JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

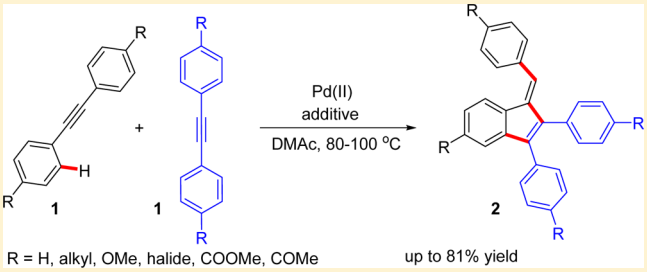
# Synthesis of Benzofulvene Derivatives from Diarylacetylenes via Pd(II)-Catalyzed Alkyne-Directed C($sp^2$)−H Bond Activation

Biao Guo, Liyao Zheng, Lei Zhang, and Ruimao Hua*

Department of Chemistry, Key Laboratory of Organic Optoelectronics & Molecular Engineering of Ministry of Education, Tsinghua University, Beijing 100084, China

Supporting Information

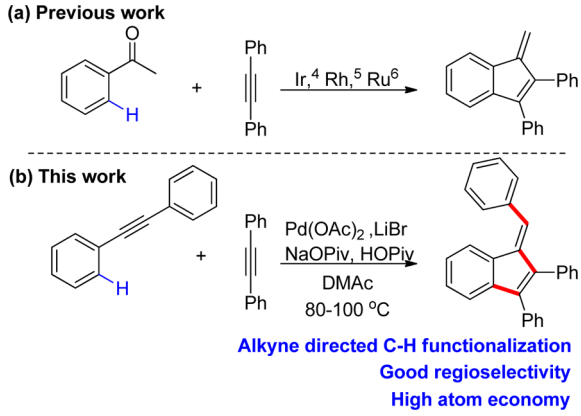
**ABSTRACT:** A novel and efficient protocol for the synthesis of benzofulvene derivatives from easily available diarylacetylenes has been developed. The reaction proceeds through rarely reported carboxylate-assisted alkyne-directed *ortho*-C($sp^2$)−H palladation followed by insertion of another diarylacetylene.




Benzofulvene and its derivatives have attracted growing attention due to their extensive utility in the fields of material science[1] and medicinal chemistry.[2] In the past few decades, many different synthetic approaches to benzofulvene derivatives have been reported.[3] Among numerous accesses to benzofulvene derivatives, transition-metal-catalyzed C−H activation followed by cyclization is an interesting and efficient route as it obviates the needs for prior activation and reduces byproduct and cost. Before long, Shibata, Glorius, and Jeganmohan, respectively, reported Ir-, Rh-, and Ru-catalyzed *ortho*-C−H activation of aryl ketones followed by coupling with internal alkynes to give benzofulvenes (Scheme 1a).[4−6] All of them used carbonyl, which has been demonstrated to be suitable for *ortho*-C−H functionalization as a directing group.[7]

In the past decades, acetylene chemistry experienced a renaissance due to not only its versatility for organic synthesis and broad applications in material science but also its low price and hypotoxicity.[8] Within alkyne chemistry, the direct functionalization of alkynes represents an ideal and highly desired reaction, especially the direct cyclopolymerization of alkynes. Although various elegant pioneering work on transition-metal-catalyzed cycloaddition of acetylenes has been published, most of them focused on access to multisubstituted benzenes via [2 + 2 + 2] cyclotrimerization of various alkynes.[9] Meanwhile, Kisch reported the rhodium-catalyzed cyclodimerization of diarylacetylenes to give multisubstituted naphthalenes,[10] and Miura even realized highly chemoselective synthesis of multisubstituted naphthalene derivatives through cross-cyclodimerization of two different internal alkynes.[11]

**Scheme 1. Synthesis of Benzofulvenes via Transition-Metal-Catalyzed C−H Activation**




However, an efficient and simple approach to benzofulvenes through direct cyclodimerization of alkynes has still not been established. In view of our continuing interest in transition-metal-catalyzed C−H activation and alkyne chemstry,[12] herein we report a new protocol to benzofulvenes through direct cyclodimerization of diarylacetylenes via Pd-catalyzed alkyne-directed *ortho*-C−H activation followed by cyclization (Scheme 1b). It is worth noting that using alkynyl as the directing group (DG) is very rare.[13]

Our initial investigation was carried out by treating diphenylacetylene **1a** using $Pd(OAc)_2$ (10 mol %), LiBr (1.0 equiv), and NaOAc (1.0 equiv) in DMAc at 120 °C for 30 h, but no desired product was observed (Table 1, entry 1). We repeated the reaction using HOAc (1.5 equiv) to replace NaOAc and found it still did not work (Table 1, entry 2). However, when we added NaOAc (1.0 equiv) and HOAc (1.5 equiv) together in the system, the reaction afforded the product of (*E*)-1-benzylidene-2,3-diphenyl-1*H*-indene (**2a**) in 21% yield with high regioselectivity (Table 1, entry 3), and the structure

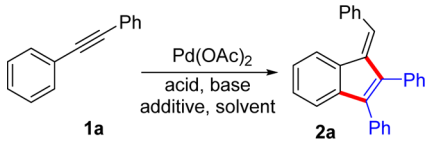
**Received:** June 10, 2015
**Published:** August 4, 2015





DOI: 10.1021/acs.joc.5b01304
J. Org. Chem. 2015, 80, 8430−8434

**Table 1. Reaction Optimization for the Synthesis of 2a**[a]




| entry | additive | acid | base | temp (°C) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | LiBr | | NaOAc | 120 | 0 |
| 2 | LiBr | HOAc | | 120 | 0 |
| 3 | LiBr | HOAc | NaOAc | 120 | 21 |
| 4 | LiBr | PrCOOH | NaOAc | 120 | 35 |
| 5 | LiBr | PhCOOH | NaOAc | 120 | 0 |
| 6 | LiBr | HOPiv | NaOAc | 120 | 56 |
| 7 | LiBr | TFA | NaOAc | 120 | 0 |
| 8 | LiBr | HOPiv | LiOAc | 120 | 33 |
| 9 | LiBr | HOPiv | KOAc | 120 | 40 |
| 10 | LiBr | HOPiv | $Na_2CO_3$ | 120 | 0 |
| 11 | LiBr | HOPiv | $Li_2CO_3$ | 120 | 0 |
| 12 | LiBr | HOPiv | NaOPiv | 120 | 62 |
| 13 | LiBr | HOPiv | NaOPiv | 80 | 70 |
| 14 | LiBr | HOPiv | NaOPiv | 60 | 24 |
| 15 | LiCl | HOPiv | NaOPiv | 80 | 0 |
| 16 | NaBr | HOPiv | NaOPiv | 80 | 44 |
| 17 | NaI | HOPiv | NaOPiv | 80 | 0 |
| 18 | $CuBr_2$ | HOPiv | NaOPiv | 80 | 39 |
| 19 | $NBu_4Br$ | HOPiv | NaOPiv | 80 | 27 |
| 20[c] | LiBr | HOPiv | NaOPiv | 80 | 68 |
| 21[d] | LiBr | HOPiv | NaOPiv | 80 | trace |
| 22[e] | LiBr | HOPiv | NaOPiv | 80 | 25 |
| 23[f] | LiBr | HOPiv | NaOPiv | 80 | 0 |

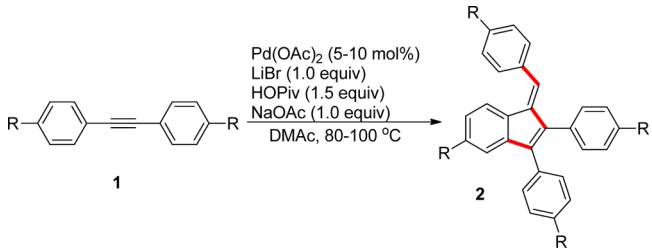
[a]Reaction conditions: **1a** (0.4 mmol), $Pd(OAc)_2$ (10 mol %), additive (0.4 mmol), acid (0.6 mmol), base (0.4 mmol), DMAc (2 mL), 30 h. DMAc: *N*,*N*-dimethylacetamide. [b]Isolated yield. [c]$PdCl_2$ instead of $Pd(OAc)_2$. [d]$Pd(PPh_3)_4$ instead of $Pd(OAc)_2$. [e]DMF instead of DMAc. [f]DCE, toluene, 1,4-dioxane, or DMSO instead of DMAc.

was clearly confirmed by X-ray crystallography (see the Supporting Information). We then investigated a variety of acids instead of HOAc in this reaction (Table 1, entries 4−7). It was found that both PrCOOH and PivOH could improve the yield to some extent, and PivOH led to a higher yield of 56%; however, stronger acids, such as PhCOOH and TFA, hindered the occurrence of the reaction. Therefore, we chose PivOH as the acid to screen different bases instead of NaOAc (Table 1, entries 8−12). It was found that sodium pivalate (NaOPiv) was the most efficient base, which could increase the yield to 62% (Table 1, entry 12). On the other hand, some inorganic bases were totally inefficient, and these results strongly indicated that carboxylate is key factor for promoting the activation of C−H bonds (Table 1, entries 10 and 11).[14] In addition, when the reaction temperature decreased to 80 °C, the yield was further improved to 70% (Table 1, entry 13), but the yield of **2a** declined at lower temperature (Table 1, entry 14).

We also screened additives (Table 1, entries 15−19). The results implied that other metal halides, except metal bromides like LiCl and NaI, were invalid for this transformation. Other metal or organic bromides such as NaBr, $CuBr_2$, or $NBu_4Br$ could promote the reaction but were less efficient compared with LiBr. Other palladium(II) salts such as $PdCl_2$ had almost the same activity for the reaction (Table 1, entry 20), but palladium(0) seemed inactive for the conversion (Table 1, entry 21). In addition, we screened some other solvents (Table 1, entries 22 and 23) and found that DMAc was almost the only efficient solvent for this transformation.

With the optimized conditions in hand, we turned our attention to the substrate scope of the reaction. We first investigated the substitution effect on the benzene ring of **1**. The substrates bearing electron-withdrawing groups (EWGs) such as halide (Table 2, entries 2−4), acetyl (Table 2, entry 5),

**Table 2. Scope of Diarylacetylenes for Benzofulvene Synthesis**[a]




| entry | substrate | | | yield (%)[b] |
|---|---|---|---|---|
| 1 | **1a** | R = H | **2a** | 70 |
| 2 | **1b** | R = F | **2b** | 61 |
| 3 | **1c** | R = Cl | **2c** | 55 |
| 4 | **1d** | R = Br | **2d** | 48 |
| 5 | **1e** | R = COMe | **2e** | 66 |
| 6 | **1f** | R = $CF_3$ | **2f** | 47 |
| 7 | **1g** | R = COOMe | **2g** | 81 |
| 8[c] | **1h** | R = Me | **2h** | 68 |
| 9[c] | **1i** | R = Et | **2i** | 54 |
| 10[c,d] | **1j** | R = $^t$Bu | **2j** | 43 |
| 11[c,d] | **1k** | R = OMe | **2k** | 39 |

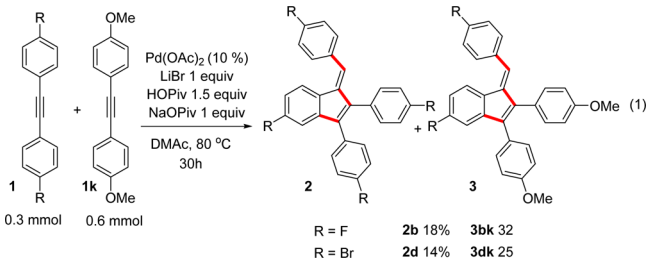
[a]Reaction conditions: **1** (0.4 mmol), $Pd(OAc)_2$ (10 mol %), additive (0.4 mmol), acid (0.6 mmol), base (0.4 mmol), DMAc (2 mL), 80 °C, 30 h. [b]Isolated yield. [c]$PdCl_2$ instead of $Pd(OAc)_2$, 100 °C. [d]40 h.

or even trifluoromethyl (Table 2, entry 6) were effectively transformed to the expected benzofulvenes in moderate to good yields. Notably, the acid-labile functional group COOMe was tolerant under the reaction conditions to give desired product **2g** in high yield (Table 2, entry 7, 81%). Subsequently, we tried to apply our protocol to substrates with electron-donating groups (EDGs), but the conversion of the reactant was very sluggish, even at an elevated temperature of 120 °C. Therefore, we tried more active palladium catalyst $PdCl_2$ instead of $Pd(OAc)_2$ and increased the temperature to 100 °C at the same reaction time. To our delight, the substrates with methyl (**2h**, 68%) and ethyl (**2i**, 54%) could undergo the transformation smoothly under the modified conditions. and $^t$Bu (**2j**, 43%) and OMe (**2k**, 39%) were also compatible for the system with a prolonged reaction time (40 h).

The scope of the investigation illustrated that the electronic effect was dramatic in the catalytic system. EWGs could activate the alkynes, but on the contrary, EDGs could inactivate the starting materials. Inspired by the unique electronic effect, we could realize cross-cyclodimerization of two different diarylacetylenes. As shown in eq 1, we employed diarylacetylene bearing EWG **1b** (0.3 mmol) or **1d** (0.3 mmol) with 1,2-bis(4-methoxyphenyl)acetylene **1k** (0.6 mmol), which was had an EDG in one pot under the optimized conditions. The cross-dimerization products **3bk** or **3dk** could be isolated, respectively, in 32 and 25% (based on **1b** and **1d**) yield. Unfortunately, even though **1k** was twice as much as **1b**, the

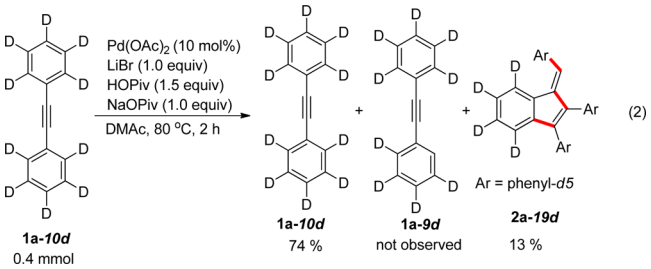


DOI: 10.1021/acs.joc.5b01304
J. Org. Chem. 2015, 80, 8430−8434



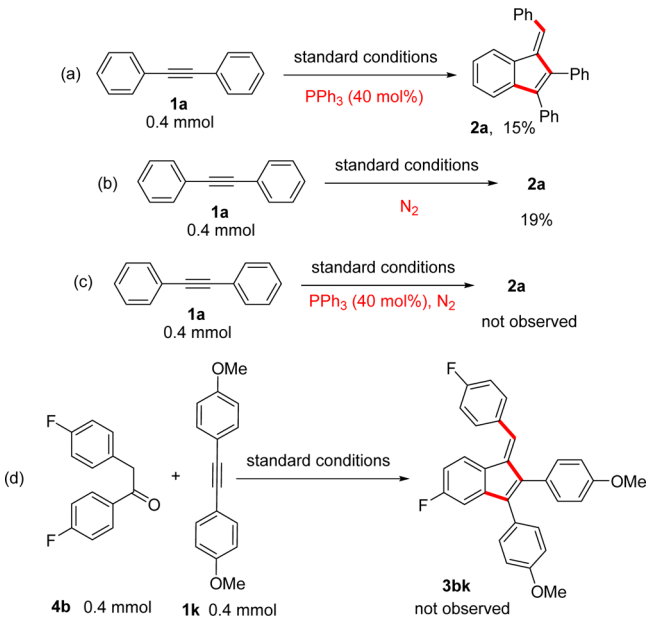

homodimerization product **2b** could not be suppressed efficiently.[15]

In order to figure out the mechanism of the reaction, we did a series of condition-controlled experiments. The deuterium-labeling experiment (eq 2) indicated that the *ortho*-C−H




activation was irreversible, as no scrambling of *ortho*-deuterium atoms (**1a-9*d***) was observed in the reactant. As noted in the discussion of optimizing reaction conditions, the starting material **1a** could barely convert to the product **2a** when we used $Pd(PPh_3)_4$ instead of $Pd(OAc)_2$ (Table 1, entry 21). We assumed that Pd(II) was the efficient catalyst and Pd(0) was invalid. Therefore, we added 40% $PPh_3$ to our standard conditions in order to reduce Pd(II) to Pd(0). As we had expected, it gave the product in a low yield of only 15% (Scheme 2a). To avoid the influence of oxygen in the air, the same experiment under the protection of nitrogen atmosphere was carried out and the desired dimerization was not observed at all (Scheme 2c). It was found that the conversion would be

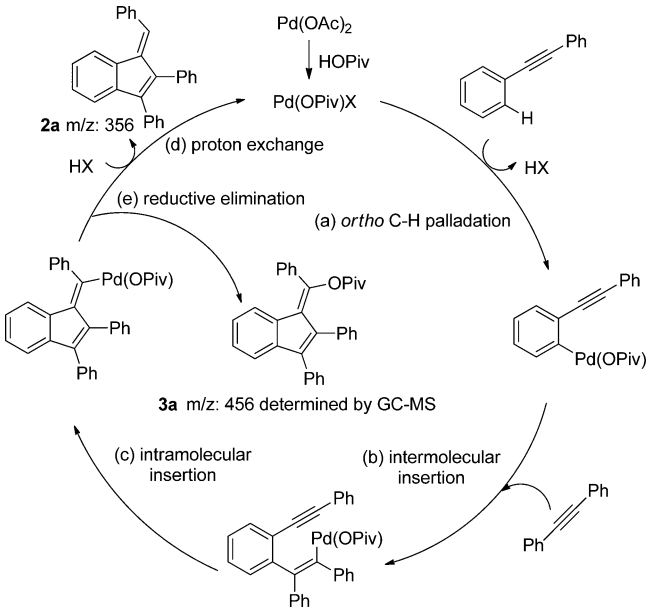
**Scheme 2. Condition-Controlled Experiments**




seriously inhibited under nitrogen atmosphere even without reductant (Scheme 2b). The result implied that a certain amount of oxygen was crucial for the formation of **2a**. In addition, the result from another controlled experiment, as shown in Scheme 2d), can exclude the possible mechanism for the formation of **2a** via palladium-catalyzed carbonyl-directed *ortho*-C−H bond functionalization. In this case, both **4b** and **1k** were recovered completely.

Although the detailed mechanism remained unclear, we proposed a plausible mechanism for the formation of benzofulvenes based on previous studies of palladium catalysis[16] and our experimental results (Scheme 3): (a)

**Scheme 3. Proposed Mechanism**




irreversible *ortho*-C−H palladation of aryl via carboxylate-assisted C−H bond cleavage, (b) intermolecular insertion of the other diarylacetylene to the generated arylpalladium species, (c) intramolecular alkyne insertion, (d) proton exchange to give product **2a** and palladium(II), or (e) reductive elimination to produce **3a**[17] and regenerate palladium(0). A similar mechanism was reported by Segawa and Itami for the $PdCl_2$-catalyzed dehydrogenation oxidation coupling of diarylacetylenes, except for step (d) proton exchange.[13a]

In conclusion, we have developed an efficient and concise protocol to synthesize benzofulvenes from easily available diarylacetylenes with high atom economy and high regioselectivity. The transformation occurs through a novel cascade process including carboxylate-assisted Pd-catalyzed alkyne-directed *ortho*-C−H activation followed by intermolecular insertion of the other diarylacetylene and intramolecular alkyne insertion.

## EXPERIMENTAL SECTION

**General Methods.** All commercial reagents are analytically pure and used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded using $CDCl_3$ as solvent at 298 K. $^1H$ NMR (400 MHz) chemical shifts ($\delta$) were referenced to internal standard tetramethylsilane (for $^1H$, $\delta$ = 0.00 ppm). $^{13}C$ NMR (101 MHz) chemical shifts were referenced to internal solvent $CDCl_3$ (for $^{13}C$, $\delta$ = 77.16 ppm). HRMS experiments were performed on a high-



DOI: 10.1021/acs.joc.5b01304
J. Org. Chem. 2015, 80, 8430−8434

resolution magnetic sector mass spectrometer. The melting points are uncorrected.

**Typical Experimental Procedure for the Synthesis of Benzofulvene 2a from Diphenylacetylene 1a.** A mixture of diphenylacetylene (**1a**, 71.2 mg, 0.4 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol, 10 mol %), PivOH (61.2 mg, 0.6 mmol, 1.5 equiv), NaOPiv (49.6 mg, 0.4 mmol, 1.0 equiv), LiBr (34.7 mg, 0.4 mmol, 1.0 equiv), and DMAc (2.0 mL) was heated at 80 °C (oil bath temperature) with stirring in a 25 mL screw-capped thick-walled Pyrex tube under air atmosphere for 12 h. After removal of the solvent under reduced pressure, purification was performed by flash column chromatography on silica gel with petroleum ether/DCM (gradient mixture ratio from 100:0 to 96:3) as eluent to give (*E*)-1-benzylidene-2,3-diphenyl-1*H*-indene **2a** in 70% yield (50.0 mg).

*(E)-1-Benzylidene-2,3-diphenyl-1H-indene (**2a**):*[18] orange red solid (50.0 mg,70% yield); mp 176−178 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.59−7.47 (m, 2H), 7.46−7.10 (m, 13H), 7.05−6.97 (m, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 143.9, 141.6, 140.6, 139.9, 137.2, 135.2, 134.9, 134.7, 134.6, 131.4, 129.7, 129.4, 128.6, 128.3, 128.1, 128.1, 127.4, 127.1, 125.4, 123.4, 120.2; HRMS (APPI-Orbitrap) $m/z$ $[M + H]^+$ calcd for $C_{28}H_{21}$ 357.1637, found 357.1624.

*(E)-5-Fluoro-1-(4-fluorobenzylidene)-2,3-bis(4-fluorophenyl)-1H-indene (**2b**):* orange red solid (52.0 mg,71% yield); mp 184−186 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.52−7.43 (m, 3H), 7.23−7.16 (m, 4H), 7.24−7.16 (m, 2H), 7.05−6.95 (m, 6H), 6.72 (td, $J$ = 8.7, 2.4 Hz, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 163.3 (d, $^1J_{C-F}$ = 246.6 Hz), 162.8 (d, $^1J_{C-F}$ = 249.0 Hz), 162.3 (d, $^1J_{C-F}$ = 247.2 Hz), 162.3 (d, $^1J_{C-F}$ = 247.5 Hz), 146.0 (d, $^3J_{C-F}$ = 8.7 Hz), 140.6, 140.5, 139.1 (d, $^4J_{C-F}$ = 1.4 Hz), 133.5, 132.7 (d, $^3J_{C-F}$ = 7.9 Hz), 132.6 (d, $^4J_{C-F}$ = 3.2 Hz), 131.3 (d, $^3J_{C-F}$ = 8.0 Hz), 131.1 (d, $^3J_{C-F}$ = 7.9 Hz), 130.4 (d, $^4J_{C-F}$ = 3.1 Hz), 130.0 (d, $^4J_{C-F}$ = 2.7 Hz), 124.4 (d, $^3J_{C-F}$ = 8.9 Hz), 115.8 (d, $^2J_{C-F}$ = 21.5 Hz), 115.7 (d, $^2J_{C-F}$ = 21.4 Hz), 115.4 (d, $^2J_{C-F}$ = 21.3 Hz), 112.0 (d, $^2J_{C-F}$ = 22.8 Hz), 107.6 (d, $^2J_{C-F}$ = 24.0 Hz); HRMS (APPI-Orbitrap) $m/z$ $[M + H]^+$ calcd for $C_{28}H_{17}F_4$ 429.1261, found 429.1263.

*(E)-5-Chloro-1-(4-chlorobenzylidene)-2,3-bis(4-chlorophenyl)-1H-indene (**2c**):* orange red solid (54.0 mg, 55% yield); mp 204−206 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.47−7.38 (m, 5H), 7.34−7.28 (m, 4H), 7.25 (m, 1H), 7.18−7.12 (m, 4H), 7.05−7.00 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 145.1, 140.8, 140.2, 139.2, 134.8, 134.8, 134.47, 134.2, 133.9, 133.8, 132.7, 132.4, 132.4, 132.3, 130.8, 130.8, 129.0, 129.0, 128.7, 125.6, 124.3, 120.5; HRMS (APPI-Orbitrap) $m/z$ $[M + H]^+$ calcd for $C_{28}H_{17}Cl_4$ 493.0079, found 493.0085.

*(E)-5-Bromo-1-(4-bromobenzylidene)-2,3-bis(4-bromophenyl)-1H-indene (**2d**).* orange red solid (64.0 mg, 48% yield); mp 210−212 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.56 (d, $J$ = 8.2 Hz, 2H), 7.49−7.43 (m, 4H), 7.40−7.33 (m, 4H), 7.17 (m, 1H), 7.09 (t, $J$ = 8.1 Hz, 4H), 7.03 (s, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 145.3, 140.8, 140.0, 139.2, 135.2, 134.4, 133.0, 132.8, 132.7, 132.0, 131.7, 131.0, 128.6, 124.6, 123.4, 123.1, 122.7, 122.1, 122.09; HRMS (APPI-Orbitrap) $m/z$ $[M]^+$ calcd for $C_{28}H_{16}{}^{79}Br_4$ 667.7980, found 667.7986; $[M]^+$ calcd for $C_{28}H_{16}{}^{79}Br_3{}^{81}Br$ 669.7959, found 669.7965; $[M]^+$ calcd for $C_{28}H_{16}{}^{79}Br_2{}^{81}Br_2$ 671.7939, found 671.7944.

*(E)-5-Acetyl-1-(4-acetylbenzylidene)-2,3-bis(4-acetylphenyl)-1H-indene (**2e**):* orange red solid (69.0 mg, 66% yield); mp 206−208 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.06 (d, $J$ = 8.2 Hz, 2H), 7.94 (dd, $J$ = 8.3, 3.1 Hz, 4H), 7.91 (s, 1H), 7.70 (dd, $J$ = 8.0, 1.4 Hz, 1H), 7.65 (d, $J$ = 8.2 Hz, 2H), 7.58 (d, $J$ = 8.0 Hz, 1H), 7.38 (t, $J$ = 8.0 Hz, 4H), 7.25 (s, 1H), 2.68 (s, 3H), 2.62 (s, 6H), 2.58 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 197.8, 197.71, 197.68 197.5, 143.6, 141.5, 141.0, 140.9, 140.5, 139.1, 138.6, 138.4, 137.3, 137.2, 136.5, 136.4, 136.0, 131.3, 129.7, 128.8, 128.5, 127.0, 123.5, 119.8, 26.9, 26.8, 26.7; HRMS (APPI-Orbitrap) $m/z$ $[M + H]^+$ calcd for $C_{36}H_{29}O_4$ 525.2060, found 525.2050.

*(E)-5-Trifluoromethyl-1-(4-trifluoromethylbenzylidene)-2,3-bis(4-trifluoromethylphenyl)-1H-indene (**2f**):* orange red solid (59.0 mg, 47% yield); mp 172−176 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.74 (d, $J$ = 8.2 Hz, 2H), 7.69−7.61 (m, 6H), 7.53 (d, $J$ = 7.4 Hz, 2H), 7.39 (m, 5H), 7.23 (s, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 143.6, 141.5, 140.5, 140.4, 139.8, 137.6, 137.1, 135.8, 131.4, 131.1 (q, $^2J_{C-F}$ = 32.8 Hz), 130.9 (q, $^2J_{C-F}$ = 32.4 Hz), 130.4 (q, $^2J_{C-F}$ = 32.6 Hz), 130.7 (q, $^2J_{C-F}$ = 32.9 Hz),129.8, 129.7, 125.9, 125.63, 125.59, 124.3 (q, $^1J_{C-F}$ = 272.5 Hz), 124.18 (q, $^1J_{C-F}$ = 272.1 Hz), 124.13 (q, $^1J_{C-F}$ = 272.2 Hz), 124.09 (q, $^1J_{C-F}$ = 272.3 Hz), 123.4, 123.3, 117.1, 117.0; HRMS (APPI-Orbitrap) $m/z$ $[M + H]^+$ calcd for $C_{32}H_{17}F_{12}$ 629.1133, found 629.1138.

*(E)-5-Methoxycarbonyl-1-(4-(methoxycarbonyl)benzylidene)-2,3-bis(4-methoxycarbonylphenyl)-1H-indene (**2g**):* orange red solid (95.0 mg, 81% yield); mp 254−256 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.13 (d, $J$ = 8.2 Hz, 2H), 8.01 (dd, $J$ = 8.3, 1.1 Hz, 4H), 7.96 (d, $J$ = 1.1 Hz, 1H), 7.78 (dd, $J$ = 8.0, 1.5 Hz, 1H), 7.62 (d, $J$ = 8.2 Hz, 2H), 7.56 (d, $J$ = 8.1 Hz, 1H), 7.35 (d, $J$ = 8.4 Hz, 2H), 7.33 (d, $J$ = 8.4 Hz, 2H), 7.24 (s, 1H), 3.97 (s, 3H), 3.92 (s, 6H), 3.89 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 167.0, 166.8(2), 166.7, 143.3, 141.4, 140.9, 140.8, 140.4, 139.0, 138.5, 138.3, 136.0, 131.1, 130.4, 130.2, 130.0, 129.9, 129.64, 129.57, 129.49, 129.45, 127.8, 123.3, 121.2, 52.4, 52.3; HRMS (APPI-Orbitrap) $m/z$ $[M + H]^+$ calcd for $C_{36}H_{29}O_8$ 589.1857, found 589.1840.

*(E)-5-Methyl-1-(4-methylbenzylidene)-2,3-bis(4-methylphenyl)-1H-indene (**2h**):* orange red solid (56.0 mg, 68% yield); mp 188−190 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.52 (d, $J$ = 7.8 Hz, 1H), 7.43 (d, $J$ = 7.9 Hz, 2H), 7.24−7.12 (m, 4H), 7.11−7.07(m, 4H), 5.05(s, 1H), 6.82 (d, $J$ = 7.8 Hz, 1H), 2.40 (s, 3H), 2.34 (s, 6H), 2.32 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 144.4, 141.2, 140.0, 139.9, 138.1, 137.9, 136.8, 136.5, 134.4, 133.7, 132.4, 132.2, 132.1, 131.2, 129.6, 129.6, 129.2, 129.0, 128.8, 125.8, 123.1, 120.9, 21.8, 21.6, 21.5, 21.4; HRMS (APPI-Orbitrap) $m/z$ $[M + H]^+$ calcd for $C_{32}H_{29}$ 413.2263, found 413.2249.

*(E)-5-Ethyl-1-(4-ethylbenzylidene)-2,3-bis(4-ethylphenyl)-1H-indene (**2i**):* orange red solid (50.0 mg, 54% yield); mp 114−116 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.57 (d, $J$ = 7.8 Hz, 1H), 7.47 (d, $J$ = 8.0 Hz, 2H), 7.25−7.19 (m, 5H), 7.13 (m, 6H), 7.07 (s, 1H), 6.86 (d, $J$ = 7.8 Hz, 1H), 2.73−2.58 (m, 8H), 1.28 (t, $J$ = 7.5 Hz, 3H), 1.25 (t, $J$ = 7.5 Hz, 3H), 1.24 (t, $J$ = 7.5 Hz, 3H), 1.20 (t, $J$ = 7.5 Hz, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 144.5, 144.4, 143.0, 142.8, 141.1, 140.0, 139.8, 134.7, 133.8, 132.7, 132.4, 132.3, 131.3, 129.7, 129.6, 127.9, 127.7, 127.5, 124.6, 123.2, 119.8, 29.4, 28.9, 28.8, 28.7, 16.2, 15.6, 15.5, 15.4; HRMS (APPI-Orbitrap) $m/z$ $[M + H]^+$ calcd for $C_{36}H_{37}$ 469.2889, found 469.2882.

*(E)-5-(tert-Butyl)-1-(4-(tert-butyl)benzylidene)-2,3-bis(4-(tert-butyl)lphenyl)-1H-indene (**2j**):* orange red solid (50.0 mg, 43% yield); mp 232−234 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.63 (d, $J$ = 8.1 Hz, 1H), 7.50 (m, 2H), 7.43 (m, 3H), 7.30 (m, 4H), 7.25 (m, 2H), 7.15 (m, 2H), 7.09 (dd, $J$ = 8.1, 1.7 Hz, 1H), 7.06 (s, 1H), 1.37 (s, 9H), 1.33 (s, 9H), 1.32 (s, 9H), 1.31 (s, 9H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 151.3, 151.3, 149.8, 149.6, 144.0, 141.1, 140.1, 139.9, 134.5, 133.8, 132.5, 132.1, 132.1, 131.0, 129.4, 125.3, 125.1, 124.8, 122.9, 122.1, 117.3, 35.1, 34.9, 34.7, 34.7, 31.6, 31.5; HRMS (APPI-Orbitrap) $m/z$ $[M + H]^+$ calcd for $C_{44}H_{53}$ 581.4141, found 581.4124.

*(E)-5-Methoxy-1-(4-methoxybenzylidene)-2,3-bis(4-methoxyphenyl)-1H-indene (**2k**):* orange red solid (37.0 mg, 39% yield); mp 162−164 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.60 (d, $J$ = 8.4 Hz, 1H), 7.48 (d, $J$ = 8.5 Hz, 2H), 7.21 (d, $J$ = 8.0 Hz, 2H), 7.16 (d, $J$ = 8.0 Hz, 2H), 6.97 (s, 1H), 6.93 (d, $J$ = 8.2 Hz, 2H), 6.91 (d, $J$ = 1.6 Hz, 1H), 6.84 (d, $J$ = 8.0 Hz, 2H), 6.83 (d, $J$ = 8.0 Hz, 2H), 6.57 (dd, $J$ = 8.3, 1.5 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 160.0, 159.6, 158.64, 158.60, 146.0, 140.4, 140.2, 138.7, 132.4, 132.4, 131.1, 130.8, 129.6, 127.7, 127.4, 127.4, 124.0, 113.9, 113.8, 113.5, 110.0, 106.2, 55.6, 55.4, 55.3; HRMS (APPI-Orbitrap) $m/z$ $[M + H]^+$ calcd for $C_{32}H_{29}O_4$ 477.2060, found 477.2052.

*(E)-5-Fluoro-1-(4-fluorobenzylidene)-2,3-bis(4-methoxyphenyl)-1H-indene (**3bk**):* orange red solid (43.0 mg, 32% yield); mp 198−200 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.50 (d $J$ = 8.5, 1H), 7.49 (d $J$ = 8.4, 1H), 7.42 (m, 1H), 7.21 (d, $J$ = 8.6 Hz, 2H), 7.18 (d, $J$ = 8.6 Hz, 2H), 7.13 (t, $J$ = 8.7 Hz, 2H), 7.08−7.03 (m, 2H), 6.88 (m, 4H), 6.70 (td, $J$ = 8.8, 2.4 Hz, 1H), 3.826 (s, 3H), 3.822 (s, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$163.3 (d, $^1J_{C-F}$ = 246.1 Hz), 162.7 (d, $^1J_{C-F}$ = 248.4 Hz), 159.0, 158. 9, 146.6 (d, $^3J_{C-F}$ = 8.8 Hz), 141.0, 140.5, 139.0, 133.0 (d, $^4J_{C-F}$ = 3.4 Hz), 132.6, 132.3, 131.3 (d, $^3J_{C-F}$ = 8.0 Hz), 130.7,



DOI: 10.1021/acs.joc.5b01304
J. Org. Chem. 2015, 80, 8430−8434

130.2 (d, $^4J_{C-F}$ = 2.4 Hz), 127.0, 126.7, 124.2 (d, $^3J_{C-F}$ = 8.9 Hz), 115.7 (d, $^2J_{C-F}$ = 21.4 Hz),114.0, 113.7, 111.4 (d, $^2J_{C-F}$ = 22.7 Hz), 107.6 (d, $^2J_{C-F}$ = 23.9 Hz), 55.3; HRMS (APPI-Orbitrap) $m/z$ [M + H]$^+$ calcd for $C_{30}H_{23}F_2O_2$ 453.1660, found 453.1652.

*(E)-5-Bromo-1-(4-bromobenzylidene)-2,3-bis(4-methoxyphenyl)-1H-indene (**3dk**):* orange red solid (43.0 mg, 25% yield); mp 218−220 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.55 (d, $J$ = 8.4 Hz, 2H), 7.45 (d, $J$ = 1.7 Hz, 1H), 7.37 (d, $J$ = 8.3 Hz, 2H), 7.33 (d, $J$ = 8.2 Hz, 1H), 7.19 (d, $J$ = 8.8 Hz, 2H), 7.15 (d, $J$ = 8.7 Hz, 2H), 7.14 (dd, $J$ = 8.1, 1.9 Hz, 1H), 7.05 (s, 1H), 6.87 (d, $J$ = 8.7 Hz, 2H), 6.86 (d, $J$ = 8.8 Hz, 2H). 3.81 (s, 6H); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 159.0, 158.9, 146.3, 141.4, 140.0, 139.3, 135.8, 133.2, 133.1, 132.3, 131.9, 131.1, 130.8, 127.9, 126. 8, 126.5, 124.4, 123.3, 122.6, 122.5, 114.0, 113.8, 55.4; HRMS (APPI-Orbitrap) $m/z$ [M + H]$^+$ calcd for $C_{30}H_{23}Br_2O_2$ 573.0059, found 573.0046.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01304.

Copies of $^1$H and $^{13}$C NMR spectra charts and HRMS charts of all products (PDF)

X-ray structural details of **2a** (CIF)

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: ruimao@mail.tsinghua.edu.cn.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This project was supported by National Natural Science Foundation of China (21473097, 21273125).

## ■ REFERENCES


(1) (a) Martinelli, C.; Cardone, A.; Pinto, V.; Talamo, M. M.; D'arienzo, M. L.; Mesto, E.; Schingaro, E.; Scordari, F.; Naso, F.; Musio, R.; Farinola, G. M. *Org. Lett.* **2014**, *16*, 3424. (b) Kosaka, Y.; Kitazawa, K.; Inomata, S.; Ishizone, T. *ACS Macro Lett.* **2013**, *2*, 164. (c) Cappelli, A.; Galeazzi, S.; Giuliani, G.; Anzini, M.; Grassi, M.; Lapasin, R.; Grassi, G.; Farra, R.; Dapas, B.; Aggravi, M.; Donati, A.; Zetta, L.; Boccia, A. C.; Bertini, F.; Samperi, F.; Vomero, S. *Macromolecules* **2009**, *42*, 2368. (d) Cappelli, A.; Galeazzi, S.; Giuliani, G.; Anzini, M.; Donati, A.; Zetta, L.; Mendichi, R.; Aggravi, M.; Giorgi, G.; Paccagnini, E.; Vomero, S. *Macromolecules* **2007**, *40*, 3005. (e) Basurto, S.; García, S.; Neo, A. G.; Torroba, T.; Marcos, C. F.; Miguel, D.; Barberá, J.; Ros, M. B.; de La Fuente, M. R. *Chem. - Eur. J.* **2005**, *11*, 5362. (f) Nakano, T.; Yade, T.; Fukuda, Y.; Yamaguchi, T.; Okumura, S. *Macromolecules* **2005**, *38*, 8140. (g) Nakano, T.; Yade, T. *J. Am. Chem. Soc.* **2003**, *125*, 15474. (h) Kondo, K.; Goda, H.; Takemoto, K.; Aso, H.; Sasaki, T.; Kawakami, K.; Yoshida, H.; Yoshida, K. *J. Mater. Chem.* **1992**, *2*, 1097.

(2) (a) Muthusamy, S.; Sivaguru, M. *Org. Lett.* **2014**, *16*, 4248. (b) Jeffrey, J. L.; Sarpong, R. *Tetrahedron Lett.* **2009**, *50*, 1969. (c) Walters, M. J.; Blobaum, A. L.; Kingsley, P. J.; Felts, A. S.; Sulikowski, G. A.; Marnett, L. J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3271. (d) Alcalde, E.; Mesquida, N.; Frigola, J.; López-Pérez, S.; Merce, R. *Org. Biomol. Chem.* **2008**, *6*, 3795. (e) Felts, A. S.; Siegel, B. S.; Young, S. M.; Moth, C. W.; Lybrand, T. P.; Dannenberg, A. J.; Marnett, L. J.; Subbaramaiah, K. *J. Med. Chem.* **2008**, *51*, 4911. (f) Reggio, P. H.; Basu-Dutt, S.; Barnett-Norris, J.; Castro, M. T.; Hurst, D. P.; Seltzman, H. H.; Roche, M. J.; Gilliam, A. F.; Thomas, B. F.; Stevenson, L. A.; Pertwee, R. G.; Abood, M. E. *J. Med. Chem.* **1998**, *41*, 5177.

(3) For examples of synthetic approaches to benzofulvenes, see: (a) Sousa, C. M.; Berthet, J.; Delbaere, S.; Coelho, P. J. *J. Org. Chem.* **2014**, *79*, 5781. (b) Bryan, C. S.; Lautens, M. *Org. Lett.* **2010**, *12*, 2754. (c) Kim, K. H.; Kim, S. H.; Park, B. R.; Kim, J. N. *Tetrahedron Lett.* **2010**, *51*, 3368. (d) Ye, S.; Yang, X.; Wu, J. *Chem. Commun.* **2010**, *46*, 2950. (e) Ye, S.; Gao, K.; Zhou, H.; Yang, X.; Wu, J. *Chem. Commun.* **2009**, 5406. (f) Cordier, P.; Aubert, C.; Malacria, M.; Lacôte, E.; Gandon, V. *Angew. Chem., Int. Ed.* **2009**, *48*, 8757. (g) Li, C.; Zeng, Y.; Wang, J. *Tetrahedron Lett.* **2009**, *50*, 2956. (h) Vavilala, C.; Byrne, N.; Kraml, C. M.; Ho, D. M.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **2008**, *130*, 13549. (i) Schmittel, M.; Mahajan, A. A.; Bucher, G.; Bats, J. W. *J. Org. Chem.* **2007**, *72*, 2166. (j) Lee, C.-Y.; Wu, M.-J. *Eur. J. Org. Chem.* **2007**, *2007*, 3463. (k) Lian, J.-J.; Chen, P.-C.; Lin, Y.-P.; Ting, H.-C.; Liu, R.-S. *J. Am. Chem. Soc.* **2006**, *128*, 11372. (l) Abdur Rahman, S. M.; Sonoda, M.; Ono, M.; Miki, K.; Tobe, Y. *Org. Lett.* **2006**, *8*, 1197. (m) Peabody, S. W.; Breiner, B.; Kovalenko, S. V.; Patil, S.; Alabugin, I. V. *Org. Biomol. Chem.* **2005**, *3*, 218. (n) Kovalenko, S. V.; Peabody, S.; Manoharan, M.; Clark, R. J.; Alabugin, I. V. *Org. Lett.* **2004**, *6*, 2457. (o) Schreiner, P. R.; Prall, M.; Lutz, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5757.

(4) Tsuchikama, K.; Kasagawa, M.; Endo, K.; Shibata, T. *Synlett* **2010**, *2010*, 97.

(5) Patureau, F. W.; Besset, T.; Kuhl, N.; Glorius, K. *J. Am. Chem. Soc.* **2011**, *133*, 2154.

(6) Chinnagolla, R. K.; Jeganmohan, M. *Eur. J. Org. Chem.* **2012**, *2012*, 417.

(7) For examples of carbonyl-directed C−H activation, see: (a) Schröder, N.; Wencel-Delord, J.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 8298. (b) Patureau, F. W.; Besset, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1064.

(8) For reviews of acetylene chemistry, see: (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2014**, *114*, 1783. (b) Nizami, T. A.; Hua, R. *Molecules* **2014**, *19*, 13788. (c) Thirumurugan, P.; Matosiuk, D.; Jozwiak, K. *Chem. Rev.* **2013**, *113*, 4905. (d) Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *111*, 6513. (e) Hua, R.; Abrenica, M. V. A.; Wang, P. *Curr. Org. Chem.* **2011**, *15*, 712. (f) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (g) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285.

(9) (a) Rodrigo, S. K.; Powell, I. V.; Coleman, M. G.; Krause, J. A.; Guan, H. *Org. Biomol. Chem.* **2013**, *11*, 7653. (b) Kawatsura, M.; Yamamoto, M.; Namioka, J.; Kajita, K.; Hirakawa, T.; Itoh, T. *Org. Lett.* **2011**, *13*, 1001. (c) Yoshida, K.; Morimoto, I.; Mitsudo, K.; Tanaka, H. *Tetrahedron* **2008**, *64*, 5800. (d) Li, J.; Jiang, H.; Chen, M. *J. Org. Chem.* **2001**, *66*, 3627.

(10) Huang, L.-Y; Aulwurm, U. R.; Heinemann, F. W.; Kisch, H. *Eur. J. Inorg. Chem.* **1998**, *1998*, 1951.

(11) Sakabe, K.; Tsurugi, K.; Hirano, K.; Satoh, T.; Miura, M. *Chem. - Eur. J.* **2010**, *16*, 445.

(12) (a) Zhang, L.; Zheng, L.; Guo, B.; Hua, R. *J. Org. Chem.* **2014**, *79*, 11541. (b) Zheng, L.; Hua, R. *J. Org. Chem.* **2014**, *79*, 3930. (c) Guo, B.; Zheng, L.; Yang, L.; Hua, R. *J. Org. Chem.* **2014**, *79*, 4352. (d) Zheng, L.; Ju, J.; Bin, Y.; Hua, R. *J. Org. Chem.* **2012**, *77*, 5794.

(13) For example of alkyne-directed C−H activation, see: (a) Maekawa, T.; Segawa, Y.; Itami, K. *Chem. Sci.* **2013**, *4*, 2369. (b) Hong, P.; Mise, T.; Yamazaki, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 247. (c) Chernyak, N.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 5636.

(14) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.

(15) Unfortunately, the reaction of **1b** and **1c** in a ratio of 1:1, or the reaction of two different R groups on the same molecule (e.g., [1-(*para*-chlorophenyl)-2-(*para*-fluorophenyl)]acetylene) under the optimized conditions produced four expected products, which are difficult to isolate from the reaction mixtures.

(16) (a) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 11147. (c) Sehnal, P.; Taylor, R. J. K.; Fairlamb, I. J. S. *Chem. Rev.* **2010**, *110*, 824.

(17) A byproduct under optimized conditions has a molecular weight of 456; its structure is tentatively assigned to **3a** (see Scheme 3) on the basis of the results of GC-MS.

(18) Hong, P.; Mise, T.; Yamazaki, H. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 247.




DOI: 10.1021/acs.joc.5b01304
*J. Org. Chem.* 2015, 80, 8430−8434