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Transition-Metal-Free Coupling Annulation of Arynes with Ketones and Alkynoates: Assembly of Functionalized Naphthalenes

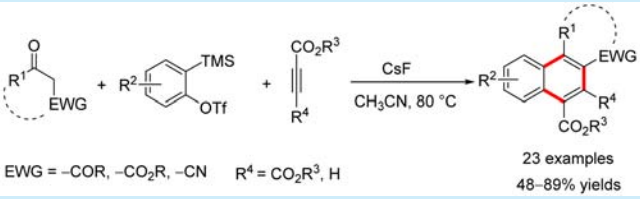
Wen-Ming Shu,*[,†,‡] Kai-Lu Zheng,[†] Jun-Rui Ma,[†] and An-Xin Wu*[,†]

[†]Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Hubei, Wuhan 430079, P. R. China

[‡]College of Chemistry and Environmental Engineering, Yangtze University, Jingzhou 434023, P. R. China

Supporting Information

ABSTRACT: A transition-metal-free coupling annulation reaction of arynes, ketones, and alkynoates has been demonstrated. Using this formal [2 + 2 + 2] cycloaddition reaction, a wide variety of naphthalene derivatives were conveniently constructed in one pot with high efficiency. In addition, this novel and valid annulation has been successfully applied to the synthesis of 1-phenanthrenol derivatives.



Naphthalene and its derivatives are of interest to scientists in several areas of research, from environmental chemistry to supramolecular chemistry or materials science.[1] In addition, naphthalene has also constituted the core of many biologically and pharmaceutically active molecules.[2] Moreover, natural products, including the vast family of arylnaphthalene lignans (such as chinensin, taiwanin C and E, justicidin A and B, and diphyllin) have also contained this important skeleton (Figure 1).[3] Therefore, the development of novel and efficient methods would be greatly valuable for the synthesis of naphthalene from easily available substrates.[4]

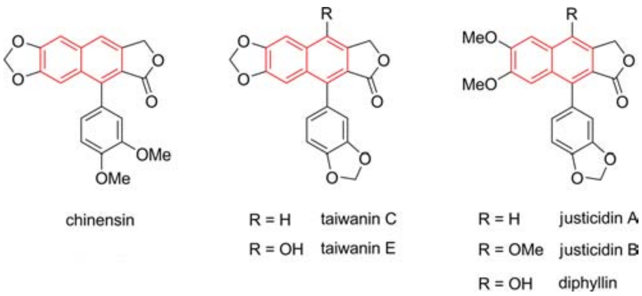
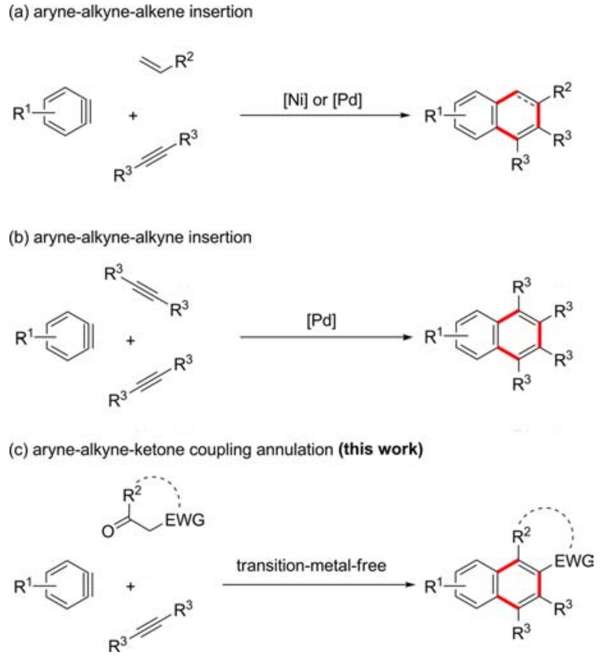


Figure 1. Examples of arylnaphthalene lignans.

Versatile arynes as reactive intermediates have received considerable attention over the past decades.[5] They can easily be generated from 2-(trimethylsilyl)aryl triflates under very mild conditions (only in the presence of fluoride).[6] Hence, arynes have been widely applied in various procedures to afford aromatic compounds.[7] In particular, assembling naphthalene rings via [2 + 2 + 2] cycloaddition reactions is one of the most valuable methods.[8] For example, Xie and Yamamoto et al. reported nickel- and palladium-catalyzed aryne–alkyne–alkene coupling reactions giving a series of substituted naphthalene derivatives, respectively (Scheme 1a).[9] In addition, palladium-catalyzed aryne–alkyne–alkyne cocyclization reaction also provides convergent access to a variety of polysubstituted naphthalene rings (Scheme 1b).[1a,10] Herein, we report a transition-metal-free aryne–alkyne–ketone coupling annulation reaction for the direct construction of polyfunctional naphthalene derivatives (Scheme 1c).

Scheme 1. Strategies of Coupling Annulation Involving Arynes



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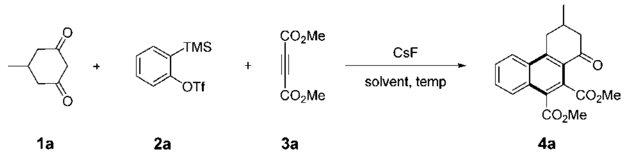
Our initial investigation to realize this new route to naphthalenes focused on the three-component reaction of 5-methyl-1,3-cyclohexanedione (**1a**) with 2-(trimethylsilyl)-phenyl triflate (**2a**) and dimethyl acetylenedicarboxylate (DMAD) (**3a**). To our delight, the desired product **4a** was furnished in 15% yield when the reaction proceeded in CH_3CN in the presence of 1.0 equiv of CsF at 80 °C for 2 h (Table 1, entry 1). Encouraged by the aforementioned result, other reaction conditions were investigated, and the results are summarized in Table 1. First, the amount of CsF was examined (entries 1−4). To our satisfaction, the best result was obtained in the presence of 3.0 equiv of CsF with a yield of 79% (entry 2). Subsequently, various temperatures were screened, revealing that 80 °C was the optimum choice (entries 5−8). When the same reaction was carried out in other solvents, such as dioxane, THF, DCE, toluene, and EtOAc, the efficiency was less than it was when carried out in CH_3CN (entries 9−13).

Table 1. Optimization of the Reaction Conditions[a]

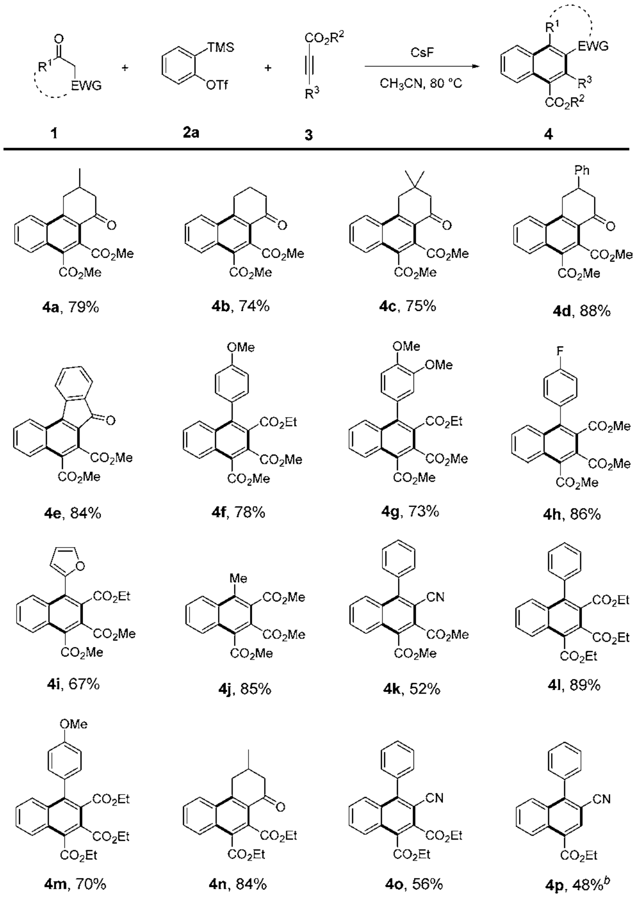


entry	solvent	CsF (equiv)	temp (°C)	yield (%)[b]
1	CH_3CN	1	80	15
2	**CH_3CN**	**3**	**80**	**79**
3	CH_3CN	5	80	77
4	CH_3CN	6	80	79
5	CH_3CN	3	rt	46
6	CH_3CN	3	40	63
7	CH_3CN	3	60	74
8	CH_3CN	3	70	76
9	dioxane	3	80	75
10	THF	3	70	0
11	DCE	3	80	71
12	toluene	3	80	28
13	EtOAc	3	80	0

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.1 mmol, 1.0 equiv), **3a** (0.1 mmol, 1.0 equiv), and solvent (2 mL) for 2 h in sealed tube. [b] Isolated yields.

With the optimized conditions in hand, we next examined the scope of ketone substrates (**1**), as shown in Scheme 2. The developed conditions proved equally effective for cyclic and noncyclic ketones. The various 1,3-cyclohexanedione substrates smoothly transformed into their corresponding products in good yields (74−88%; **4a**−**4d**). Much to our satisfaction, 1,3-indandione was also compatible, giving the expected product **4e** in 84% yield. Moreover, with *β*-ketoesters bearing various substituents, the desired products (**4f**−**4j**) were obtained in moderate to good yields (67−86%). The benzoyl acetonitrile substrate was also tolerated in this reaction, leading to the expected product **4k** in 52% yield. Next, the scope of the alkynoates (**3**) was investigated. Diethyl acetylenedicarboxylate was also utilized in the annulation reaction, affording the naphthalene products in moderate to excellent yields (56−89%; **4l**−**4o**). Furthermore, ethyl propiolate was also tolerated in this coupling annulation reaction successfully to gain corresponding product **4p** in 48% yield. Finally, the structure of **4a** was determined by single-crystal X-ray diffraction analysis (see Supporting Information).

Scheme 2. Scope of Ketones and Alkynoates[a]



[a] Reactions were carried out with **1** (0.5 mmol, 1.0 equiv), **2a** (0.5 mmol, 1.0 equiv), **3** (0.5 mmol, 1.0 equiv), and CsF (3.0 equiv) in CH_3CN at 80 °C for 2 h. Isolated products. [b] Another 3.0 equiv Cs_2CO_3 were added.

Encouraged by the results achieved above, the scope of the 2-(trimethylsilyl)aryl triflates (**2**) was subsequently examined (Scheme 3). Symmetrically substituted 2,3-naphthalyne and 4,5-dimethoxybenzyne precursors were explored, and the corresponding products were obtained in moderate to good yields (59−85%; **5a**−**5c**). Notably, the reaction of 3-methoxyl and 3-methyl substituted aryne precursors also took place smoothly with excellent regioselectivity, giving the single products **5d** and **5f** in 68% and 70% yield, respectively. Moreover, nonsymmetrical 4-methoxybenzyne and 4-methyl-benzyne precursors also participated in the reactions to afford inseparable regioisomeric mixtures **5e**/**5e′** and **5g**/**5g′**, respectively.

Based on the above-mentioned experimental results, a plausible reaction mechanism for this reaction was proposed as shown in Scheme 4 (**4a** as an example). Initially, 5-methylcyclohexane-1,3-dione **1a** transformed into the corresponding anion **1a′** in the presence of CsF, which subsequently reacted with DMAD **3a**, thus affording the vinyl anion **A**.[11] Meanwhile, 2-(trimethylsilyl)phenyl triflate **2a** furnished the benzyne **2a′** and further reacted with the intermediate **A** through an annulation reaction to afford intermediate **B**. Quickly, the intermediate **B** was converted to the desired product **4a** via an aromatization reaction with the elimination of H_2O.

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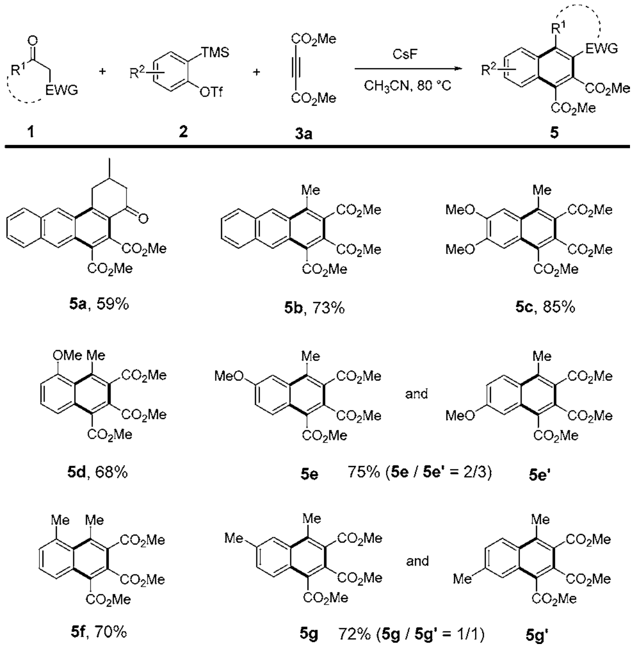
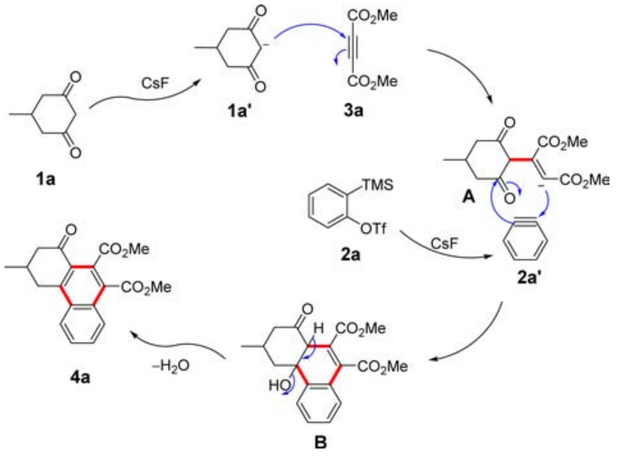
Scheme 3. Scope of 2-(Trimethylsilyl)aryl Triflates[a]



[a] Isolated products.

Scheme 4. A Plausible Mechanism



We further explored the applications of the functionalized naphthalenes in organic synthesis as shown in Scheme 5 (**4a** as an example). The compound **4a** could well be converted into 1-phenanthrenol compound **6** with a 67% yield in the presence of catalytic iodine in DMSO at 100 °C for 13 h.[12]

In summary, we have developed a novel transition-metal-free multicomponent coupling annulation involving arynes for the efficient and convenient synthesis of naphthalene derivatives from simple available ketones, arynes, and alkynoates under mild conditions. This formal [2 + 2 + 2] cycloaddition reaction demonstrated good functional group tolerability and afforded complex structures in high chemoselectivity. Further studies on the method for the synthesis of natural products are in progress in our laboratory.

Scheme 5. Synthesis of 1-Phenanthrenol Derivatives (4a as an Example)[a]

[a] Isolated product.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01782.

Experimental procedures, product characterizations, crystallographic data, and copies of the ^{1}H and ^{13}C NMR spectra (PDF)
X-ray data for **4a** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: culture520@126.com.
*E-mail: chwuax@mail.ccnu.edu.cn.

Notes

The authors declare no competing financial interest.

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