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Expanding the Suzuki–Heck-Type Coupling Cascade: A New Indeno[1,2,3]-Annelation of Polycyclic Aromatic Hydrocarbons

Jennifer M. Quimby[a] and Lawrence T. Scott[a,*]

[a] Department of Chemistry, Merkert Chemistry Center, Boston College, Chestnut Hill, MA 02467-3860, USA
Fax: (+1)-617-552-6454; phone: (+1)-617-552-8024; e-mail: lawrence.scott@BC.edu

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Dedicated to Professor Dr. Armin de Meijere on the occasion of his 70th birthday.

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Abstract: Fluoranthene derivatives can be constructed in a single operation by a palladium-catalyzed cascade reaction sequence, starting from a *peri*-dichloronaphthalene derivative and various arylboronic acids.

Keywords: aryl halides; C$-$H activation; cross-coupling; microwave heating; palladium; synthetic methods

Methods for the synthesis of fully unsaturated 6-membered (benzenoid) carbocycles greatly outnumber those available for the synthesis of fully unsaturated 5-membered carbocycles.[1] To address this imbalance, we introduced two complementary Suzuki–Heck-type coupling cascades several years ago (Scheme 1, *top*) that provide expedient means for the indeno[1,2,3]-annelation of polycyclic aromatic hydrocarbons (PAHs).[2] The overall processes build the new 5-membered rings by two distinct aryl-aryl coupling reactions, both catalyzed by palladium, starting from simple, mono-functional derivatives of the PAH.

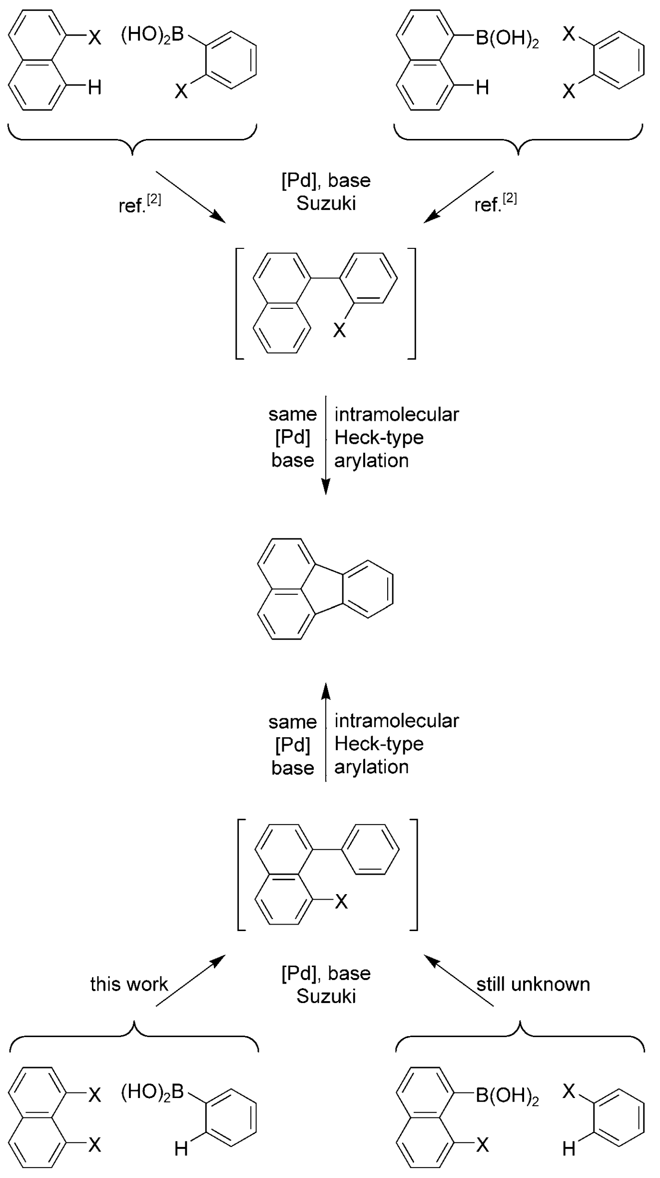
The first step involves a classical intermolecular Suzuki–Miyaura cross-coupling of an arylboronic acid [$\mathrm{Ar{-}B(OH)_2}$] with an aryl bromide ($\mathrm{Ar'{-}Br}$).[3] A second halogen atom, strategically located on one or the other of the two reaction partners, then directs a second palladium insertion, which sets the stage for an intramolecular Heck-type arylation reaction[4] on the *peri*-position of the PAH (Scheme 1, *top*).

Both of these incarnations of the Suzuki–Heck-type coupling cascade start from a mono-functionalized PAH and an *ortho*-difunctionalized benzene as the two reaction partners. In principle, however, it should be possible to implement this same strategy starting from a *peri*-difunctionalized PAH and a singly-functionalized benzene derivative (Scheme 1, *bottom*). Herein we report the successful realization of this latter variation on the indeno[1,2,3]-annelation cascade, starting from a *peri*-dihalo-PAH (Scheme 1, *bottom left*). The fourth variation, starting from a *peri*-halo-arylboronic acid remains unknown at this time (Scheme 1, *bottom right*).

The lack of general methods for accessing *peri*-difunctionalized PAHs will undoubtedly limit the utility of indeno-annelations that require such substrates as starting materials; however, many *peri*-dihalo-PAHs are readily available; *Chemical Abstracts* lists nearly 2000 known *peri*-dihalo-PAHs (X = Cl, Br, or I, excluding X = F), of which more than 100 can be obtained commercially.

For our experiments, we chose 5,6-dichloroacenaphthene (**1**), which is easily prepared by direct chlorination of acenaphthene.[5] After screening several catalysts, ligands, bases, and other reaction conditions, we were pleased to find that **1** can be indeno-annelated with 3,4-dimethoxybenzeneboronic acid (**2**) to produce the bridged dimethoxyfluoranthene (**3**) in 89% isolated yield (Scheme 2).

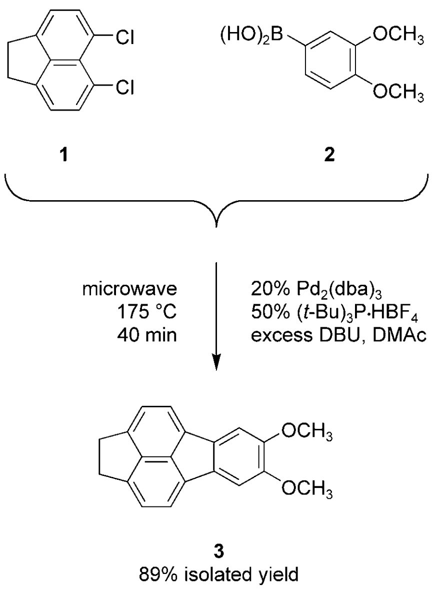
The conditions that give this yield employ 20% tris(dibenzylideneacetone)dipalladium(0) as the catalyst, 50% tri-*tert*-butylphosphonium tetrafluoroborate as the ligand source, and 29 equiv. of 1,8-diazabicyclo[5.4.0]undec-7-ene as the base. The reaction is run in anhydrous *N,N*-dimethylacetamide under a nitrogen atmosphere at 175 °C with microwave heating for 40 min. It should be noted that palladium catalyzes two coupling reactions for each molecule of product formed and that the ratio of phosphine ligand to palladium is 1.25/1.00. Using these same conditions, the substituted fluoranthenes pictured in Scheme 3 were likewise prepared from **1** (isolated yields indicated).



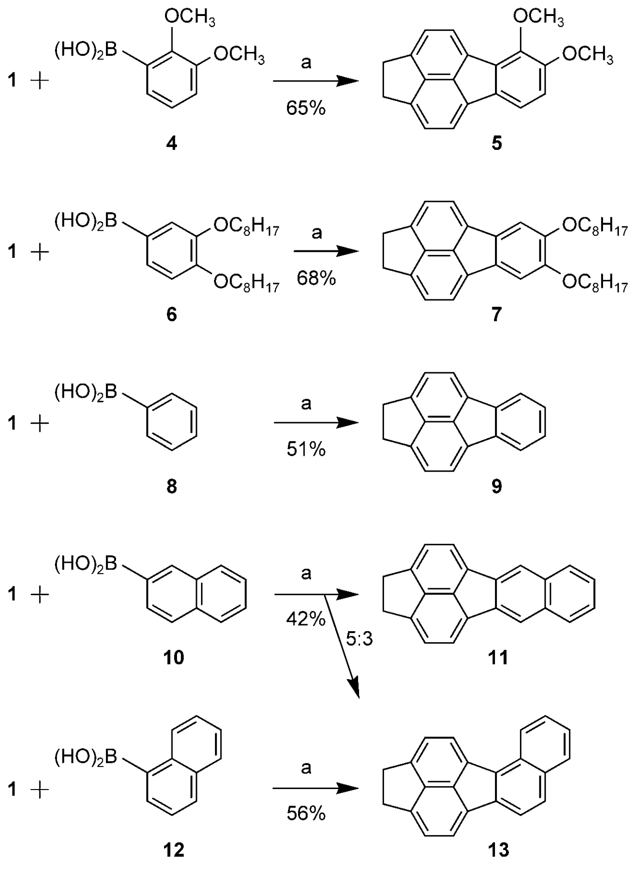
Scheme 1. Four possible Suzuki–Heck-type coupling cascades for the indeno[1,2,3]-annelation of polycyclic aromatic compounds (X = halogen), illustrated here for naphthalene.

In general, these cascade reactions tend to give higher yields with the alkoxy-substituted benzeneboronic acids than with the purely hydrocarbon systems. This may reflect the ability of alkoxy substituents to accelerate the intramolecular arylation reaction,[4] but other factors may also be at work.

The regioselectivities of these cyclizations deserve comment. In the case of boronic acid **2**, for example, the possibility exists for competitive formation of fluoranthene **5**; however, no trace of **5** could be detected in the NMR spectrum of the unpurified product mixture obtained from the reaction shown in Scheme 2. The same selectivity was likewise observed with the corresponding di-*n*-octyloxybenzeneboronic acid (**6**). Naphthalene-2-boronic acid (**10**), on the other hand,



Scheme 2. Indeno[1,2,3]-annelation of a *peri*-dihalo-PAH by a Suzuki–Heck-type coupling cascade.



Scheme 3. Additional indeno[1,2,3]-annelations of 5,6-dichloroacenaphthene (**1**) by the Suzuki–Heck-type coupling cascade: (a) 20% $Pd_2(dba)_3$, 50% $(t\text{-}Bu)_3P{\cdot}HBF_4$, excess DBU, DMAc, microwave 175 °C, 40 min.

gives the symmetrical hydrocarbon (**11**) as the major product, but it is accompanied by significant amounts of the unsymmetrical compound (**13**) as a minor product. In principle, naphthalene-1-boronic acid (**12**) could have given a 6-membered ring closure product (a perylene, not shown), but we see only the product of 5-membered ring closure (**13**).

Numerous variations on the standard conditions reported above were explored, using unsubstituted benzeneboronic acid (**8**) as the annelation partner. Some reactions were run at 175 °C in the microwave reactor, and some were run at 155 °C using conventional heating. In the latter case, the chemistry also works, but reaction times as long as 36 h were sometimes required. By contrast, the reaction is nearly done in just 20 min in the microwave reactor; although we settled on 40 min as our standard reaction time to ensure completion.

Increasing the catalyst loading from 20% to 30% improves the yield to 61% (NMR integration),[6] whereas decreasing the catalyst loading to 5% or even 10% dramatically diminishes the yield. Increasing the ratio of ligand to palladium from 1.25/1.00 to 2.00/1.00 also causes a noticeable drop in the yield.[7]

Other ligands and ligand precursors were also tested for this reaction. Most did work, but $(t\text{-Bu})_3P{\cdot}HBF_4$ proved superior to $Me(t\text{-Bu})_2P{\cdot}HBF_4$, $Cy_3P{\cdot}HBF_4$, Cy_3P, X-phos,[8] and Buchwald's new Ruphos precatalyst.[9,10] With the less hindered $Cy_3P{\cdot}HBF_4$, a degradation in regioselectivity was observed; the reaction shown in Scheme 2 no longer gives a single product (**3**) in high yield but also produces 5–10% of the unsymmetrical dimethoxy compound (**5**).

An attempt to scale up the indeno-annelation of **1** with unsubstituted benzeneboronic acid (**8**) in the microwave reactor (volume limited) by increasing the concentrations 10-fold caused the yield to drop from 51% to *ca.* 35% (unoptimized). With conventional heating, on the other hand, the reaction can be run at the original concentration and scaled up 10-fold to give hydrocarbon **9** in 42% isolated yield (also unoptimized).

The ability to effect multiple indeno-annelations in one operation represents an especially attractive feature of these cascade reactions. A four-fold indenoannelation of pyrene by application of our earlier Suzuki–Heck-type coupling method, for example, built four new rings and eight new aryl–aryl bonds in a single reaction.[11] Indeed, our development of the alternative methodology reported here was motivated by the prospect that it might give us easy access to larger perindeno-PAHs, such as pentaindenocorannulene (**16**)[12] and hexaindenocoronene (**17**)[13] from the readily available perchlorocorannulene (**14**)[14] and perchlorocoronene (**15**)[15] (Figure 1). Cyclodehydrogenations of **16** and **17** would generate C_{5v} and C_{6v} arm-chair end caps of [5,5] and [6,6] single-walled carbon nanotubes, respectively. Applications of the chemistry reported here toward these objectives has been initiated.

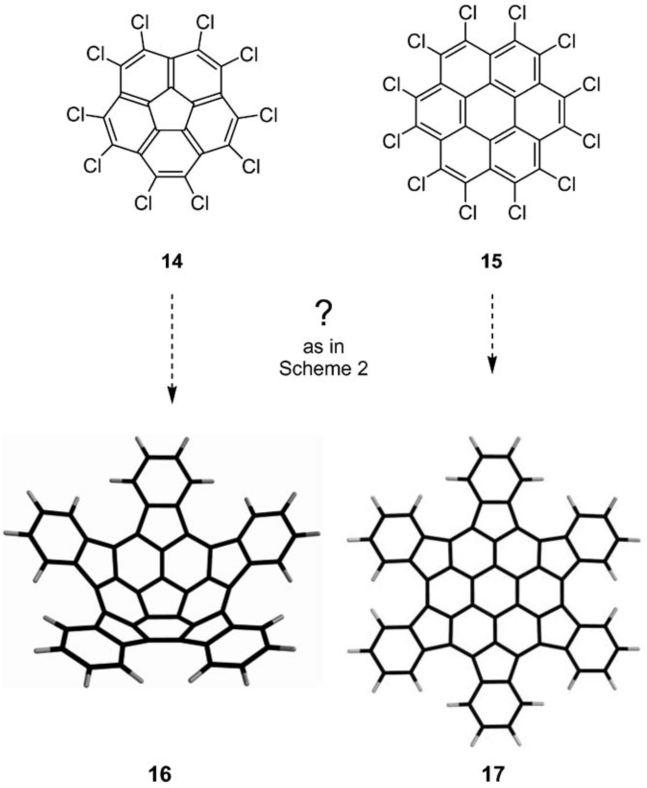


Figure 1. Multiple indeno[1,2,3]-annelations of polyhalo-PAHs by Suzuki–Heck-type coupling cascades.

Experimental Section

Materials

The 5,6-dichloroacenaphthene (**1**) used here was prepared by the direct chlorination of acenaphthene[5] and purified by recrystallization from benzene and hexanes; failure to use properly purified material produced erratic results. Reagent-Plus grade *N,N*-dimethylacetamide (DMAc) purchased from Aldrich was dried on an alumina column using a solvent dispensing system constructed by Contour Glass. The phosphonium tetrafluoroborate salts were purchased from Strem Chemicals; tris(dibenzylideneacetone)dipalladium(0) was purchased from Aldrich; 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was purchased from Acros; and the boronic acids were purchased from Acros, Aldrich, or Combi-Blocks, except for **6**, the synthesis of which is described below. All reagents were used without further purification. A CEM Discover microwave reactor unit was used with a standard temperature control method. The brine used was a saturated solution of aqueous sodium chloride.

1,2-Dihydrocyclopenta[*cd*]fluoranthene (9) in Microwave Reactor; Typical Procedure

An oven-dried 10-mL microwave vessel equipped with a magnetic stir bar was flushed with an atmosphere of nitrogen. To this was added 5,6-dichloroacenaphthene (**1**, 50.8 mg, 0.228 mmol), tris(dibenzylideneacetone)dipalladium(0) (42.3 mg, 0.046 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (33.4 mg, 0.115 mmol), and benzeneboronic acid (**8**, 41.8 mg, 0.343 mmol). Anhydrous *N,N*-dimethylacetamide (4.5 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.00 mL, 6.69 mmol) were then added by syringe with nitrogen purging to free the system of oxygen. The reaction mixture was heated at 175 °C for 40 min in a microwave reactor. After being cooled to room temperature, the solution was poured through a short Celite plug, and the plug was flushed with dichloromethane. The resulting filtrate was washed with 10% HCl (4×20 mL), once with 15 mL of distilled water, and finally with 15 mL of brine. This solution was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was adsorbed onto silica and chromatographed using 3:1 hexanes:dichloromethane as the eluent. Hydrocarbon **9** was obtained as a yellow solid; yield: 26.7 mg (51%). The ^{1}H NMR and ^{13}C NMR spectra of this material (see Supporting Information) matched those reported previously.[16,17]

1,2-Dihydrocyclopenta[*cd*]fluoranthene (9) with Conventional Heating; Typical Procedure

Under an atmosphere of nitrogen, 5,6-dichloroacenaphthene (**1**, 0.51 g, 2.27 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.42 g, 0.45 mmol), tri-*tert*-butylphosphonium tetrafluoroborate (0.33 g, 1.14 mmol), and benzeneboronic acid (**8**, 0.42 g, 3.42 mmol), were added to a flame-dried 150-mL pressure vessel equipped with a magnetic stir bar and sealed with a septum. Anhydrous *N,N*-dimethylacetamide (45 mL) and 1,8-diazabicyclo[5.4.0]undec-7-ene (10.2 mL, 68.2 mmol) were then added by syringe with nitrogen purging to free the system of oxygen. The rubber septum was replaced with a pressure vessel cap, and the reaction mixture was heated at 155 °C in an oil bath for 36 h. After being cooled to room temperature, the solution was poured through a short Celite plug, and the plug was flushed with dichloromethane. The resulting filtrate was washed with 10% HCl (4×50 mL), once with 50 mL of distilled water, and finally with 50 mL of brine. This solution was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude mixture was adsorbed onto silica and chromatographed using 3:1 hexanes:dichloromethane as the eluent. Hydrocarbon **9** was obtained as a yellow solid that had the same properties as the material prepared in the microwave reactor; yield: 0.216 g (42%).

3,4-Bis(*n*-octyloxy)phenylboronic Acid (6)

To a flame-dried 250-mL round-bottom flask with a stir bar was added 4-bromo-1,2-bis(*n*-octyloxy)benzene (5.28 g, 12.8 mmol) by syringe. Tetrahydrofuran (100 mL) was added under an atmosphere of nitrogen, and the flask was cooled in a −78 °C acetone/dry ice bath. Freshly titrated *n*-butyllithium (10.0 mL, 2.5 M in hexanes, 25.0 mmol) was syringed dropwise into the reaction mixture. After the end of the addition, the reaction mixture was allowed to continue stirring in the cold bath for 1 h. A slight excess of triisopropyl borate (7.0 mL, 30.3 mmol) was then added in a single portion to the reaction mixture still at −78 °C. After 30 min, the round-bottom flask was removed from the cold bath, and the reaction mixture was allowed to warm to room temperature. The reaction was quenched with 6 M HCl (20 mL). The reaction mixture was extracted three times with 20 mL portions of diethyl ether. The combined organic layers were washed three times with 15 mL portions of distilled water and once with 15 mL of brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated to dryness under reduced pressure. The crude material was dried with P_2O_5 overnight under vacuum. The resulting pink or yellowish solid was washed with cold diethyl ether to give a pale yellow or white solid; yield: 3.25 g (67%); mp 117–119 °C. The product is stored in the refrigerator. Spectroscopic characterization of this material (see Supporting Information) confirmed that it is the cyclic trimer (anhydride) of the boronic acid.

Acknowledgements

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