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Expeditious synthesis of fluorinated styrylbenzenes and polyaromatic hydrocarbons

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ABSTRACT

A series of fluorinated styrylbenzene derivatives were synthesized by the Mizoroki–Heck reaction using phosphine-free catalytic conditions or by adopting the one-pot Wittig–Heck reaction sequence. The fluorinated styrylbenzenes were converted into polyaromatic hydrocarbons such as phenanthrenes, [4]helicenes, and benzo[*ghi*]perylene by a modified photocyclization procedure involving I_2-THF condition.

Fluorinated polyaromatic hydrocarbons (F-PHCs) play an important role in understanding the action and the mechanism of carcinogenesis of this class of compounds. Presence of fluorine at different positions of the PHC helps to narrow the possible active sites to bind with DNA[1] or in modulating the carcinogenicity from the remote sites[2] or understanding other conformational parameters.[3] The study has established that certain F-PHCs have lower biological activity due to the presence of fluorine at the crucial section of the molecular framework and hence are less tumorigenic than the parent PHCs.[1b,4] The derivatives of F-PHCs also have a significant role in the study of reactions of standard nucleophiles with radical cations.[5] Recently polyaromatic compounds such as hexabenzocoronenes with the presence of a number of fluorine substituents have shown novel metastable molecular conformations.[6] Besides these the F-PHCs have a wide range of applications in molecular recognition, Host–Guest interactions, material chemistry, biologically important compounds,[7] medicinal chemistry,[8] liquid crystals,[9] and crystal engineering.[10]

The area of chemistry of fluorinated organic molecules has been a subject of immense research and several monograms and books are now available for reference.[11] Generally the fluorine atom is introduced by various special fluorinating methods on the substrate molecules.[12] This approach of accessing F-PHCs often has a drawback of formation of unwanted isomers.[12c,13–16] The other option is to select an appropriately fluorinated starting molecule and build the structure of F-PHC and has been successfully demonstrated in some cases.[17–21]

Recently we have developed phosphine-free catalyst systems for efficient Mizoroki–Heck reaction[22] as well as a one-pot Wittig–Heck reaction sequence.[23] One of the useful methods of synthesis of phenanthrenes, benzo[*c*]phenanthrenes, and helicenes is photocyclization of the corresponding stilbene derivatives.[24] In our earlier studies we have also developed an efficient modification of this photocyclization procedure by replacing the conventionally preferred propylene oxide as the acid scavenger with readily available tetrahydrofuran.[25] In this communication we present a combination of these two methods to synthesize fluorinated polyaromatic hydrocarbons.

The Path A of Scheme 1 describes the basic Mizoroki–Heck reaction to construct styrylbenzene derivative. The phosphine free catalyst system [comprising of the in situ mixture of ligand 1-(α-aminobenzyl)-2-naphthols **L** and $Pd(OAc)_2$] was screened for standard Mizoroki–Heck reaction with fluorinated aromatic bromo compounds **1**, **7,** or **10** with good conversions, Scheme 2. The stilbenes obtained are isolated in excellent yield under the experimental conditions.

However, this approach is limited to the availability of the corresponding styrene derivatives. To overcome this limitation we had developed the one-pot approach of in situ synthesis of styrene from the aldehydes by the Wittig reaction and utilized it for the subsequent Mizoroki–Heck reaction.[23] The advantage of this reaction is the availability of a range of aldehydes with varied functional groups and the elimination of the need of purification of

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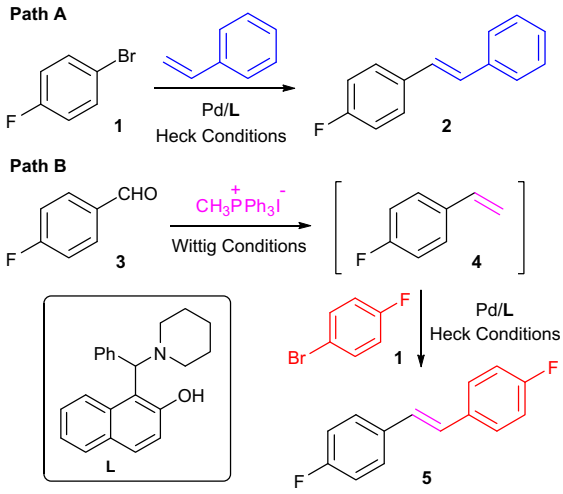
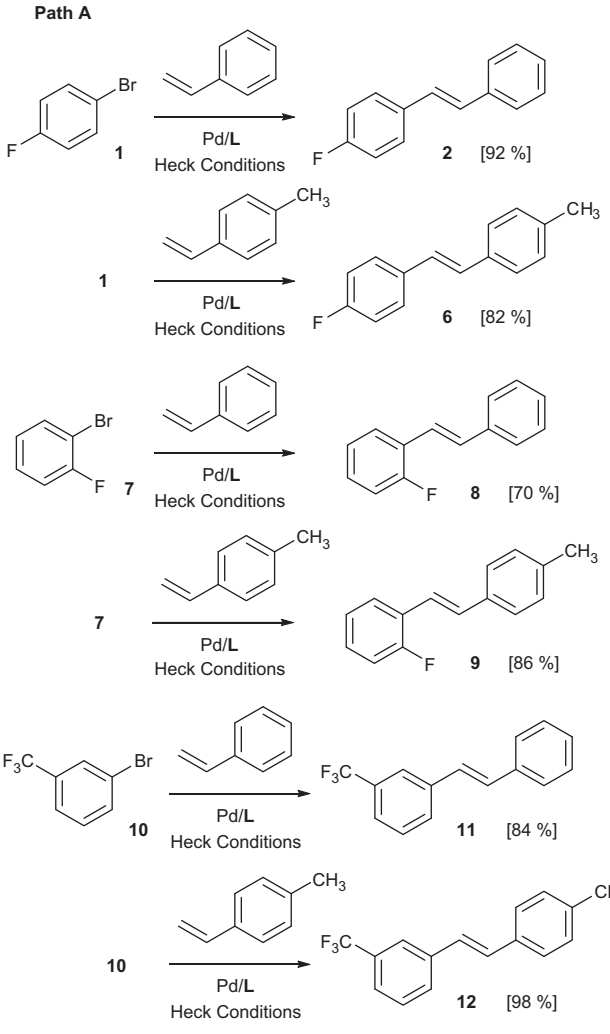
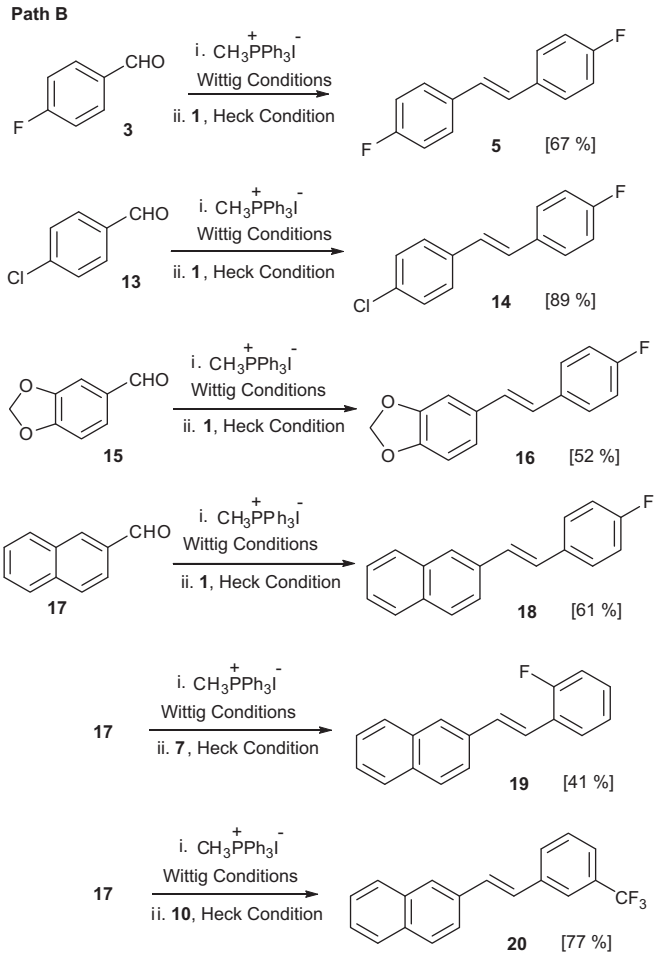


Scheme 1. Synthesis of fluorinated stilbenes.

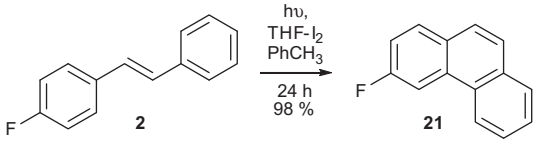


Scheme 2. Synthesis of stilbene derivatives by Path A. *Heck conditions*: Ar-Br (1.0 equiv), styrene (1.5 equiv), $Pd(OAc)_2$ (0.5 mol %), L (0.6 mol %), K_2CO_3 (2.5 equiv), TBAB (0.2 equiv), DMA, N_2 atm, 140 °C, 40 h.

the styrene for the coupling reactions. This strategy utilizes two aromatic moieties (Ar_1CHO and Ar_2X), to construct the stilbene unit and offers a variety of two different fluorine or fluorine containing substitutions as shown in Path B of Scheme 1.



Scheme 3. Synthesis of stilbene derivatives by Path B. *One-pot Wittig–Heck conditions*: Ar-CHO (1.5 equiv), CH_3PPh_3I (1.5 equiv), Ar-Br (1.0 equiv), $Pd(OAc)_2$ (0.5 mol %), L (0.6 mol %), K_2CO_3 (4.0 equiv), TBAB (0.2 equiv), DMA, N_2 atm, 140 °C, 40 h.



Scheme 4. Photodehydrocyclization of fluorinated stilbenes.

A series of fluorine containing styrylbenzenes were synthesized from corresponding aromatic aldehydes **3**, **13**, **15**, and **17** via their in situ conversion to styrenes and the subsequent Mizoroki–Heck reaction with suitable aryl halide as outlined in Scheme 3. As an example the reaction of 4-fluorobenzaldehyde **3** with one carbon phosphonium salt (Ph_3PCH_3I) and base will produce 4-fluorostyrene **4**, which will undergo in situ Mizoroki–Heck reaction with 1-bromo-4-fluorobenzene **1** to form 4,4′-difluoro stilbene **5** in moderate yield. Although the overall yields of such approach are slightly lower as the conditions are not currently fully optimized, this path offers wider scope for easy access to a variety of fluorinated stilbenes.

The standard method of photodehydrocyclization of stilbene in the presence of iodine as the oxidant produces phenanthrene and hydriodic acid, HI. Since this acid needs to be neutralized usually propylene oxide is used as an acid scavenger. However, the use of propylene oxide requires slight care as it has low boiling point