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$B(C_6F_5)_3$-Catalyzed Sequential Additions of Terminal Alkynes to *para*-Substituted Phenols: Selective Construction of Congested Phenol-Substituted Quaternary Carbons

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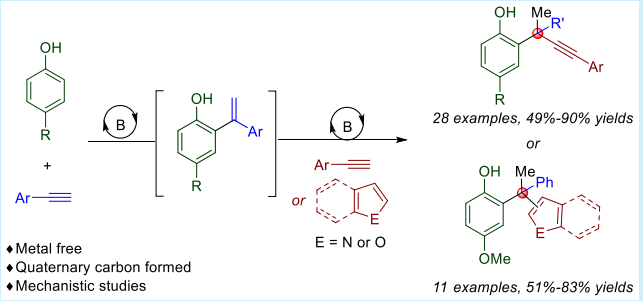
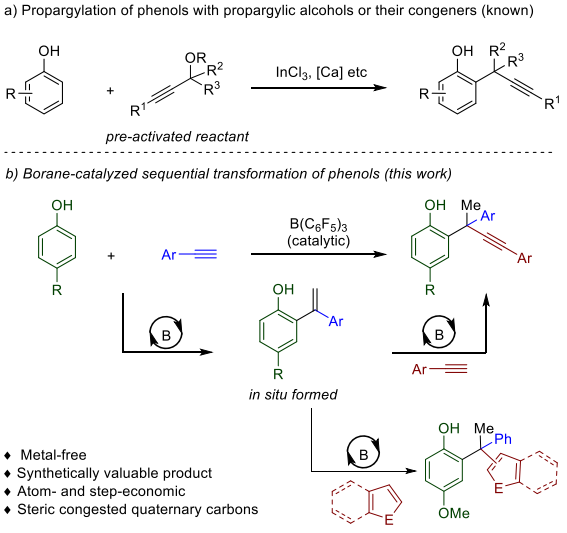
ABSTRACT: We have developed a borane-catalyzed sequential addition of terminal alkynes to *para*-substituted phenols, which affords a wide range of *ortho*-propargylic alkylated phenols bearing congested quaternary carbons. Control experiments combined with DFT calculations suggest that the reaction undergoes a sequential phenol alkenylation/hydroalkynylation process. Further extension of this strategy to the construction of triaryl-substituted quaternary carbons demonstrates the broad utility of this method.



The phenol motif is particularly prevalent in bioactive molecules, pharmaceuticals, and functional materials.[1] Direct functionalization of phenols or phenol ethers is highly attractive because of their broad availability from industrialized Hock process[2] or depolymerization of lignin.[3,4] Recently, transition-metal catalysis offers an efficient approach for the regio- and chemo-selective modification of phenols through directed C−H bond functionalization strategy.[5] Alternatively, one can utilize the classical electrophilic aromatic substitution strategy ($E_{Ar}S$) to prepare substituted phenols.[6] In this context, acid-catalyzed Friedel−Crafts reaction,[7,8] is one of the most classical strategies to afford alkylated phenols. However, the alkylation of phenolics with alkynes has been less explored. Although the reaction of phenols with propargylic alcohols or their congeners can give propargylic alkylated phenols, an additional synthetic operation is required to obtain these propargylic reactants (Scheme 1a).[9] Given that the alkyne is one of the most accessible chemicals in petrochemicals,[10] the development of a new method for direct alkylation of phenol with alkyne is highly desired. However, direct alkylation of phenol with alkyne may face the following challenges: (1) phenol may undergo C- or O-alkenylation reactions with alkyne;[11,12] (2) the *ortho*-alkenylated product can further undergo cascade cyclization reaction;[13] (3) a mixture of mono- and multisubstituted products may be formed.[14]

Inspired by our research on borane-catalyzed hydroarylation of 1,3-diene with phenols,[15] we envisioned that the association of the OH group of phenol with $B(C_6F_5)_3$ would probably lead to the reaction of phenol and alkyne affording propargylic alkylated phenols.[16] In addition to the potential competing pathways discussed above, another challenge is to suppress the carboboration reaction between $B(C_6F_5)_3$ and terminal alkynes..[17] Here, we report an OH-assisted propargylation of phenols via sequential additions of aryl terminal alkynes to phenols using $B(C_6F_5)_3$ as catalyst (Scheme 1b). The reaction features step- and atom-economy and enables one to directly

Scheme 1. Propargylic Alkylation of Phenols with Alkynes



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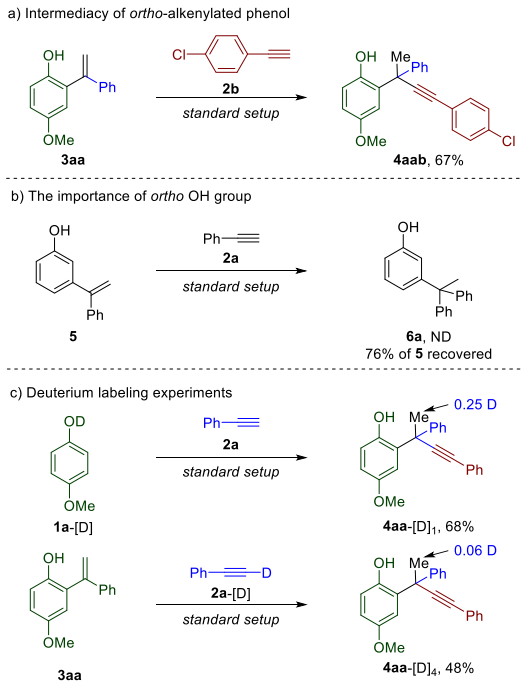
introduce the sterically congested quaternary carbons to *para*-substituted phenols with the reactive OH group untouched. Control experiments and density functional theory (DFT) calculations show that the reaction proceeds through a phenol alkenylation/hydroalkynylation sequence with the assistance of the phenolic OH group. Moreover, the prominent kinetic differentiation between the alkenylation and hydroalkynylation processes enables us to construct unique triaryl-substituted quaternary carbons.

We began investigating the reaction of 4-methoxyphenol **1a** and phenylacetylene **2a** in CH_2Cl_2 using 10 mol % of $B(C_6F_5)_3$ as the catalyst (see Tables S1 for optimization details). Treatment of **1a** with **2a** at room temperature could only afford **4aa** in poor yields along with **3aa** as a major product. It is probably due to the deterioration of $B(C_6F_5)_3$ via the carboboration reaction[17] with terminal alkyne or other unknown processes (see Figures S1−S2 for NMR analysis). We were delighted to find that lowering the reaction temperature to −20 °C could increase the yield of **4aa** to 85% isolated yield. Other Lewis acids, including BCl_3, BBr_3, $(C_6F_5)CH_2CH_2B(C_6F_5)_2$, $FeCl_3$, and $ZnCl_2$, afford little or no desired products **4aa** or related alkenylation product **3aa** (Table S1 and S2), probably due to the generation of other unidentifiable byproducts. Although the reaction was speculated to involve the protonation of alkyne with $B(C_6F_5)_3$-phenol adduct, no desired product was detected in the presence of Brønsted acids.

To shed light on the mechanism, we subjected 2-vinylphenol **3aa** to the standard reaction conditions in the presence of 4-chlorophenylacetylene **2b**, the corresponding phenol **4aab** could be obtained in 67% yield (Scheme 2a). However, the reaction of *meta*-alkenyl phenol **5** with phenylacetylene **2a** did not give the related hydroalkynylation product with 76% recovery of the starting material **5** (Scheme 2b). These results indicate the propargylation reaction of phenol may proceed through a sequential phenol-alkenylation/alkene-hydroalkynylation mechanism,[18] and the existence of the OH group at the *ortho*-position of phenol is important for the hydroalkynylation step. Furthermore, deuterium labeling experiments confirmed the involvement of the protonation of alkyne in the alkenylation step and the deprotonation of terminal alkyne in the hydroalkynyaltion step, respectively (see Scheme 2c and Scheme S1 in the SI).

Scheme 2. Control Experiments



To elucidate the mechanistic details of this reaction, DFT calculations at the M06-2X/cc-pVTZ//M06-2X/6-311G(d,p) level[19] were performed on the model reaction of 4-methoxyphenol **1a** and phenylacetylene **2a** with $B(C_6F_5)_3$ as the catalyst (see SI for computational details, and other kinetically less favorable pathways). As shown in Figure 1, proton transfer from the OH group of **INT1** to alkyne **2a** forms a tight ion-pair **INT2** with a barrier of 16.6 kcal mol^{-1} (via **TS1**). **INT2** consists of a highly electrophilic vinyl cation and a borate-phenol anion as the counteranion, which could readily undergo electrophilic addition reaction to afford the Wheland intermediate **INT3** (via **TS2**, $\Delta G^{\ddagger}$ = 13.9 kcal mol^{-1}). Subsequent rearomatization of **INT3** followed by the dissociation of $B(C_6F_5)_3$ affords the alkenylated phenol **3aa** and regenerates the catalyst.

In competing with catalyst regeneration, **3aa**-$B(C_6F_5)_3$ complex **INT5** could also undergo intramolecular protonation reaction (via **TS4**, $\Delta G^{\ddagger}$ = 12.7 kcal mol^{-1}) to generate a borane-stabilized tertiary carbenium ion **INT6** (Figure 1, right). It then undergoes electrophilic addition reaction with another molecule **2a** to form a zwitterionic intermediate **INT7** (via **TS5**). This step has a barrier of 21.8 kcal mol^{-1}, and the formation of **INT7** is endergonic by 10.7 kcal mol^{-1} relative to **2a** and **INT6**. Then, **INT7** is deprotonated to provide the neutral complex **INT8** with a barrier of 12.2 kcal mol^{-1}. Finally, Lewis acid−base dissociation of **INT8** regenerates $B(C_6F_5)_3$ and releases the *ortho*-propargylation product **4aa**, which is the major product obtained experimentally. Along the whole reaction process, the rate-determining step is the hydroalkynylation step (**3aa** → **4aa**) with a barrier of 21.8 kcal mol^{-1} (via **TS5**). The alkenylation step is kinetically favored over the hydroalkynylation step by 5.2 kcal mol^{-1}, but the former is thermodynamically less favored than the latter. These computational results can account for the experimental observation that the *ortho*-propargyl phenols are accessible through the reaction of phenol with a terminal alkyne under mild conditions. Besides, the proton-initiated mechanism[20] or the direct addition of phenol toward $B(C_6F_5)_3$/alkyne adduct[17] could also be excluded because of the involvement of high-energy transition states (see Figures S8−S9 in the SI for details).

Then, the scope of phenols was examined with phenylacetylene **2a** (Scheme 3). *Para*-substituted phenols bearing electron-donating substituents, including alkoxyl, phenoxyl, and alkyl, could undergo *ortho*-propargylation reactions to give the related phenols in good to excellent yields (**4ba**−**4ga**, 61%−88%). *Para*-halogenated phenols are also applicable to the method, affording the corresponding *ortho*-propargylation products in moderate to excellent yields (**4ha**−**4ka**) in the presence of 15 mol % of $B(C_6F_5)_3$ at −40 °C. It should be noted that the compatibility of synthetically valuable C−Br and C−I bonds provide opportunities for further synthetic manipulations. Trisubstituted phenol **1l** could also be used as the coupling partners to afford the desired product **4la** in moderate yield. However, the current strategy is not applicable to phenols containing groups with a strong coordinating ability

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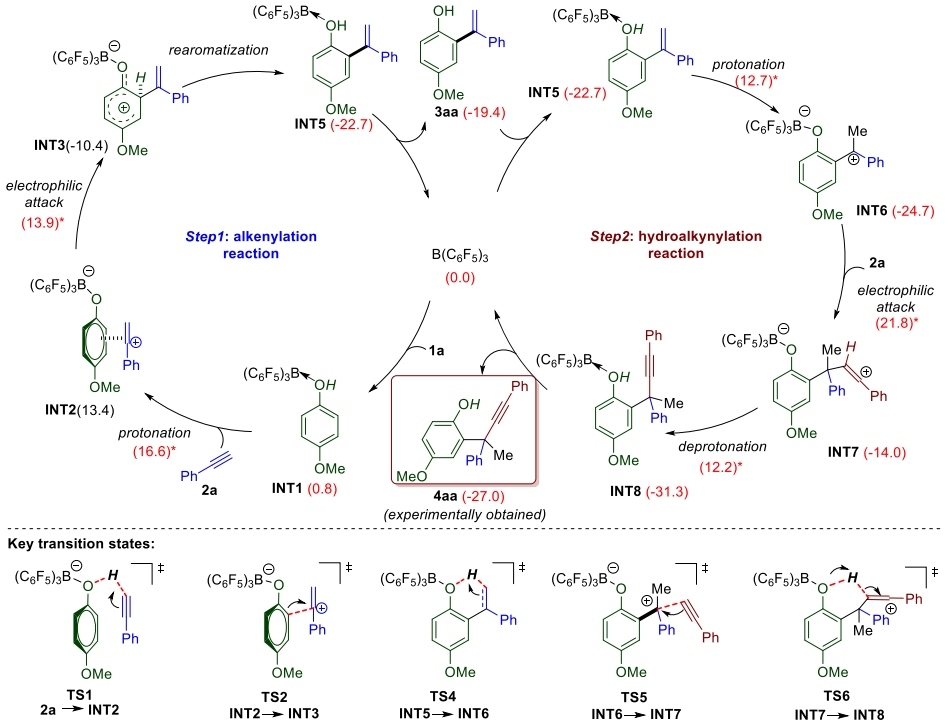
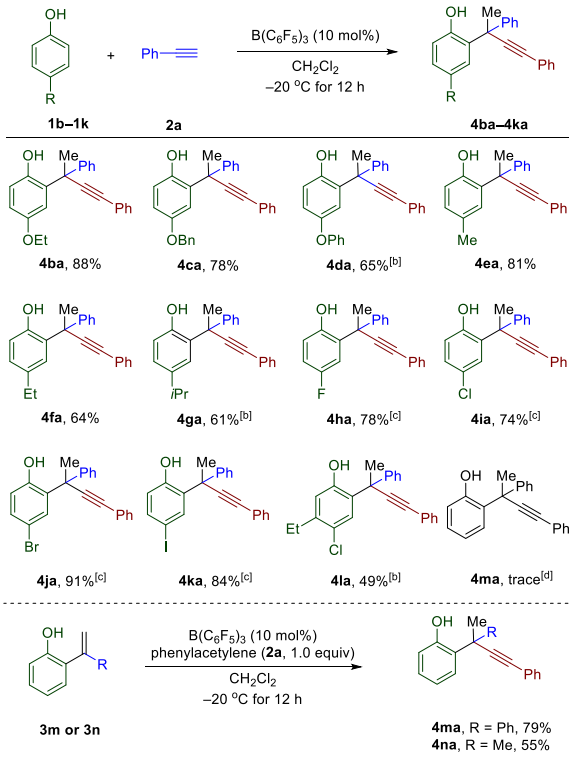


Figure 1. Catalytic cycle of the $B(C_6F_5)_3$ catalyzed propargylation of 4-methoxyphenol **1a** with **2a** via a sequential addition mechanism. Computed Gibbs free reaction energies and barriers (labeled with an asterisk) in kcal mol^{-1} are colored red.

Scheme 3. Scope of Phenols[a]



[a]Isolated yields. [b]15 mol % $B(C_6F_5)_3$. [c]−40 °C with 15 mol % $B(C_6F_5)_3$. [d]a complicated mixture.

(e.g., carbonyl, nitro, nitrile, and amide, see Scheme S2 for unsuccessful substrates). In addition, the reaction of phenol **1m** could not produce the related C−H functionalized product **4ma**, only resulting in a messy mixture. The procedure is also not suitable for *ortho*- or *meta*- substituted phenols. Pleasingly, when we subjected 2-vinylphenols **3m** and **3n** to the standard conditions, the corresponding phenols **4ma** and **4na** could be obtained in 79% and 55% yield respectively (Scheme 3, bottom). This strategy provides a complementary way to synthesize the products that cannot be achieved via the direct reaction of phenol and terminal alkynes.

Subsequently, the substituent effect of alkynes was explored (Scheme 4). The position of substituents on arylacetylene has a significant influence on this reaction. For example, aryl acetylenes bearing neutral, electron-rich, and weak electron-withdrawing substituents at the *para*-position reacted effectively to produce the desired product in moderate to good yields (**4ab**−**4ah**). *Meta*-substituted arylacetylenes could also smoothly react with **1a** to afford *ortho*-propargylic alkylated phenols (**4ai**−**4al**), although 20 mol % of $B(C_6F_5)_3$ is required for *m*-F or *m*-Cl substituted arylacetylene. However, the reaction of *ortho*-substituted arylacetylene **2m** with **1a** stopped at the initial alkenylation step, affording 2-vinylphenol **3am** in excellent yield. It is perhaps because the substituents at *ortho*-position increase the steric crowding at the reaction center. Gratifyingly, the trimethylsilyl (TMS) group which is known to be labile under acidic conditions, is also compatible with our method. The corresponding arylacetylene (**2n**) could be converted to the *ortho*-propargylation product with good efficiency (**4an**, 76% yield). Finally, the reaction of *ortho*-alkenyl phenol **3aa** and *ortho*-methyl phenylacetylene **2m** was conducted to explore the influence of the steric effect (Scheme 4, bottom). Alkene hydroalkynylated product **4aam** could be obtained in 74% yield, which suggests that the introduction of methyl on the *ortho*-position of alkyne did not affect the hydroalkynylation step.

The practicality of this method could be demonstrated by performing a gram-scale synthesis of **4aa** (Scheme 4). With 7.5 mol % $B(C_6F_5)_3$, the desired product **4aa** could be obtained in

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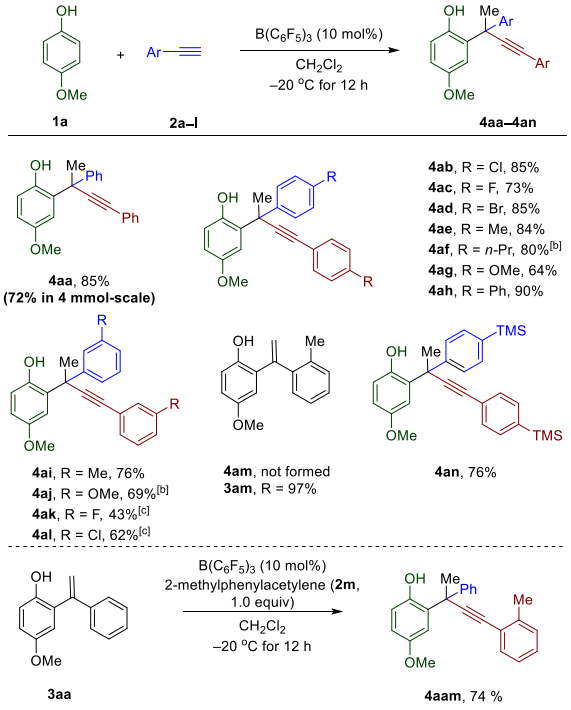
Scheme 4. Scope of Terminal Alkynes[a]



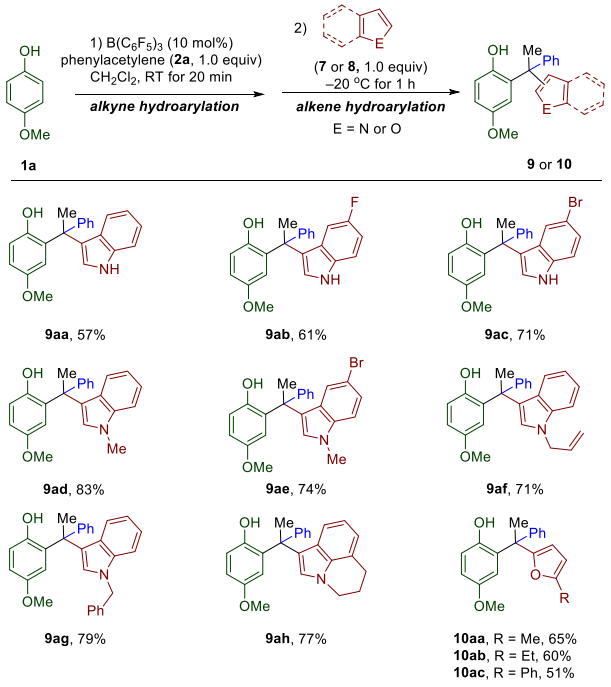
[a]Isolated yields. [b]15 mol % $B(C_6F_5)_3$. [c]20 mol % $B(C_6F_5)_3$.

good yield (952 mg, 72% yield). Both the phenol and alkyne fragments in **4aa** are amendable to afford heterocycles or other phenol analogues, potentially relevant to medicinal applications (see the Supporting Information for these transformation details and related discussion).

Furthermore, the current strategy is also applicable to the construction of triaryl-substituted quaternary carbons, which are significant motifs in biologically active compounds.[21] Under slightly modified reaction conditions, 1,1,1-triaryl ethanes could be obtained in good yields by the direct addition of electron-rich heterocycles into a 2:1 reaction mixture of **1a** and **2a**. As shown in Scheme 5, the reaction proceeds well for both N-protected and unprotected indoles to afford the corresponding products in good efficiency (**9aa**–**9ag**). Alternatively, tricyclic indole derivative lilolidine **7h** formed 1,1,1-triaryl ethane **9ah** in 77% yield. More challenging furan-derived substrates formed products **10aa**–**10ac** in 51–65% yields. Attempts to extend this process to other heterocycles such as benzofuran, pyrrole, and thiophene were unsuccessful, probably due to the low nucleophilicity of these substrates. This procedure not only provides a facile protocol to congested triaryl quaternary carbons but also supports the intermediacy of tertiary carbocation via the intermolecular protonation of the in situ formed 2-vinylphenol.

In summary, we have developed a metal-free, step- and atom-economic method for the propargylation of *para*-substituted phenols with arylacetylenes using $B(C_6F_5)_3$ as the catalyst. The new reaction involves a phenol alkenylation/hydroalkynylation sequence, eventually affording *ortho*-propargyl phenols rather than alkenylated phenols that were observed in metal Lewis acid catalysis. The propargylation products containing a phenolic group and an internal alkyne, could undergo a wide range of transformations to afford heterocycles and other phenol analogues. Control experiments combined with DFT calculations show that the pathway

Scheme 5. Scope Extension: $B(C_6F_5)_3$-Catalyzed One-Pot Construction of Triaryl Substituted Quaternary Carbons



involving borane-assisted sequential inter- and intramolecular protonation reaction is responsible for the formation of the desired products. Further extension of this strategy to the construction of 1,1,1-triaryl ethane also supports the proposed mechanism.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01863.

Calculated full free energy profiles, optimized geometries, experimental procedures, compound characterization, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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