawing *p*-fluoro substituent was present, the yield of **3c** dropped to 47%. The presence of an electron-donating substituent on the phenol ring increased the yields of **3d–f** and **3h** to as much as 82%. However, in the case of

the *m*-methoxy-substituted phenol, the yield of **3g** decreased to 33%, which matched the yield of **2e**. Heterocycles, as exemplified by thiophene, were also compatible with this reaction, giving **3i** and **3k** in yields of 64 and 71%, respectively. Furthermore, cyclopropylethyne could also be used in this reaction to give the cyclopropane-containing 2,3-disubstituted benzofuran **3j** in 47% yield.

To further demonstrate the potential utility of this alkynylation of *o*-QMs and the subsequent cyclization reaction, an additional gram-scale experiment was performed. Under the optimal reaction conditions, the desired 2-benzyl-3-biphenyl-4-yl-1-benzofuran derivative **3l** was synthesized straightforwardly in 80% yield (Scheme 4). Interestingly, terminal alkynes made by a Corey–Fuchs protocol can be used directly in our reaction. Thus, after treatment of the 1,1-dibromoolefin **5** with BuLi at a low temperature, the corresponding terminal alkynyllithium salt was formed through a Fritsch–Buttenberg–Wiechell rearrangement. Subsequent reaction with **1a** and treatment with KO*t*-Bu provided the corresponding 2,3-disubstituted benzofuran **3m**, an isomer of **3l**, in 53% yield.



Scheme 4 Practical syntheses of biphenylylbenzofuran derivatives

In summary, we have developed a new method for the effective synthesis of 2,3-disubstituted benzofurans in one-pot through transition-metal-free conjugate alkynylation of *o*-QMs and a subsequent cyclization sequence in the presence of KO*t*-Bu. This efficient strategy exhibits good functional-group compatibility with moderate to good yields. The present reaction might serve as an attractive method for the synthesis of polysubstituted benzofurans.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691739.

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(13) **4-Fluoro-2-[1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-yl]phenol (2b); Typical Procedure**

A 2.5 M solution of BuLi in hexanes (1.5 mmol) was added dropwise to a solution of ethynylbenzene (1.5 mmol) in anhyd THF (2 mL) at –20 °C under N_2, and the mixture was stirred for 30 min at –20 °C. A 1.0 M solution of $ZnBr_2$ in THF (1.5 mL) was added, and the resulting mixture was stirred for about 15 min at 0 °C. 4-fluoro-2-((4-methoxyphenyl)(tosyl)methyl)phenol **1b** (193 mg, 0.5 mmol) was then added, and the mixture was stirred at rt for 15 h until the reaction was complete. The reaction was then quenched by adding sat. aq NH_4Cl (5 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic phase was washed with H_2O (3 × 10 mL), dried (Na_2SO_4), concentrated in vacuo, and purified by flash chromatography (silica gel, petroleum ether/EtOAc = 5:1) to give a yellow solid; yield: 140 mg (84%); mp 89–90 °C (PE–EtOAc); R_f = 0.66 (PE–EtOAc, 3:1). IR (neat): 3380, 2221, 1605, 1512, 1234, 1182, 1024 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.46 (m, 2 H), 7.37 (d, *J* = 8.8 Hz, 2 H), 7.32–7.30 (m, 3 H), 7.14–7.11 (m, 1 H), 6.89–6.82 (m, 3 H), 6.76–6.73 (m, 1 H), 5.37 (s, 1 H), 5.29 (s, 1 H), 3.79 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.6 (d, J_{C-F} = 40 Hz), 156.0, 149.1, 131.7, 131.6, 129.4, 129.3, 128.8, 128.3, 128.2, 122.7, 117.4 (d, J_{C-F} = 7.9 Hz), 115.7 (d, J_{C-F} = 24 Hz), 114.7 (d, J_{C-F} = 22.8 Hz), 114.2, 88.5, 85.4, 55.3, 37.7. HRMS (ES$^+$-TOF): *m/z* [M + H]$^+$ calcd for $C_{22}H_{18}FO_2$: 333.1291; found: 333.1288.