Synthetic Methods

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Rhodium(II)-Catalyzed Cyclization of Bis(*N*-tosylhydrazone)s: An Efficient Approach towards Polycyclic Aromatic Compounds**

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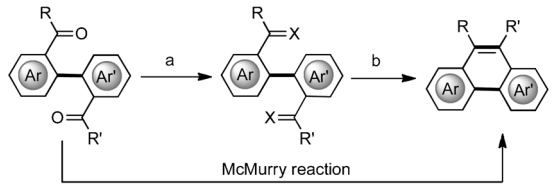
In memory of Howard E. Zimmerman

Polycyclic aromatic compounds (PACs), which include polycyclic aromatic hydrocarbons (PAHs) and their heterocyclic analogues, play important roles in various areas of organic chemistry, medicinal chemistry, and material sciences.[1] Consequently, the construction of such aromatic structures is of great importance. In past decades enormous efforts have been devoted to the development of efficient syntheses of PACs.[2] Among the various methods, the construction of PACs through the combination of cross-coupling reactions and intramolecular C=C bond formation is particularly attractive. With such combinations, PACs can be rapidly accessed from relatively simple aromatic substrates.[3] For the intramolecular C=C bond formation the McMurry reaction is a powerful tool which can convert dicarbonyl functionality into C=C bonds (Scheme 1, method A).[4] However, in the McMurry reaction, a stoichiometric amount of a reductive metal reagent is required, and may result in moderate functional group compatibility.



Method A: McMurry reaction
Method B: X = CH_2 a) Witting reaction, CH_2=PPh_3; b) RCM.
Method C: X = NNHTs a) $TsNHNH_2$; b) Rh-catalyzed cyclization (this work).

Scheme 1. PAC synthesis through intramolecular C=C bond formation. Ts = 4-toluenesulfonyl.

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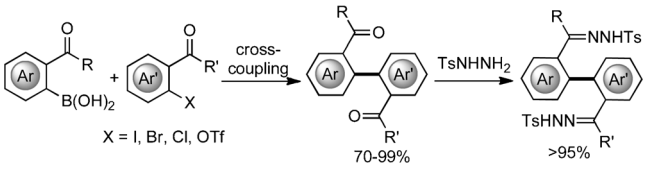
In the past decades, ring-closing metathesis (RCM) has evolved into another highly efficient and versatile strategy for intramolecular C=C bond formation.[5] RCM has also been applied to the construction of benzene rings in various aromatic systems in recent years.[5e,g,6] In the RCM strategy, the commonly used starting materials, 2,2′-dicarbonylbiaryl derivatives, need to be first converted into the corresponding 2,2′-divinylbiaryl derivatives by the Wittig olefination (Scheme 1, method B).[3c,6d,e,g,k] However, the Wittig olefination, although highly reliable, usually affords the divinyl compounds in only moderate yields. Moreover, the divinyl compounds in some cases are unstable, thus resulting in the failure of Wittig/RCM process in PAC synthesis.[6e] In view of the importance of the synthesis of PACs and the drawbacks of the existing methods, we consider it highly desirable to develop alternative and efficient process to access various PACs.

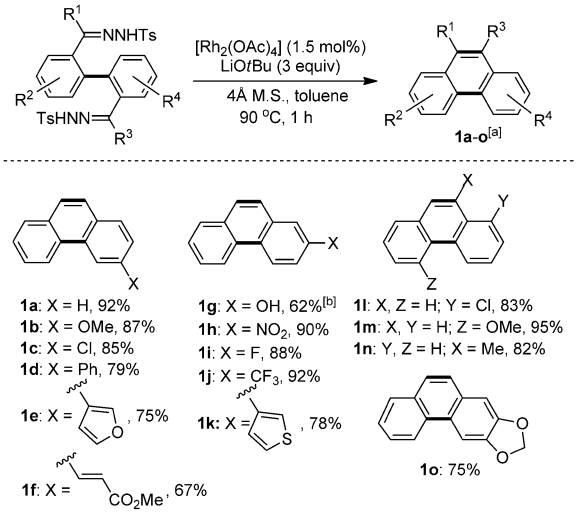
Diazo compounds are versatile substrates in organic synthesis, particularly in transition-metal-catalyzed transformations.[7] The formation of C=C bonds from diazo compounds in transition-metal-catalyzed process, the so-called carbene dimer formation, has been well documented.[8–10] However, this type of C=C bond formation has not attracted much attention, presumably because of the following reasons: 1) diazo compounds, particularly bis(diazo) compounds, are relatively unstable and not easily accessible; 2) the diverse reaction pathways of carbene or metal carbenes make carbene dimer formations undesired side-reactions in many cases; 3) for the intermolecular dimerization of two different carbenes, the selectivity is inevitably a grave problem. Regardless of these challenges, significant progress has been made recently in the development of C=C bond formation based on carbene dimerization. Davies and co-workers have realized the cross-coupling of two different diazo compounds with rhodium(II) catalysts.[9e] Doyle and co-workers have reported the construction of macrocycles through rhodium(II)-catalyzed reactions of bis(diazocarbonyl) compounds.[10c] Che and co-workers developed a similar macrocycle synthesis based on their ruthenium(II) catalysts.[10d] Recently, *N*-tosylhydrazones, which can be easily obtained from the corresponding ketones or aldehydes, have been extensively utilized as precursors of diazo compounds.[11–13] Herein we report that the rhodium(II)-catalyzed intramolecular cyclization of bis(*N*-tosylhydrazone)s is a highly efficient process for converting dicarbonyl functionality into C=C bonds.[14] This transformation provides an alternative and efficient strategy for PAC synthesis (Scheme 1, method C).

The starting material for PAC synthesis, 2,2′-dicarbonylbiaryls, can be easily prepared in good yields by Suzuki–Miyaura cross-coupling with the protocol developed by Fu and co-workers (Scheme 2).[15] The dicarbonyl compounds



Scheme 2. Substrate preparation for the PAC synthesis. Tf = trifluoromethanesulfonyl.

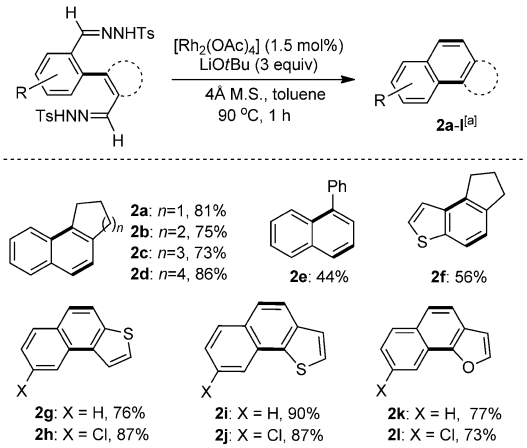
were then converted into the corresponding bis(*N*-tosylhydrazone)s in almost quantitative yields by the reaction with *p*-toluenesulfonyl hydrazine. Subsequently, the bis(*N*-tosylhydrazone)s were used as substrates for the intramolecular C=C bond formations. It was found that catalytic $[Rh_2(OAc)_4]$ combined with 3 equivalents of Li*O*t*Bu was suitable for this transformation, which converted the bis(*N*-tosylhydrazone) of 2,2′-diformylbiphenyl into the desired phenanthrene **1a** in 92% yield (Scheme 3).[16]



Scheme 3. Phenanthrene synthesis through intramolecular C=C bond formation. Reaction conditions: The reaction was carried out in 0.3 mmol scale. [a] Yield of isolated product. [b] 4 Equivalents of Li*O*t*Bu was used and then 4 equivalents of AcOH were added for work-up. M.S. = molecular sieves.

The optimized reaction conditions were then applied to the construction of phenanthrene derivatives (Scheme 3). A series of substituted phenanthrenes, **1a–o**, were synthesized in good to excellent yields. The reaction is marginally affected by the substituents on the aromatic rings. Both electron-donating (**1b**,**g**,**m**,**o**) and electron-withdrawing (**1c**,**f**,**h–j**,**l**) groups are well tolerated in this reaction. The aryl-substituted phenanthrenes **1d**,**e**,**k** could also be obtained. It is noteworthy that the free hydroxy group on phenol, which may hinder the RCM process,[17] can be tolerated under these reaction conditions to give phenanthren-2-ol (**1g**), albeit in slightly lower yield. The chlorine-substituted phenanthrenes **1c** and **1l** can be further employed in various cross-coupling reactions, thus showing their potential applications in material science and biochemistry. Moreover, the 2-acetyl-2′-formylbiphenyl can also be used as a starting material, thus affording the 9-substituted phenanthrene **1n**, which is difficult to obtain through the RCM process reported by Iuliano et al.[3c] Thus, this reaction can be used to synthesize phenanthrene derivatives with substituents at various positions with excellent functional-group compatibility.

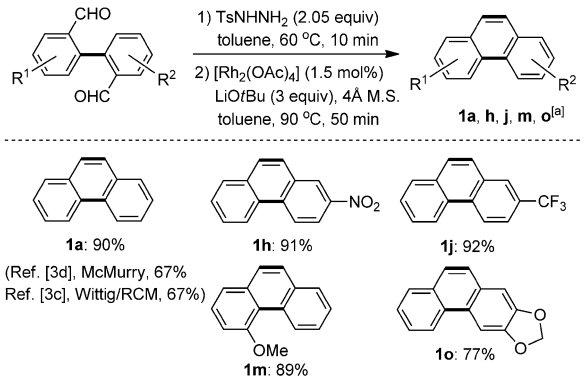
Furthermore, this reaction was applied to the synthesis of other aromatic compounds. As shown in Scheme 4, a series of aromatic compounds have been obtained with this transformation. Under the optimized reaction conditions, carbo-



Scheme 4. Synthesis of other aromatic systems through intramolecular C=C bond formation. Reaction conditions: The reaction was carried out in 0.3 mmol scale. [a] Yield of isolated product.

cyclic ring-fused naphthalenes (**2a–d**) can be smoothly synthesized. It is noteworthy that aromatic heterocycles, including thiophene- (**2f–j**) and furan-fused (**2k–l**) aromatic systems, can also be produced in good to excellent yields. Moreover, the halogen-substituted heteroaromatic compounds **2h**,**j**,**l** can be used in additional transformations using metal-catalyzed cross-coupling reactions, and may find potential applications in material sciences and biochemistry.

Since the conversion of dicarbonyl compounds into the bis(*N*-tosylhydrazone)s with $TsNHNH_2$ is highly efficient, the possibility of a one-pot synthesis of PACs directly from dicarbonyl compounds without separation of bis(*N*-tosylhydrazone) was then investigated. Thus, the solution of 2,2′-diformylbiaryl and $TsNHNH_2$ in toluene was heated for 10 minutes at 60 °C, then the reaction mixture was subjected to the optimized reaction conditions without work-up. The intramolecular C=C bond formation occurred smoothly and afforded the substituted phenanthrene products in excellent yields (Scheme 5). In the case of phenanthrene **1a**, this one-pot protocol has been compared with phenanthrene syntheses through McMurry[3d] and Wittig/RCM[3c] processes. The carbene dimerization approach has the obvious advantages in terms of the reaction efficiency.



Scheme 5. One-pot synthesis of phenanthrenes. Reaction conditions: The reaction was carried out in 0.3 mmol scale. [a] Yield of isolated product.

Next, this one-pot methodology was applied to large PAHs (Figure 1). The diformyl precursor for PAHs **3** and **4** were obtained through Suzuki–Miyaura cross-coupling in good yields.[18] Then they were smoothly transformed into the corresponding PAHs **3** and **4** under the optimized one-pot

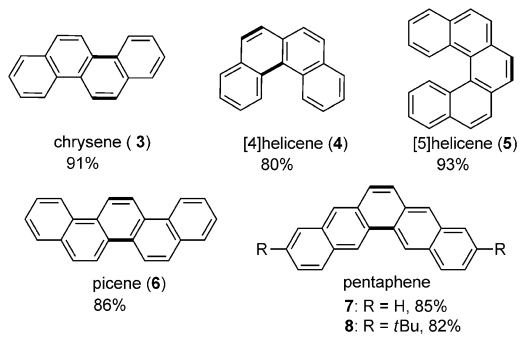
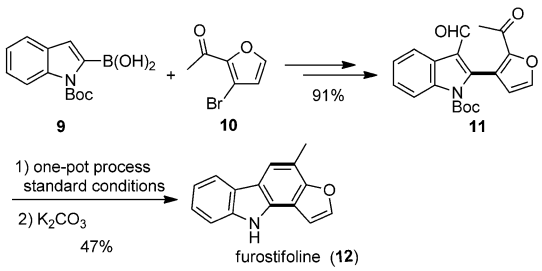


Figure 1. Application of one-pot process in the synthesis of large PAHs.

process. Recently, helicene chemistry has attracted much attention because of the extraordinary optical, electronic properties and their inherent chirality.[6g,19] To our delight, this methodology could be applied to the synthesis of [5]helicene (**5**) in excellent yield. Moreover, picene (**6**), which has attracted recent attention because of its potential application as an organic electronic material,[20] can be easily synthesized by our methodology. The effectiveness of this one-pot method is also demonstrated by the synthesis of pentaphene (**7**) and di-*tert*-butylpentaphene (**8**).

Finally, this methodology was utilized in the total synthesis of furostifoline (**12**), a naturally occurring carbazole alkaloid first isolated in 1990 from the root bark of *Murraya euchrestifolia* Hayata (Scheme 6).[21] The leaves and bark of this plant have been used as traditional Chinese medicine.[22] Up to now, at least six total syntheses for **12** have been reported.[22] In 2005, de Koning and co-workers intended to apply the Wittig/RCM process to synthesize the Boc-protected **12**, but failed as a result of the unstable diene



Scheme 6. A concise synthesis of furostifoline (**12**). Boc = *tert*-butoxycarbonyl.

precusor.[6e] With the bis(*N*-tosylhydrazone) approach, **12** can be synthesized in six steps with an overall yield of 42.7%, starting from the boronic acid **9** and bromide **10**.[18]

In conclusion, we have demonstrated a general catalytic approach to polycyclic aromatic compounds. Starting from the readily available dicarbonyl precursors, this rhodium(II)-catalyzed cyclization process can be applied in the synthesis of various aromatic ring systems. This methodology was successfully applied in the synthesis of large PAHs, such as chrysene, helicene, picene, and pentaphenes, and also used as the key step in the concise synthesis of furostifoline. In many cases, the one-pot synthesis of PACs starting directly from dicarbonyl precursor through bis(*N*-tosylhydrazone)s outperforms the classical McMurry reaction and Wittig/RCM process. Additionally, diaryl-substituted cyclic alkenes of different ring sizes could also be accessed using this method.[18] In view of the easy availability of the precusors, the high efficiency, and simple operation of the process, as well as the high functional-group compatibility, it can be expected that this methodology will become a useful tool for the construction of PACs and related unsaturated ring systems.

Experimental Section

General procedure of rhodium(II)-catalyzed cyclization of bis(*N*-tosylhydrazone)s: Under an argon atmosphere, $[Rh_2(OAc)_4]$ (2 mg, 0.0045 mmol), bis(*N*-tosylhydrazone) (0.30 mmol), LiO*t*Bu (72 mg, 0.90 mmol), and 4 Å molecular sieves (100 mg) were successively added to a flame-dried 100 mL Schlenk flask. The reaction flask was degassed three times with argon and then toluene (30 mL) was added using a syringe. The resulting solution was stirred at 90 °C for the indicated time. The mixture was then cooled to room temperature and filtered through a short plug of silica gel and washed with petroleum ether/EtOAc = 1:1 (50 mL). The solvent was then removed in vacuo to provide a crude reaction mixture, which was purified by silica gel column chromatography to afford pure product.

General procedure of one-pot reaction from dicarbonyl compounds: Under an argon atmosphere, the dicarbonyl compounds (0.30 mmol), $TsNHNH_2$ (114 mg, 0.615 mmol, 2.05 equiv), and toluene (2 mL) were successively added to a flame-dried 100 mL Schlenk flask. The reaction was heated at 60 °C with stirring for 10 min. Toluene then (14 mL) was added, and the solution cooled to room temperature. Then 4 Å molecular sieves (100 mg), LiO*t*Bu (72 mg, 0.90 mmol), $Rh_2(OAc)_4$ (2 mg, 0.0045 mmol), and toluene (14 mL) were added successively. The reaction system was degassed three times with argon and the resulting solution was stirred at 90 °C for the indicated time. The mixture was then cooled to room temperature and filtered through a short plug of silica gel washed with petroleum ether/EtOAc = 1:1 (50 mL). The solvent was then removed in vacuo

to provide a crude mixture, which was purified by silica gel column chromatography to afford pure product.

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