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Tandem [4 + 2]/[2 + 2] Cycloaddition Reactions Involving Indene or Benzofurans and Arynes

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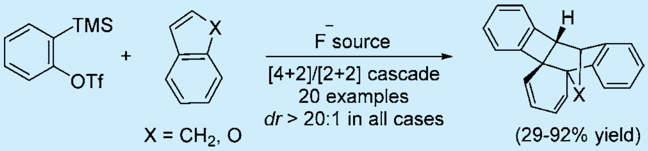
Supporting Information

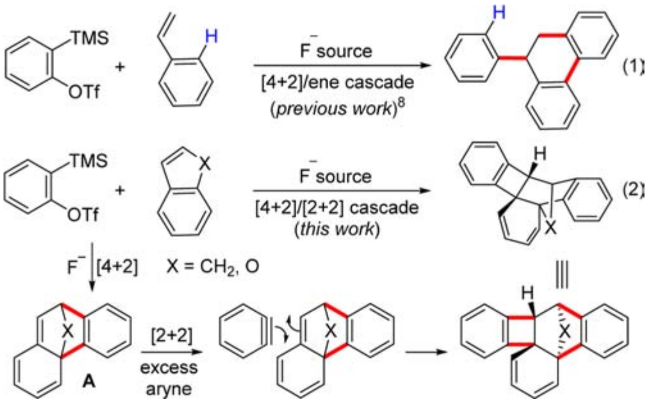
ABSTRACT: The reaction of arynes with indene/benzofurans has been developed. The arynes were generated from 2-(trimethylsilyl)aryl triflates by the fluoride-induced 1,2-elimination react with indene or various benzofurans proceeding via a cascade reaction involving the Diels–Alder reaction and a [2 + 2] cycloaddition reaction. The tandem process afforded functionalized dihydrobenzocyclobutaphenanthrenes in moderate to good yields. Moreover, the method has been utilized for the one-pot synthesis of benzo[*b*]fluoranthene.



Ever since Wittig's original demonstration on the Diels–Alder reaction of furan with arynes,[1,2] the synthetic utility of arynes as a dienophile component in Diels–Alder reactions have been widely used for the construction of benzo-fused carbocycles and heterocycles.[3] In many cases, the Diels–Alder reaction employing arynes generated from conventional methods (such as treating haloarenes with a strong base, halogen–metal exchange of 1,2-dihalobenzenes with organolithium or -magnesium reagents, and decomposition of *o*-benzene diazonium carboxylate) suffer from drawbacks including low yield of products, incompatibility with various functional groups, and/or harsh reaction conditions.[4] The generation of arynes by the fluoride induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates is a better alternative,[5] and a wide range of cyclic and acyclic dienes can be utilized as 4π-component in Diels–Alder reaction with arynes generated using this method.[6] In addition, the Diels–Alder reaction of arynes can be coupled with other organic transformations thereby leading to efficient cascade processes.[7]

We have recently reported the reaction of arynes with styrenes leading to the synthesis of 9-aryldihydrophenanthrene derivatives (Scheme 1, eq 1).[8,9] The reaction proceeds via a cascade process initiated by a Diels–Alder reaction of styrenes with arynes followed by a selective ene reaction. In this context, we envisioned that if the reaction of arynes is performed with cyclic systems such as indenes or benzofurans, there is a possibility of isolating the initial Diels–Alder adducts **A** (eq 2) as the ene reaction can be avoided in this case. Surprisingly, however, the reaction proceeds via a tandem [4 + 2]/[2 + 2] process.[10] Notably, a single example on the reaction of benzofuran with aryne generated by the thermolysis of *o*-benzene diazonium carboxylate leading to the synthesis of cascade adduct in 32% yield has been reported by Anthony and Wege.[11] Herein, we report the unexpected results of our studies on a [4 + 2]/[2 + 2] cascade reaction involving indene or benzofurans, and arynes resulting in the formation of dihydrobenzocyclobutaphenanthrene derivatives in moderate to good yields and excellent diastereoselectivity (eq 2). In addition, the application of this method for the one-pot synthesis of benzo[*b*]fluoranthene has been presented.

Scheme 1. Reaction of Arynes with Styrenes and Indene/Benzofuran



With a view to synthesize the Diels–Alder adduct of aryne and indene, our present study was initiated by treating indene **2a** with aryne generated in situ from 2-(trimethylsilyl)aryl triflate **1a** (1.2 equiv) using 2.4 equiv of CsF and CH_3CN as the solvent. Surprisingly, the expected Diels–Alder adduct **4a** was not isolated, but instead the dihydrobenzocyclobuta phenanthrene **3a** was isolated in 48% yield and in excellent diastereoselectivity of >20:1 (Scheme 2). The product **3a** was formed by a tandem Diels–Alder reaction between **2a** and aryne generated from **1a** followed by a stereoselective [2 + 2] cycloaddition reaction of the initially formed cycloadduct **4a** with excess aryne. Interestingly, when the reaction was carried out using 2.4 equiv of **1a** and 4.8 equiv of CsF, **3a** was formed in an improved yield of 86%

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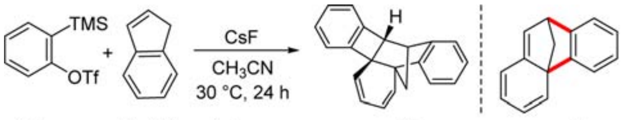
Scheme 2. Reaction of Benzyne with Indene



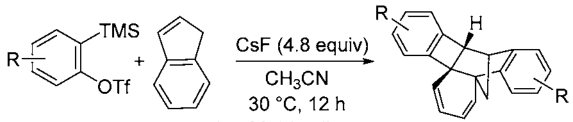
1a **2a** (1.0 equiv) **3a** **4a**

With 1.2 equiv of **1a** and 2.4 equiv of CsF, **3a** = 48% (*dr* > 20:1), **4a** = <1%
With 2.4 equiv of **1a** and 4.8 equiv of CsF, **3a** = 86% (*dr* > 20:1), **4a** = <1%

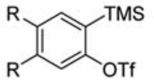
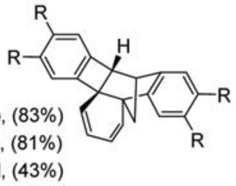
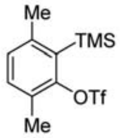
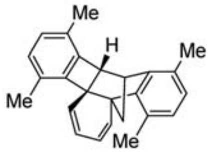
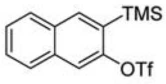
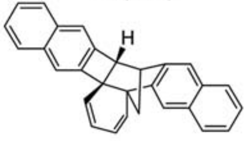
maintaining the diastereoselectivity of >20:1.[12] Notably, CsF was found to be best fluoride source and CH_3CN was found to be the solvent of choice for this tandem process.

This tandem [4 + 2]/[2 + 2] cycloaddition reaction was found to be quite general with various symmetrically substituted arynes (Table 1). Electron-donating and -withdrawing groups at 4,5-positions of the arynes are well tolerated, and these reactions afforded the expected dihydrobenzocyclobuta phenanthrene derivatives **3b−e** in moderate to good yields (entries 1−4). In the case of compound **3c**, the structure and stereochemistry was unequivocally confirmed by single-crystal X-ray analysis (Figure 1).[13] Moreover, the symmetrical 3,6-dimethylaryne and the naphthalyne also afforded the expected products in moderate yields (entries 5 and 6). Gratifyingly, in all cases, the desired product was obtained in excellent diastereoselectivity of >20:1.[14−16]

Table 1. Tandem [4 + 2]/[2 + 2] Reaction: Scope of Arynes[a]



1 **2a** **3**

entry	aryne precursor	product, yield (%)
1	 **1b**, R = Me	 **3b**, (83%)
2	**1c**, R = O(CH$_2$)O	**3c**, (81%)
3	**1d**, R = F	**3d**, (43%)
4	**1e**, R = (CH$_2$)$_3$	**3e**, (69%)[b]
5	 **1f**	 **3f**, (63%)
6	 **1g**	 **3g**, (40%)

[a] General conditions: **1** (1.20 mmol), **2a** (0.50 mmol), CsF (4.8 equiv), CH_3CN (2.0 mL), 30 °C, and 12 h. Yields of the isolated products are given. [b] Reaction was run on 0.25 mmol scale.

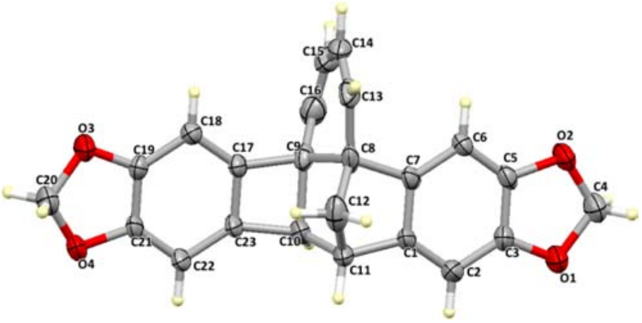
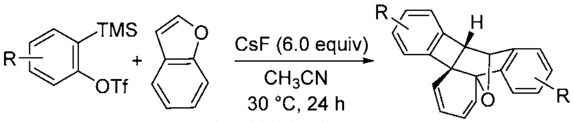


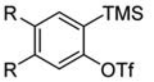
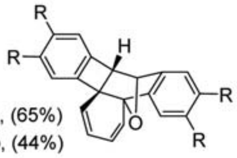
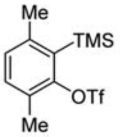
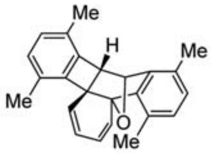
Figure 1. ORTEP diagram of **3c** (35% probability factor for the thermal ellipsoids).

Inspired by the interesting results on the reaction of arynes with indene, we then focused our attention on the reaction of arynes with benzofurans. Treatment of aryne generated from **1a** using CsF with benzofuran **5a** resulted in the formation of the [4 + 2]/[2 + 2] cascade product **6a** in 65% yield and excellent diastereoselectivity of >20:1 (Table 2, entry 1). Notably, the reaction needs 3.0 equiv of aryne precursor **1a** and 6.0 equiv of CsF, and a longer reaction time of 24 h for better results. The reaction was found to be working with electronically different 4,5-disubstituted arynes, and in all cases the expected product was formed in moderate yields and in high diastereoselectivity (entries 1−5). In the case of compound **6b**, the structure and stereochemistry was unambiguously confirmed by single-crystal X-ray analysis (Figure 2).[13] Additionally, the symmetrical 3,6-dimethylaryne also furnished the bicyclic product **6f** in 62% yield (entry 6).

Table 2. Tandem [4 + 2]/[2 + 2] Reaction of Benzofuran with Arynes: Scope of Arynes[a]



1 **5a** **6**

entry	aryne precursor	product, yield (%)
1	 **1a**, R = H	 **6a**, (65%)
2	**1b**, R = Me	**6b**, (44%)
3	**1c**, R = O(CH$_2$)O	**6c**, (46%)
4	**1d**, R = F	**6d**, (29%)
5	**1e**, R = (CH$_2$)$_3$	**6e**, (48%)[b]
6	 **1f**	 **6f**, (62%)

[a] General conditions: **5a** (0.50 mmol), **1** (1.50 mmol), CsF (6.0 equiv), CH_3CN (2.0 mL), 30 °C and 24 h. Yields of the isolated products are given. [b] Reaction was run on 0.25 mmol scale.

Then we examined the scope of the reaction with substituted benzofuran derivatives (Scheme 3). Halogen substitution at a different position in the carbocyclic ring of benzofuran is well tolerated and the reaction furnished the [4 + 2]/[2 + 2] cascade product in moderate yields (**6g−i**). Notably, the halogenated cycloadducts are amenable for further derivatization by means of traditional metal-catalyzed cross-coupling reactions. In addition,

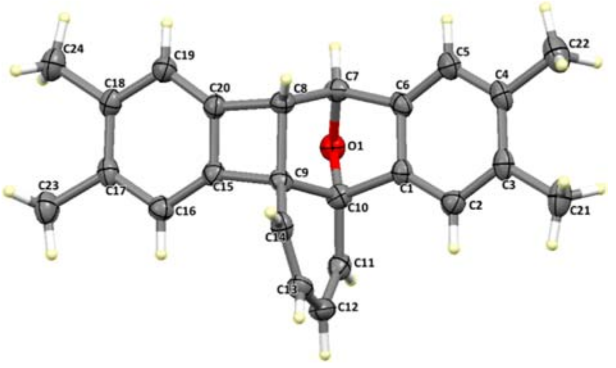
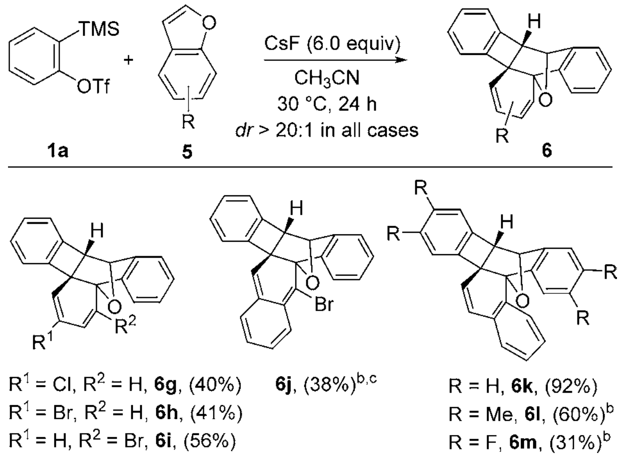


Figure 2. ORTEP diagram of **6b** (40% probability factor for the thermal ellipsoids).

Scheme 3. Scope of Benzofurans in the Tandem [4 + 2]/[2 + 2] Reaction[a]

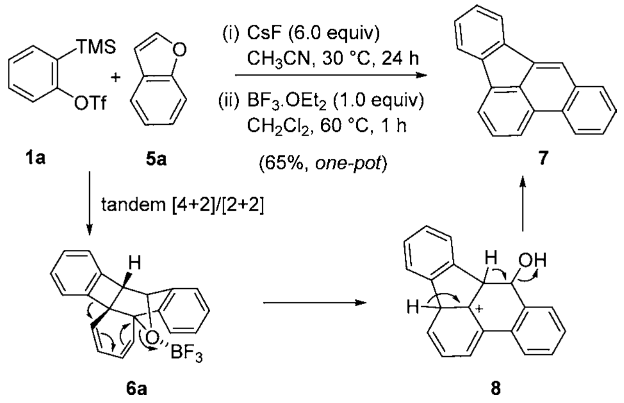


[a]General conditions: **5** (0.50 mmol), **1a** (1.50 mmol), CsF (6.0 equiv), CH_3CN (2.0 mL), 30 °C and 24 h. Yields of the isolated products are given. [b]Reaction was run on 0.25 mmol scale. [c]17% of [2 + 2] adduct was also isolated.

the reaction of arynes with 9-bromonaphthofuran furnished the cascade product **6j** in 38% yield. In this case, 17% of [2 + 2] adduct derived from aryne and the 9-bromonaphthofuran was also isolated. In all other cases, the [2 + 2] adduct was formed in <5% yield. Furthermore, the reaction of arynes with naphtho-[1,2-*b*]furan resulted in the formation of the desired cycloadduct in moderate to excellent yields (**6k**−**m**).[17]

Furthermore, the synthetic potential of this tandem [4 + 2]/[2 + 2] cycloaddition reaction has been demonstrated by the one-pot synthesis of benzo[*b*]fluoranthene, which is a potent carcinogenic polynuclear aromatic hydrocarbon.[18] The reaction of benzofuran with aryne generated from **1a** under the present reaction conditions followed by the treatment of the reaction mixture with $BF_3{\cdot}OEt_2$ resulted in the one-pot synthesis of benzo[*b*]fluoranthene **7** in 65% yield (Scheme 4).[19] The product formation can be rationalized by the initial formation of the cycloadduct **6a** followed by Lewis acid coordination to the bicyclic system and subsequent opening of the benzocyclobutane ring to generate intermediate **8**. The intermediate **8** upon proton loss and a release of a molecule of water furnished **7**. It may be mentioned in this context that the conversion of **5a** to **7** in two steps has been reported by Anthony and Wege.[11]

Scheme 4. Synthesis of Benzo[*b*]fluoranthene



In conclusion, we have developed a facile and general reaction of arynes with indene/benzofurans. The reaction took place via a tandem [4 + 2]/[2 + 2] cycloaddition sequence resulting in the formation of dihydrobenzocyclobutaphenanthrene derivatives in moderate to good yields and in excellent diastereoselectivity. Additionally, the application of this method has been demonstrated by the one-pot synthesis of benzo[*b*]fluoranthene. Further studies on aryne Diels−Alder reactions with potential dienes are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Details on experimental procedures, characterization data of all compounds, and single-crystal X-ray data of **3c** and **6b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Anthony, I. J.; Wege, D. *Aust. J. Chem.* **1984**, *37*, 1283. Interestingly, in this report, benzyne was considered as a diradical species.

(12) For details, see the Supporting Information.

(13) CCDC-1005419 (**3c**) and CCDC-1005420 (**6b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(14) The reaction of unsymmetrical arynes with indene is expected to deliver four regioisomeric products. In view of the nonpolar nature of the isomers, and its close R_f values, their purification has not been attempted.

(15) It may be noted that the reaction of **2a** with 1,3,5-trimethyl-2-vinylbenzene afforded only the [2 + 2] cycloadduct in 40% yield. In this case, the tandem [4 + 2]/[2 + 2] product was not observed.

(16) Notably, substituted indene derivatives such as 2-bromo-1*H*-indene and 2-phenyl-1*H*-indene did not afford the desired product under the optimized conditions. Moreover, 2-ethyl-1*H*-indene furnished 13% of the cascade product under the present reaction conditions.

(17) It may be noted that *N*-methylindole and benzothiophene did not afford the [4 + 2]/[2 + 2] cascade product with arynes under the present reaction conditions.

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(19) It may be noted that the preliminary studies on cationic rearrangement on indene−aryne adduct **3**, however, failed.