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Phosphine-Mediated Iterative Arene Homologation Using Allenes

Kui Zhang, **Lingchao Cai**, **Xing Jiang**, **Miguel A. Garcia-Garibay**, and **Ohyun Kwon***

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States

Abstract

A PPh_3-mediated multicomponent reaction between *o*-phthalaldehydes, nucleophiles, and monosubstituted allenes furnishes functionalized non-C_2-symmetric naphthalenes in synthetically useful yields. When the *Co*-phthalaldehydes were reacted with 1,3-disubstituted allenes in the presence of PPh_2Et, naphthalene derivatives were also obtained in up to quantitative yields. The mechanism of the latter transformation is straightforward: aldol addition followed by Wittig olefination and dehydration. The mechanism of the former is a tandem γ-umpolung/aldol/Wittig/dehydration process, as established by preparation of putative reaction intermediates and mass spectrometric analysis. This transformation can be applied iteratively to prepare anthracenes and tetracenes using carboxylic acids as pronucleophiles.

The reactivity of electron-deficient allenes under the conditions of phosphine catalysis has been investigated extensively.[1] Many reports have appeared on the reactions of monosubstituted allenes with activated olefin[2] and imine[3] electrophiles to construct carbocyclic and azacyclic compounds. Contrarily, few examples of reactions between monosubstituted allenes and aldehyde electrophiles under the influence of phosphine catalysts are known.[4] In general, the union of an allenoate and an aldehyde in the presence of a phosphine yields an olefin through a Wittig-like process.[5] Interestingly, all such reports have described reactions between α- or γ-substituted allenoates and aldehydes. In contrast, Wittig reactions involving simple allenoates are rare. We know of only one example, in which intramolecular Wittig olefination of ethyl allenoate (**3a**) and pyrrole-2-carboxaldehyde formed a pyrrolizine as a minor product (6%).[6] Here we report Wittig olefination between monosubstituted allenes and *o*-phthalaldehydes to give highly functionalized naphthalenes and higher-order acenes.

Functionalized naphthalenes are valuable building blocks for the synthesis of many important small molecules (e.g., pharmaceuticals, chiral reagents, liquid crystals, organic

***Corresponding Author**: ohyun@chem.ucla.edu.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07403.
Experimental procedures and analytical data (PDF)
Crystallographic data for **4n′** (CIF)

Notes

The authors declare no competing financial interest.

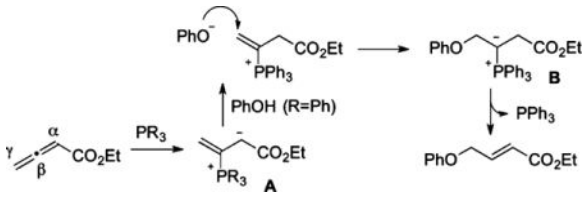
dyes). Many recent syntheses of functionalized naphthalenes employ costly transition metals or require several steps to prepare the starting materials.[8] Our phosphine-mediated multicomponent cascade reaction described herein—between *o*-phthalaldehydes, nucleophiles, and monosubstituted allenes—is an efficient and mild method for synthesizing functionalized naphthalenes from readily available starting materials.

We surveyed the reaction between **3a**, *o*-phthalaldehyde (**1a**), and *p*-toluenesulfonamide by varying the phosphine (stoichiometric), the solvent, the ratio of the reactants, the reaction temperature, and the concentration.[9] The optimized reaction conditions featured PPh_3 (1 equiv) as the mediator, an *o*-phthalaldehyde (1 equiv), a nucleophile (2 equiv), and ethyl allenoate (3 equiv) in CH_3CN at 0 °C.

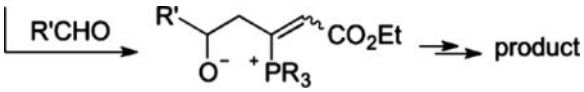
Tables 1 and 2 reveal the scope of this three-component cascade reaction. As the nucleophilic component, benzenesulfonamides bearing electron-withdrawing or -donating substituents generated naphthalene derivatives **4a**—**f** in high yields (Table 1). With acetic acid and benzoic acid as nucleophiles, the reactions were inefficient, giving low yields of naphthalene derivatives **4g** and **4h**, respectively. Adding an equimolar amount of sodium acetate or sodium benzoate as a buffer improved the yields of **4g** and **4h** dramatically.[10] When phenol and *p*-bromophenol were used as the nucleophiles, the naphthalene derivatives **4i** and **4j**, respectively, were formed quantitatively. Examining substituted phthalaldehydes, we found that 4,5-dichloro-*o*-phthalaldehyde also participated in the reaction, furnishing naphthalene derivatives **4k** and **4l** in good yields. Asymmetric 4-methyl-*o*-phthalaldehyde furnished the inseparable isomers **4m** and **4m′** in 92% yield. When 4-nitro-*o*-phthalaldehyde was used, we separated the two isomers **4n** and **4n′** in 50 and 46% yield, respectively.[11] Lastly, the combination of benzene-1,2,4,5-tetracarbaldehyde and acetic acid resulted in the expected anthracenes **4o** and **4o′** in a combined yield of 70%.[12]

We further investigated the reaction scope by treating **1a** with a suite of allenes and nucleophiles (Table 2). The reaction of *p*-toluenesulfonamide and benzyl allenoate provided naphthalene **4p** quantitatively, while that of *p*-nitrobenzenesulfonamide produced **4q** in only 40% yield, presumably because of attenuated nucleophilicity. Adding NaOAc as a buffer improved the yield of **4r** from 34 to 85%.[10] 2-(Trimethylsilyl)ethyl buta-2,3-dienoate/*p*-toluenesulfonamide and 2,*6*-dimethylphenyl buta-2,3-dienoate/phenol produced the desired products **4s** (87%) and **4t** (73%), respectively. The reaction of penta-3,4-dien-2-one and phenol gave **4u** in 98% yield.

While phosphine-catalyzed γ-umpolung additions of nucleophiles to allenoates (eq 1) have been documented amply,[10,13]

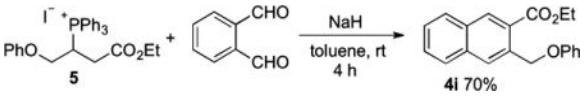


(1)

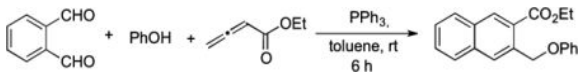


(2)

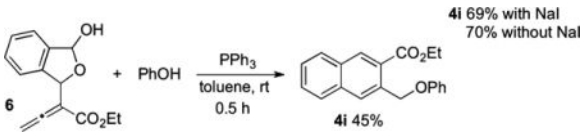
reactions between monosubstituted allenes and aldehydes other than salicylaldehyde (derivatives) have been scarce.[4a–e] In those limited examples, the phosphonium dienolate **A** adds to the aldehyde at its γ-carbon (eq 2). On the basis of this prior knowledge, we postulated a credible process involving a sequence of γ-umpolung addition, aldol reaction, Wittig olefination, and dehydration (Scheme 1). Here the ylide intermediate **B** from the initial γ-umpolung addition undergoes proton transfer to form phosphonium enolate **C**, which adds to **1a** to form lactolate **D**. Proton transfer forms ylide **E**, which undergoes Wittig olefination. Subsequent dehydration provides naphthalene **4i**. Notably, only the γ-umpolung addition product was obtained when **1a** was replaced with benzaldehyde, suggesting that the phthalaldehyde plays a crucial role in the progression of the cascade sequence by forming the lactol substructure. Indeed, when we attempted to prepare the adduct between **1a** and allenoate, we isolated the corresponding lactol product (see compound **6** in eq 5).



(3)



(4)



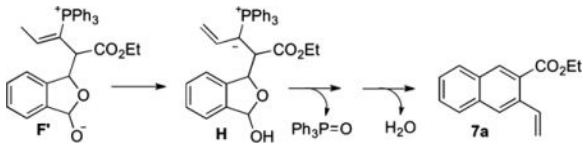
(5)

Although γ-umpolung addition/aldol reaction/Wittig olefination/dehydration is the likely sequence for the phthalaldehyde-to-naphthalene conversion, we could not exclude the alternative sequence of aldol/γ-umpolung/Wittig/dehydration (Scheme 2). In this scenario, phosphonium dienolate **A** adds to **1a** to form phosphonium lactolate **F**. Deprotonation of phenol by lactolate provides the phenoxide nucleophile, γ-umpolung addition of which yields **E**, leading to intramolecular Wittig olefination and eventual formation of **4i**.

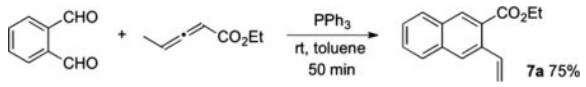
To establish which of the two possible mechanisms is more likely, we prepared phosphonium salt **5** (a precursor of **B**) and lactol **6** (a precursor of **F**).[9] Mixing **5** with NaH (1 equiv) and **1a** (1 equiv) in toluene at room temperature for 4 h yielded naphthalene **4i** in 70% isolated yield (eq 3). Because the optimized conditions for the three-component reaction differed from those of the reaction described above, we also ran the coupling reaction between **1a**, 1 equiv of phenol, 1 equiv of the allenoate, 1 equiv of PPh_3, and 1 equiv of NaI as an additive (eq 4). This reaction in toluene at room temperature went to completion within 6 h and produced naphthalene **4i** in 69% isolated yield. Alternatively, when we mixed lactol allenoate **6** with PPh_3 (1 equiv) and phenol (1 equiv) in toluene at room temperature, we obtained the expected product **4i** in 45% yield within only 30 min (eq 5). A control reaction between **1a**, phenol (1 equiv), **3a** (1 equiv), and PPh_3 (1 equiv) in toluene at room temperature afforded **4i** in 70% isolated yield after 6 h (eq 4). Thus, the NaI additive had no effect on the coupling reaction.

Although inconclusive, the experiments in eqs 3–5 hinted at the following possibility. If the aldol reaction occurred before the umpolung reaction, the rate-limiting step for the scenario in Scheme 2 would be the addition of **A** to **1a** because the conversion of **6** to the product took only 30 min. If the umpolung addition were the first event of the cascade reaction (i.e., Scheme 1), the conversion of **B** to **C** or the addition of **C** to **1a** would likely be the slowest step. Indeed, the pK_a of the **B** (21 in DMSO) is lower than that of **C** (30 in DMSO).[14] Thus, despite unfavorable thermodynamics, phosphonium dienolate **A** is likely to be funneled into ylide **B** as a result of rapid protonation by acidic phenol and subsequent γ-addition (eq 1).

Consequently, we envisioned a reaction between an allenoate and **1a** in the absence of a pronucleophile. We deduced that the presumed intermediate **F′** might form ylide **H**, which should undergo facile intramolecular Wittig olefination and dehydration to form naphthalene **7a** (eq 6). To our delight, the reaction



(6)



(7)

between **1a**, ethyl 2,3-pentadienoate (1 equiv), and PPh_3 (1 equiv) in toluene at room temperature for 50 min gave **7a** in 75% isolated yield (eq 7). This outcome not only provides an alternative pathway for arene homologation but also discounts the aldol-before-γ-umpolung addition scenario. Since the γ-umpolung/Wittig/dehydration sequence of lactol **6** took 30 min and the aldol/Wittig/dehydration sequence of **1a** and ethyl 2,3-pentadienoate

(through intermediate **F′**) took 50 min, the three-component arene homologation would have been complete within 1 h if the reaction had occurred through the aldol-first route. Therefore, the reaction likely proceeds through initial γ-umpolung addition, with the rate-limiting step being the conversion of **B** to **C** rather than the aldol addition of **C** to **1a**.

Monitoring the reaction with high-resolution mass spectrometry (HRMS) confirmed our suspicions (Figure 1). After a reaction time of 3 min (8.3% **4i** formation), the HRMS trace displayed **A** ($[M + H]^+$, *m*/*z* 375.1514) and **B** ($[M + Na]^+$, *m*/*z* 491.1752) but no **F** ($[M + H]^+$, *m*/*z* 509.1882).[9] Although the reaction progressed steadily with the peak for **B** clearly present throughout, the peak corresponding to phosphonium lactolate **F** was barely evident after 40 min (37.5% **4i** formation) and was clearly visible only after 4 h (63.2% **4i** formation), suggesting that initial γ-addition is the dominant reaction pathway.

Examination of a range of phosphines, solvents, and reaction temperatures revealed that addition of the γ-substituted allenoate (2 equiv) to a mixture of the phthalaldehyde and PPh_2Et (1 equiv) in toluene at room temperature was optimal for arene homologation (Table 3). After 30–45 min of stirring, the desired arenes **7a–g** were obtained in excellent yields. 4,5-Dichloroph-thalaldehyde was converted quantitatively to naphthalene **7b**. When naphthalene-2,3-dicarbaldehyde was used in this reaction, anthracene **7c** was obtained in 100% isolated yield. Ethyl hexa-2,3-dienoate and ethyl 4-cyclopentylbuta-2,3-dienoate gave naphthalenes **7d** and **7e**, respectively, as *E* stereoisomers. *tert*-Butyl penta-2,3-dienoate and benzyl penta-2,3-dienoate gave the expected products **7f** (93%) and **7g** (97%), respectively.

The utility of the multicomponent reaction is further illustrated by the synthesis of 2,3-disubstituted tetracene **11** (Scheme 3). Reduction of the ester groups of naphthalene **4g** yielded a diol, which was oxidized to naphthalene-2,3-dicarbaldehyde (**8**) with high efficiency. Repetition of the annulation, reduction, and oxidation sequence provided anthracene-2,3-dicarbaldehyde (**10**), which underwent another annulation to provide tetracene **11**. A variety of 2,3-substituted tetracenes should be readily obtainable from 11 through functional group manipulation, with potential applications in solar cells and light-emitting materials.[15]

We obtained fluorescence excitation and emission spectra for compounds **4g**, **9**, and **11** (Figure 2). Stronger transitions appeared in the range 250–300 nm, with weaker transitions in the range 300–500 nm. A bathochromic shift occurred in going from **4g** (326 nm) to **9** (358 nm) to **11** (450 nm). A bathochromic shift also occurred in the fluorescence emissions in going from **4g** to **9** to **11**, with 0–0 transitions at 342, 406, and 495 nm, respectively. The quantum yields for the substituted polyacenes **4g**, **9**, and **11** were 0.18, 0.65, and 0.15, respectively. These observations match well with reported photophysical data of 2-carbonylpolyacenes.[16]

In conclusion, we have developed a phosphine-mediated multicomponent reaction between allenes, *o*-phthalaldehydes, and nucleophiles that provides non-C_2-symmetric naphthalene, anthracene, and tetracene derivatives. A mechanistic investigation involving the synthesis of putative intermediates and HRMS reaction monitoring revealed that this conversion occurs through a γ-umpolung addition/aldol/Wittig/dehydration cascade. A combination of

phthalaldehydes and 1,3-disubstituted allenes also produces naphthalenes through an aldol/Wittig/dehydration sequence. This arene homologation can also be applied iteratively to prepare higher-order acenes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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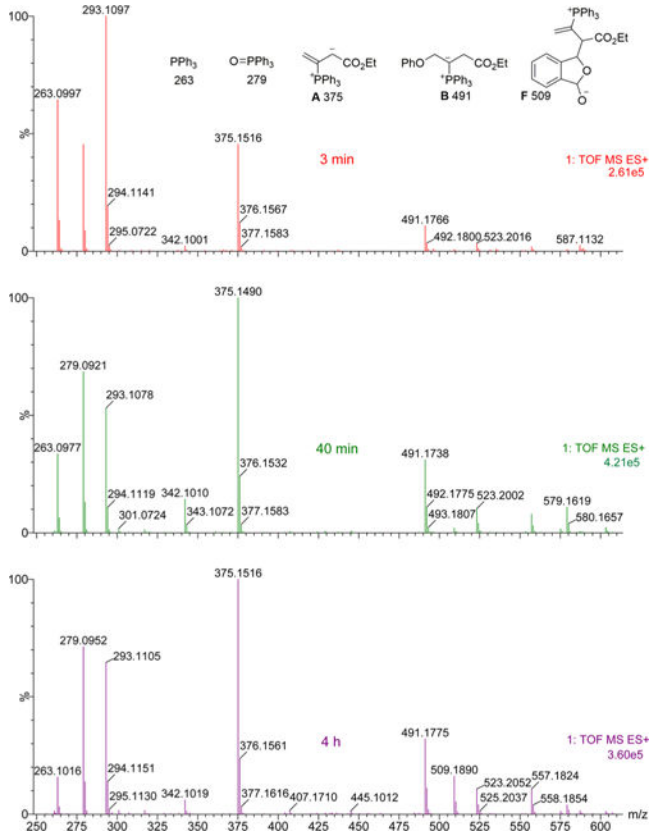


Figure 1.

HRMS spectra recorded during the reaction shown in eq 4 (without NaI). The *m*/*z* values are for $[M + H]^+$ or $[M + Na]^+$ ions.

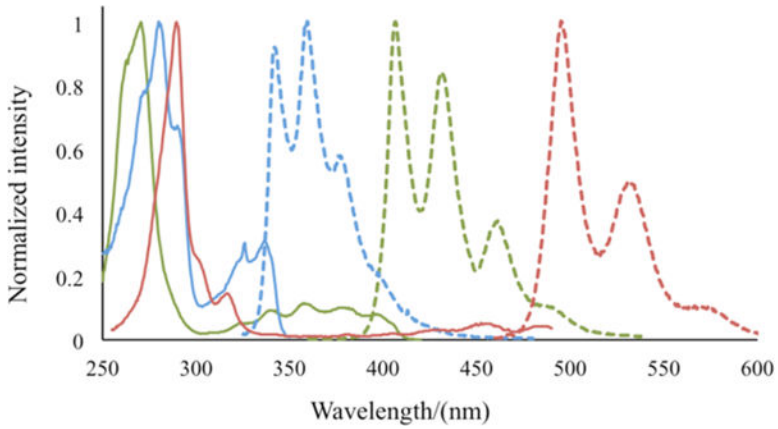
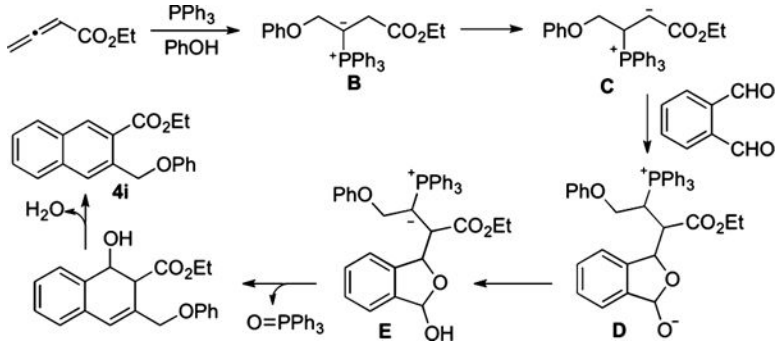


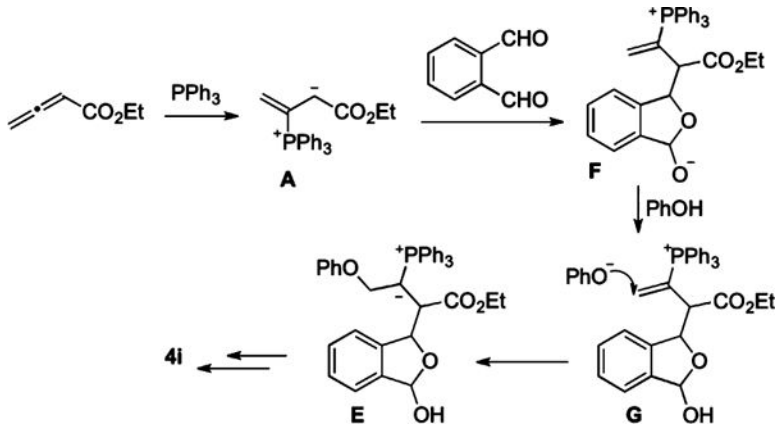
Figure 2.

Excitation (solid lines) and emission (dashed lines) spectra of **4g** (blue lines), **9** (green lines), and **11** (red lines).

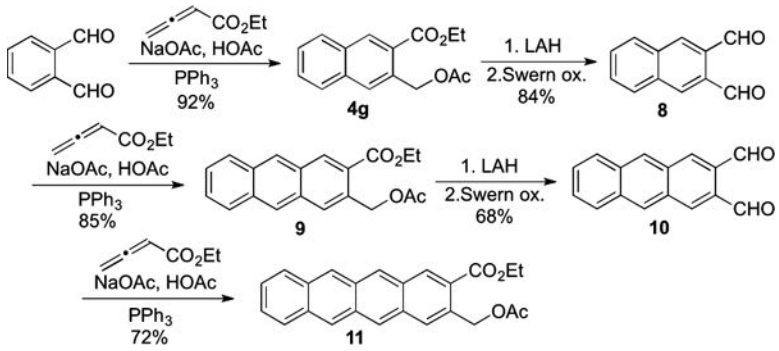


Scheme 1.

γ-Umpolung/Aldol/Wittig/Dehydration Sequence



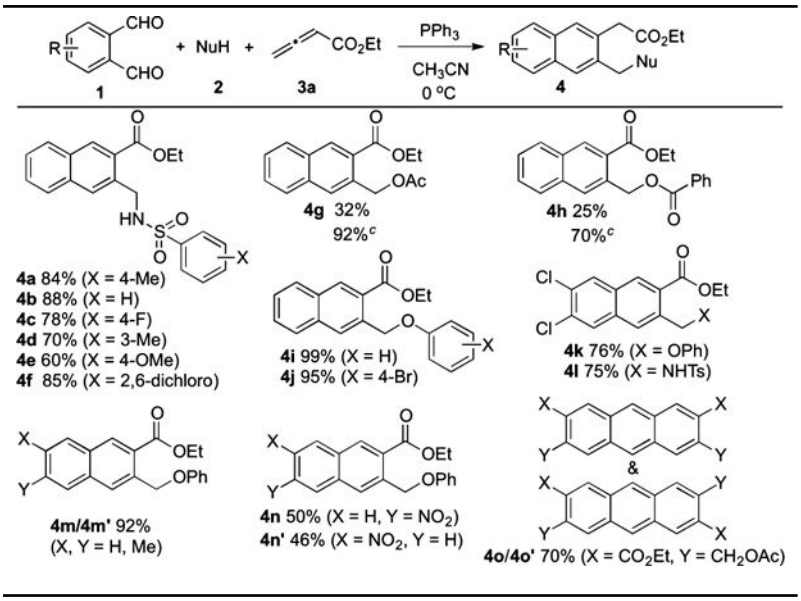
Scheme 2.
Aldol/γ-Umpolung/Wittig/Dehydration Sequence



Scheme 3.
Iterative Synthesis of Anthracene and Tetracene

Table 1

Arene Homologation Using Ethyl Allenoate (3a)[a,b]



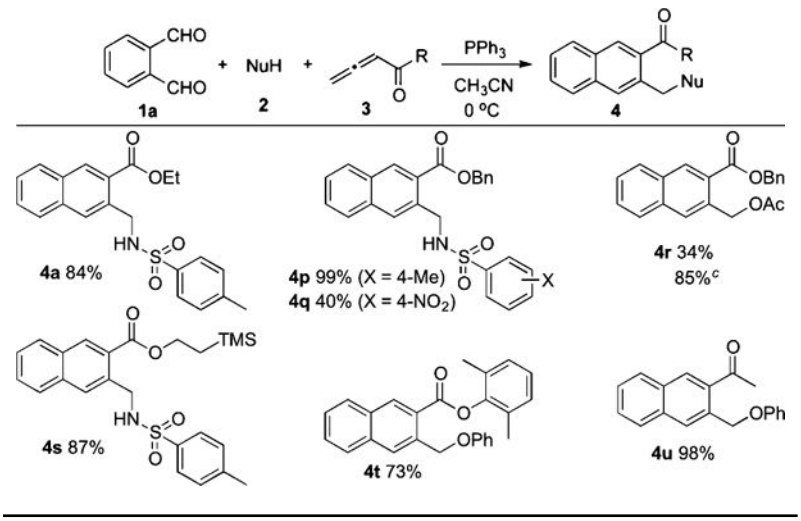
[a]The reactions were performed by adding **3** (1.5 mmol) in CH_3CN (8 mL) via syringe pump (2 mL/h) at 0 °C to a solution of 1 (0.5 mmol), 2 (1 mmol), and PPh_3 (0.5 mmol) in CH_3CN (4 mL).

[b]Isolated yields are shown.

[c]Sodium carboxylate (1 mmol) was added.

Table 2

Arene Homologation Using Phthalaldehyde (1a)[a,b]

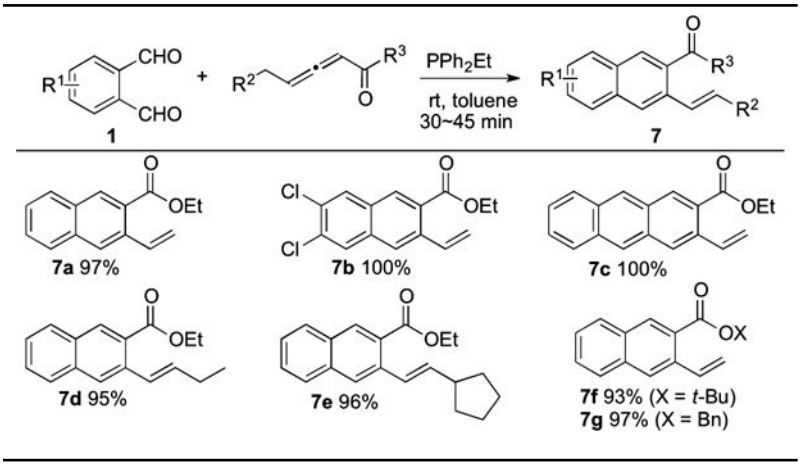


[a, b] See Table 1, footnotes *a* and *b*.

[c] NaOAc (1 mmol) was added.

Table 3

Two-Component Arene Homologation[a,b]



[a]The reactions were performed with **1** (0.4 mmol), allenoate (0.8 mmol), and PPh_2Et (0.4 mmol) in toluene (4 mL) at room temperature.

[b]Isolated yields are shown.