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Phenanthrenes/dihydrophenanthrenes: the selectivity controlled by different benzynes and allenes†

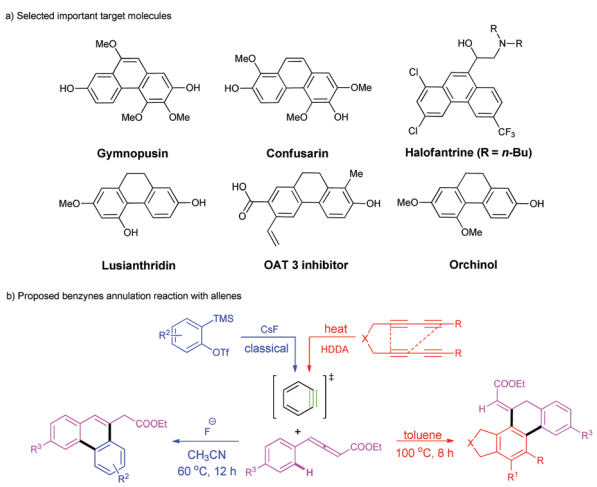
Liangliang Yao, Bo Fang, Qiong Hu, Yu Lei, Li Bao and Yimin Hu *

A method for the intermolecular annulation of benzynes with allenes is disclosed. This protocol utilized allenes as an unconventional diene component for the selective synthesis of phenanthrenes and dihydrophenanthrenes under the control of different benzyne precursors, featuring high atom-economy and good functional group compatibility. Density functional theory (DFT) calculations reveal that different migratory routes of the aromatic C–H bond are crucial for the observed selectivity.

Phenanthrenes and dihydrophenanthrenes are valuable skeletons found in many natural products and pharmaceutically active compounds[1,2] such as gymnopusin,[1a] confusarin,[1b] halofantrine,[1c] lusianthridin,[2d] and orchinol,[2e] and display a broad spectrum of biological activities (*e.g.*, antiviral and anticancer activities) (Scheme 1a). Efficient synthesis of phenanthrenes and dihydrophenanthrenes is constantly required by the pharmaceutical industry, and represents the longstanding goal of organic chemists. In this context, a variety of powerful methods have been established. These methods include the metal-catalyzed Ullman–McMurry reaction,[3] Pschorr reaction,[4] Mallory cyclization of stibenes,[5] cyclization of alkynylated biaryls,[6] and [4+2] annulation of biphenyls.[7] Although useful, these methods often suffer from harsh reaction conditions and not available to introduce new functional groups. Therefore, efficient methods with a greater diversity of substituents for the synthesis of functionalized phenanthrene derivatives are still highly desirable.

Benzynes have been recently employed in the construction of cyclic compounds.[8] Phenanthrenes and dihydrophenanthrenes have been produced by trapping classical method-derived benzynes (*i.e.*, formed by fluoride-induced *ortho*-elimination of *ortho*-silyl aryltriflates) with an allene. Cheng and co-workers described $NiBr_2(PPh_3)_4$-catalyzed co-cyclotrimerization of benzynes with allenes that afforded 10-methylene-9,10-dihydrophenanthrenes in moderate yields.[9a] Li and co-workers developed a protocol for the selective synthesis of phenanthrene derivatives *via* palladium-catalyzed annulation of benzynes with allenes.[9b] Nevertheless, the approaches used in these studies were catalyzed by transition metals, and a 2 : 1 benzyne : allene adduct was isolated as the major product. Hexadehydro-Diels–Alder (HDDA)-derived benzynes[10] have unique advantages in the construction of cyclic compounds with good regioselectivity.[11]

Herein, we developed a selective route controlled by different benzynes with the same allene for constructing different polycyclic aromatic compounds. HDDA-derived benzynes and allenes in toluene typically yield multifunctional, fused dihydrophenanthrene derivatives, whereas classical method-derived benzynes with allenes in acetonitrile provide polysubstituted phenanthrene derivatives as the major products (Scheme 1b). Although the closely related [4+2] reactions of benzynes with styrene derivatives resulting in different



Scheme 1 Selected natural and biologically active scaffolds containing phenanthrene and dihydrophenanthrene and our work.

Laboratory of Functional Molecular Solids, Ministry of Education, Anhui Key Laboratory of Molecular-Based Materials, School of Chemistry and Materials Science, Anhui Normal University, Wuhu, Anhui 241000, China. E-mail: yiminhu@ahnu.edu.cn

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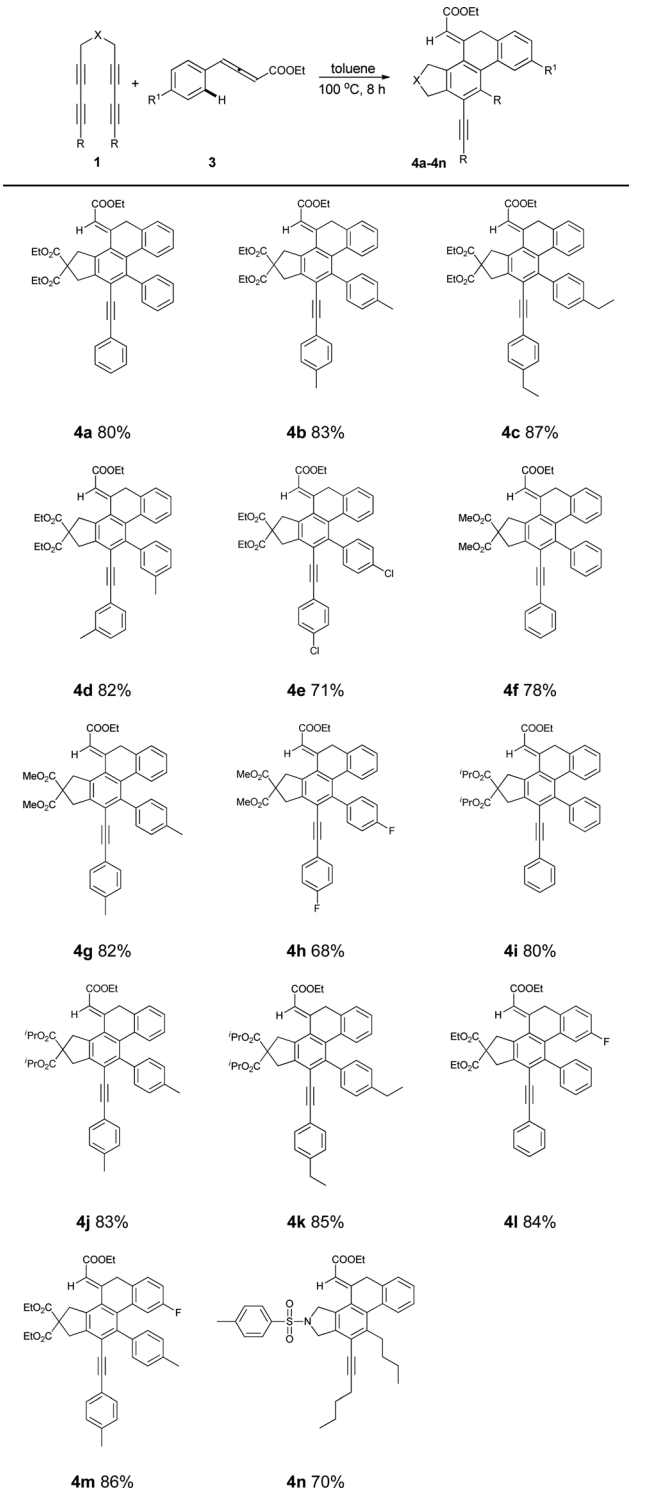
products containing a phenanthrene/dihydrophenanthrene skeleton are extensively studied,[12] the selectivity is quite special as observed for the formation of each product from different sources of benzynes. The compounds prepared *via* these two reaction pathways have multiple rings, variable structures, and wide application prospects in pharmaceutical synthesis compared to general phenanthrenes and dihydrophenanthrenes.

First, we used tetrayne (**1a**) as a precursor for an HDDA-derived benzyne with ethyl 4-phenylbuta-2,3-dienoate (**2a**) to optimize the reaction conditions. Several phenomena were observed when the experimental conditions were modified. Screening results demonstrated that the reaction temperature affected the reaction. The yield of the target product **4a** was greatly enhanced to 80% upon increasing the reaction temperature to 100 °C (8 h) with dry toluene as the solvent. When the reaction was conducted at 120 °C for 8 h, the yield of **4a** decreased to 71%. Investigation of catalysts indicated that the Pd catalytic system was the most effective system in cyclization, but the reaction proceeded well without metal catalysts or other additives. We investigated the reactions in acetonitrile, nitromethane and 1,4-dioxane and found that toluene was most effective. Collectively, the optimal conditions were identified as follows: 1.0 equiv. of tetraynes reacted with 1.1 equiv. of allenes in toluene at 100 °C for 8 h.

Having determined the optimal reaction conditions, the scope of this reaction was further investigated (Table 1). Various products (**4a–4n**) were readily isolated in good to excellent yields (ranging from 68% to 87%) from the reactions of tetraynes with ethyl 4-phenylbuta-2,3-dienoate. The effect of different tetrayne substrates on the product yield was examined. Since tetrayne substrates bearing different esters (OEt, OMe, and O^{i}Pr) were well tolerated, the yields were almost the same (**4a** (80%), **4f** (78%), and **4i** (80%)). By contrast, the substituted groups in the aryl ring of tetraynes bearing electron-donating groups, including *meta*-Me, *para*-Me, and *para*-Et (**4d**, **4g**, and **4k**), exhibited higher yields than the electron-withdrawing groups, such as *para*-Cl and *para*-F (**4e** and **4h**), likely because the electron-withdrawing groups decreased the reactivity. Compound **4c** was isolated with the highest yield (87%) among the examined substrates. Furthermore, ethyl 4-(4-fluorophenyl)buta-2,3-dienoate participated in the reaction to afford good yields of **4l** (84%) and **4m** (86%). Notably, the *N*-tetrayne substrate that contained alkyl groups instead of phenyl or substituted phenyl groups also generated products with good regioselectivity (**4n** (70%)). These results demonstrated the potential of the direct functionalization of HDDA-derived benzynes with allenes for the synthesis of multifunctionalized dihydrophenanthrenes. The structures of **4a** and **4k** were confirmed by X-ray diffraction.[13]

In contrast to the behavior of the HDDA-derived benzynes, the classical method-derived benzynes provided a different outcome when kept in toluene solution at 100 °C for 8 h. Only a trace amount of the expected HDDA-derived benzyne cyclization product was observed. Instead, ethyl 2-(phenanthren-9-yl)acetate **5a** was isolated as the principal product formed in this experiment. We presumed that this result may be attributed to the different migratory routes of the aromatic C–H bond.

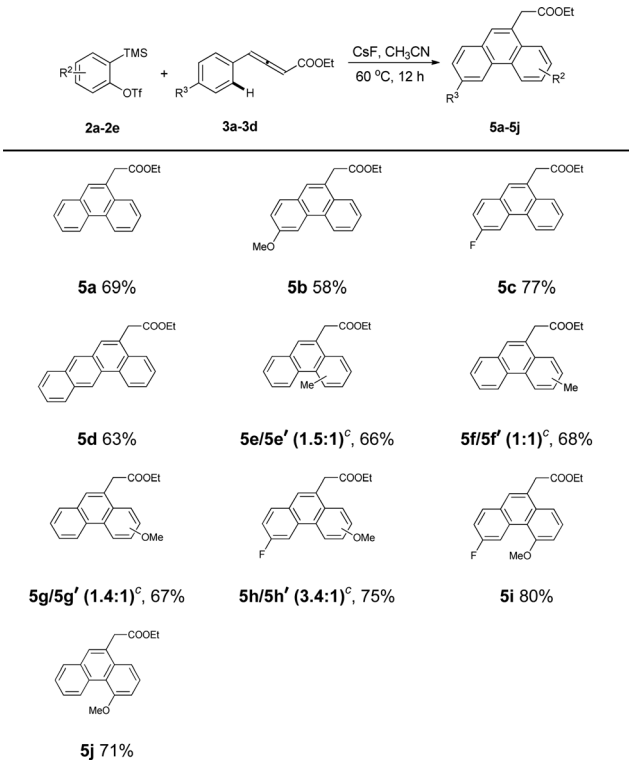
Table 1 Preparation of fused dihydrophenanthrenes **4**[ab]



[a] Reaction conditions: tetraynes **1** (1.0 mmol), allenes **3** (1.1 mmol), toluene (2 mL), stirred at 100 °C for 8 h. [b] Yield of the isolated product after flash column chromatography.

Given the interest in phenanthrene compounds, a reaction scheme for accessing classical method-derived benzynes with allenes was designed. After a brief screening of different

Table 2 Preparation of polysubstituted phenanthrenes **5**[ab]



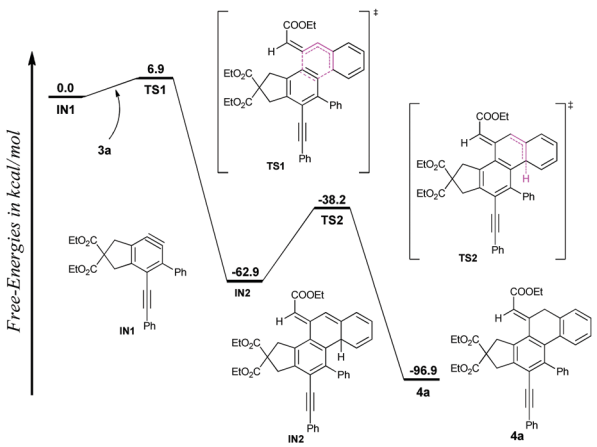
[a] Reaction conditions: classical method-derived benzyne precursors **2** (1.0 mmol), allenes **3** (1.1 mmol), CsF (3.0 equiv.), CH_3CN (2 mL), stirred at 60 °C for 12 h. [b] Yield of the isolated product after flash column chromatography. [c] The regioisomer ratio of the crude mixture was determined by ^{1}H NMR.

reaction parameters, including fluoride source, solvent, temperature, and molar ratio of reactants, the optimal reaction conditions were identified as follows: allene derivative **3a** (1.1 equiv.), classical method-derived benzyne precursor **2a** (1.0 equiv.), and CsF (3.0 equiv.) as the fluoride source in acetonitrile at 60 °C for 12 h. As shown in Table 2, a series of products (**5a–5j**) were readily isolated from the reactions of allenes **3** with the classical method-derived benzyne precursors **2**, and the yields ranged from 58% to 80%. We explored the substitution at R_3 with R_1 = H and found that the reactions of nonsubstituted substrates **2a** with **3b** and **3c** generated products **5b** and **5c**, in 58% and 77% yields, respectively. The higher yield of **5c** is a consequence of an electron-withdrawing group that increases the reactivity of phenyl allene. The naphthyl allene derivative was successfully converted into the corresponding product **5d** with 63% yield. In addition, when unsymmetrical classical method-derived benzyne precursors were used in these cyclizations, mixtures of regioisomers ((**5e**/**5e′**)–(**5h**/**5h′**)) were obtained. It should be noted that these mixtures were not separated into individual isomers, and regioisomer ratios were determined by ^{1}H NMR analysis. Interestingly, when an *ortho*-OMe-substituted classical method-derived benzyne precursor was employed, the corresponding products **5i** and **5j** were isolated in 80% and 71% yields, respectively, and with good regioselectivity likely because of steric hindrance. These results demonstrated the potential of the direct functionalization of the existing classically generated benzynes with allenes for the synthesis of polysubstituted phenanthrenes. The structure of **5j** was confirmed by X-ray diffraction.[13]

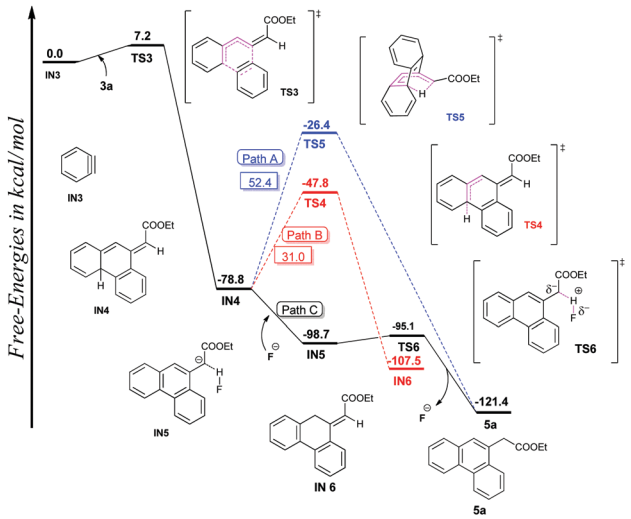
A reaction mechanism was proposed and further elucidated by density functional theory (DFT) calculations at the B3LYP+D3(BJ)/6-311+G(2d,p) level of theory (see the ESI†) to gain further insight into the reaction mechanisms and selectivity in product distribution. We used a structurally simplified HDDA-derived benzyne intermediate **IN1** from **1a** as the starting point of this investigation. Intermolecular annulation of **IN1** with the allene derivative **3a** resulted in adduct **IN2**. Computational data suggested that this annulation reaction should be a concerted process with the unique transition state **TS1**. Subsequently, an intramolecular hydrogen transfer *via* **TS2** afforded product **4a** with high selectivity.[14] The computed free-energy variations validated the rationality of the proposed reaction mechanism. The barrier height of **IN2** generation was 6.9 kcal mol^{-1}, and that of the intramolecular hydrogen transfer was 24.7 kcal mol^{-1}. Both processes were feasible at 100 °C (Scheme 2).

Transformation of the benzyne intermediate into **IN3** (Scheme 3) is predicted to occur through two individual steps from **2a** and CsF.[15] Similarly, the *in situ* generated benzyne undergoes intermolecular cycloaddition with **3a** *via* **TS3** to produce **IN4**. On the one hand, the intermediate **IN4** undergoes intramolecular hydrogen transfer to generate **IN6**/**5a** by Path A/Path B *via* **TS4**/**TS5** which should overcome a considerably high barrier (52.4 and 31.0 kcal mol^{-1}). On the other hand, the interaction of **IN4** with F^- formed a stable complex **IN5** through base-assisted intermolecular hydrogen transfer.[16] Thus, the thermodynamically and kinetically favorable formation of **IN5** *via* Path C provided the observed phenanthrene product **5a** *via* **TS6**.

In summary, we obtained polysubstituted phenanthrenes and dihydrophenanthrenes using different benzyne intermediates trapped by the same allenes. In this reaction, allene was utilized as an unconventional diene component in the intermolecular annulation which was conducted without any catalyst but exhibited high atom economy in producing different types of products. DFT



Scheme 2 DFT based mechanistic study of the HDDA-derived benzyne intermediate **IN1** cyclization with allene **3a** in CH_3CN.



Scheme 3 DFT based mechanistic study of the cyclization of the classical method-derived benzyne intermediate **IN3** with allene **3a** in CH_3CN.

calculations revealed the differences in aromatic C–H bond pathways that could be seen with classical method-derived benzynes used under basic (F^-) *versus* neutral (HDDA) conditions. Our team will continue to explore the possible applications and transformation pathways for these products.

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Conflicts of interest

There are no conflicts to declare.

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13 CCDC 1966583 (4a), 1966582 (4k) and 1966585 (5j) contain the supplementary crystallographic data for this paper†.

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