A novel and efficient synthesis of phenanthrene derivatives via palladium/norbornadiene-catalyzed domino one-pot reaction

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Abstract
Herein we report a novel palladium-catalyzed reaction that results in phenanthrene derivatives using aryl iodides, ortho-bromobenzoyl chlorides and norbornadiene in one pot. This dramatic transformation undergoes ortho-C–H activation, decarbonylation and subsequent a retro-Diels–Alder process. Pleasantly, this protocol has a wider substrate range, shorter reaction times and higher yields of products than previously reported methods.

Introduction
Phenanthrene is a polycyclic aromatic hydrocarbon which contains three benzene rings. The phenanthrenes can be used as fundamental building blocks or intermediates in the synthesis of complex natural products such as tuberosinine [1], aristolactam Ia [2] and (−)-R-tylophorine [3] (Figure 1). Meanwhile, they also demonstrate a wide range of biological activities including anticancer [4], anti-HIV [5], antibacterial [6], anti-inflammatory [7] and so on.
During the past decades, numerous methods for the preparation of phenanthrene derivatives have been developed. In 2003, Gabriel Tojo’s group reported a base-catalyzed photochemical synthesis of phenanthrene derivatives [8] through intramolecular aromatic coupling (Scheme 1a). Although this method offered an atom-economic and easier strategy for the construction of phenanthrene derivatives, the starting materials in this reaction were difficult to obtain, which limited the development of this approach. Moreover, the ultraviolet light (UV) used in this reaction may cause skin damage to experimenters. Alternatively, alkynes (Scheme 1b) played an important role in the synthesis of phenanthrene scaffolds under transition metal catalysis [9]. However, this protocol required complicated procedures, harsh reaction conditions and was incompatible with
many functional groups. Subsequently, facile one-pot approaches had been realized via norbornene-mediated palladium-catalyzed Catellani reaction by Lautens’ group [10] (Scheme 1c). Though this strategy was superior to previous methods in terms of mildness of the reaction conditions, it had a limited substrate scope and relatively low reaction efficiency. Very recently, Fuk Yee Kwong and co-workers (Scheme 1d) developed a straightforward one pot π-extension method using norbornadiene instead of norbornene as directing group to afford the phenanthrenes [11]. However, ortho-haloaryl carboxylic acids employed in this approach had low reactivity, which needed higher reaction temperatures and longer reaction time. Therefore, the development of novel, efficient, and highly functional group tolerant methods for the synthesis of phenanthrene derivatives is still desirable.

Domino reactions such as norbornene-mediated palladium-catalyzed Catellani reactions, which were originally discovered by Catellani in the 1990s [12] and further developed by groups of Catellani and Lautens et al. [13-17], hold great potential for not only settling the sequential reactions in one pot, but also providing access to multisubstituted arenes. In the previous work, we innovatively developed a strategy for the remote C–H alkylation of arenes [18]. Recently, our group also achieved aromatic ketones [19] and 2-alkynyl aromatic ketones [20] successfully through ortho-acetylation and ipso-Suzuki coupling or alkynylation for the aryl iodides. In this paper, we developed an efficient domino reaction of aryl iodides with ortho-bromobenzoyl chlorides and norbornadiene leading to phenanthrene derivatives, which could be widely used in the synthesis of vital intermediates for functional materials, pharmaceutical agents and natural products.

### Results and Discussion

We initiated our investigations by evaluating the three-component cross-coupling reaction of 2-iodotoluene (1a), ortho-bromobenzoyl chloride (2a) and norbornadiene, and we optimized the reaction conditions [21]. Firstly, the reaction took place under Pd(PPh₃)₄/PPh₃ as the catalyst, Cs₂CO₃ as base, and dimethyl formamide (DMF) as solvent at 105 °C for 10 h under N₂ atmosphere. Meanwhile, different palladium species were tested in this reaction system. It was found that Pd(OAc)₂ was the most effective palladium catalyst, and the desired product y-1 was obtained in 98% yield (Table 1, entries 1–4). Next, we studied the influence of different ligands in terms of electron-rich, electron-deficient substituents and sterically

### Table 1: Optimization of the reaction conditions.

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<th>entry</th>
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<th>base</th>
<th>solvent</th>
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aReaction conditions: 1a (0.3 mmol, 1.0 equiv), 2a (0.36 mmol, 1.2 equiv), norbornadiene (0.6 mmol, 2.0 equiv), Pd (5 mol %), ligand (12.5 mol %), base (0.675 mmol, 2.25 equiv), solvent (4 mL), 105 °C for 10 h under N₂. bYield of isolated product. N.D. = not determined. cPPh₃ = triphenylphosphine. dTFP = tris(2-furyl)phosphine. eX-PHOS = 2-dicyclohexylphosphino-2’,4’,6’-triisopropylbiphenyl.
Scheme 2: Substrate scope with various aryl iodides. Reaction conditions: 1 (0.3 mmol, 1.0 equiv), 2a (0.36 mmol, 1.2 equiv), norbornadiene (0.6 mmol, 2.0 equiv), Pd(OAc)$_2$ (5 mol %), PPh$_3$ (12.5 mol %), Cs$_2$CO$_3$ (0.675 mmol, 2.25 equiv), DMF (4 mL), 105 °C for 10 h under N$_2$.
corresponding products in 82–87% yield (z-3–z-5). At the same time, a disubstituted substrate was tolerated well to this conversion (z-6). However, the substrates containing ortho-substituents were disadvantageous for this reaction, and none of the desired products was obtained, which indicated that the reaction was strongly influenced by steric hindrance.

It was noteworthy that this sequential one-pot reaction could be carried out on the gram scale (Scheme 4). We selected 2-iodotoluene and 2-bromo-4,5-dimethoxybenzoyl chloride as substrates. When the reaction of 2-iodotoluene (1a, 3.0 mmol, 1.0 equiv, 0.654 g), 2-bromo-4,5-dimethoxybenzoyl chloride (3.6 mmol, 1.2 equiv, 1.006 g), and norbornadiene (6.0 mmol, 2.0 equiv, 0.553 g) was performed in the presence of 0.15 mmol of Pd(OAc)$_2$, 0.375 mmol of PPh$_3$ and 6.75 mmol of Cs$_2$CO$_3$ at 105 °C in DMF under N$_2$ for 30 h, the desired compound z-6 was isolated in 88% yield.

Based on the above experimental results and the use of norbornadiene in Catellani reactions followed by retro-Diels–Alder reaction firstly reported by Lautens et al. [22-24], which is mentioned in recent works [11], a proposed mechanism for this domino reaction is presented in Scheme 5. As is commonly considered, the aryl-Pd$^{II}$ complex A is formed by oxidative addition of aryl iodide to the Pd$^{0}$ complex, which is followed by the insertion of norbornadiene to the C–Pd bond of A to produce B. Then, an ortho-C–H activation reaction occurs to B, which offers compound C with a five-membered palladacycle. C undergoes the process of oxidative addition with ortho-bromobenzoyl chloride to give the Pd$^{IV}$ intermediate D, and E can be obtained via a reductive elimination reaction. A novel aryl-Pd$^{II}$ species F is formed through removing carbon monoxide from E. Ultimately, G will experience immediate retro-Diels–Alder reaction after the catalytic cycle to afford the target product while taking off cyclopentadiene.
Conclusion
In summary, we have developed a novel and efficient protocol which allows us to construct a variety of phenanthrene derivatives starting from aryl iodides, ortho-bromobenzoyl chlorides and norbornadiene in one pot. A wide range of functional groups are compatible with the reaction, including both electron-withdrawing and electron-donating groups. Compared with previous work for the synthesis of the phenanthrenes, this method shows higher reactivity, shorter reaction times, and higher yields of the target compounds. Meanwhile, these flexible approaches to the phenanthrene derivatives would be expected to provide significant references to material chemistry, pharmaceutical agents and natural product synthesis.

Experimental
General remarks
All reactions were carried out under a nitrogen atmosphere unless otherwise stated and commercially available reagents were used without further purification. Solvents were purified by standard techniques without special instructions. Thin-layer chromatography (TLC) was performed on GF254 plates, and the spots were monitored through UV light. Flash chromatography was carried out on silica gel 300–400 mesh. $^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ at 500 and 126 MHz, respectively, using the solvents as internal standards. High-resolution mass spectra were taken on Waters Synapt MS. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet. The coupling constants ($J$) are offered in Hz. The ortho-bromobenzoyl chlorides 2a–f were synthesized using the known method [25,26].

General procedure for the preparation of products
A dried round-bottomed flask was charged with aryl iodide (0.30 mmol, 1.0 equiv), ortho-bromobenzoyl chlorides (0.36 mmol, 1.2 equiv), norbornadiene (0.60 mmol, 2.0 equiv), Pd(OAc)$_2$ (5 mol %), triphenylphosphine (12.5 mol %), Cs$_2$CO$_3$ (0.675 mmol, 2.25 equiv), and DMF (4 mL). The mix-
ture was stirred at 105 °C under nitrogen atmosphere for 10 h. After cooling to room temperature, the mixture was diluted with ethyl acetate (5 mL) and brine (10 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic phase was washed with brine, dried with anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (petroleum ether/ethyl acetate as eluent) to afford the target compounds.

Supporting Information

Supporting Information File 1
Spectral data of products, and $^1$H NMR and $^{13}$C NMR spectra for the products.

[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-26-S1.pdf]

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References

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