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Site-selective Synthesis of Functionalized Dibenzo[*f*,*h*]quinolines and their derivatives involving cyclic diaryliodonium salts via Decarboxylative Annulation Strategy

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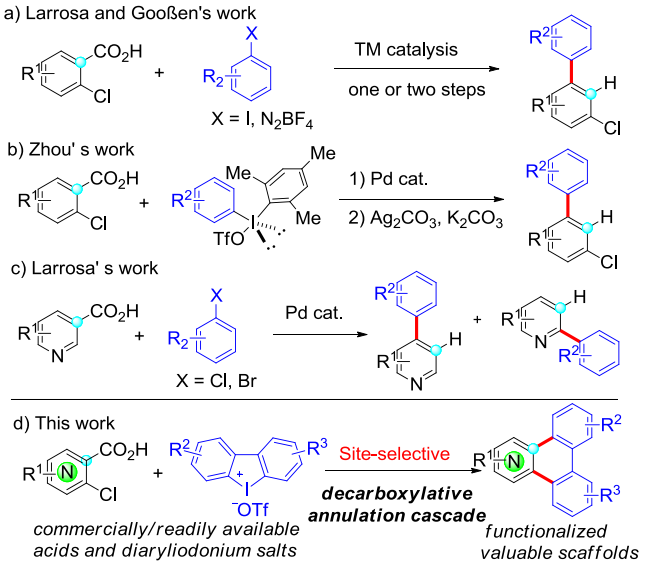
Here we report a site-selective synthesis of functionalized dibenzo[*f*,*h*]quinolines and their derivatives, which could be used as OLED materials. The key step is the double cross coupling reaction between the 2-chloropyridinyl acids and cyclic diaryliodonium salts, and the carboxylic acid was unprecedently employed as both a traceless directing group and a functional handle in an one-pot atom- and step- economical process.

Polycyclic aromatic hydrocarbons (PAHs) are regarded as segments of infinite two-dimensional graphene, and have been extensively exploited as potential electronic materials.[1] Among these, triphenylenes are the most often synthesized and investigated.[2] Compared with their all-hydrocarbon analogues, dibenzo[*f*,*h*]quinolines and their derivatives which exhibit unprecedented chemical and physical properties have been far less studied because of their limited accessibility.[3] Previously, the dibenzo[*f*,*h*]quinolines and dibenzo[*a*,*c*]acridines were mainly prepared by thermal electrocyclization starting from the quinone methides.[4] They also could be prepared by the coupling of either polyaryl carbonyl compounds with nitrogen donors[5] or polyaryl amines with carbonyl compounds.[6] In addition, the fused helicenes could be prepared either by intramolecular [2+2+2] co-cycloisomerization of aromatic cyanodiynes[7] or intramolecular annulation of biphenyls with alkynes.[8] However, there is no general method for the synthesis of dibenzo[*f*,*h*]quinolines and current available methods suffer from poor substrate scopes and long synthetic sequence. Therefore, it's desirable to develop general and efficient synthetic strategies to access functionalized dibenzo[*f*,*h*]quinolines and their derivatives, which would bridge the synthetic organic chemistry and material science.

The use of commercially available carboxylic acids for transition-metal catalyzed reactions is one of the fastest growing areas of research.[9] Previous work has shown that the carboxylic acid functionality could be used as either a functional handle for decarboxylative cross coupling reactions[10] or a removable/traceless directing group for direct arene functionalization.[11] For example, Larrosa,[12] Gooßen[13] and Zhou[14] reported the biaryl synthesis by coupling of 2-chlorobenzoic acids with iodobenzenes, arenediazonium salts or diaryl iodonium salts respectively under transition-metal catalysis (Scheme 1a-b). Larrosa also reported the direct arylation of pyridine carboxylic acids with aromatic halides,[15] which gave a mixture of pyridine *O*-arylated products in some cases due to the challenge of regioselective C–H activation/functionalization (Scheme 1c). In all those examples, the carboxylic acid functionality was used only as a traceless directing group for the *ortho*-arene arylation, which was then removed via protodecarboxylation[16] either in situ or by another extra step. Also the chlorine substituent didn't react with the coupling partners and left intact.



Scheme 1 Acid directed arylation

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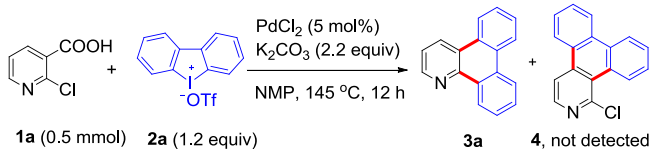
In continuation of our research interest in decarboxylative cross-coupling reactions[17] and cyclic diaryliodonium salt chemistry, [18] we would like to develop a site-selective synthesis of functionalized dibenzo[*f*,*h*]quinolines in an atom and step-economical way.[19] The key step is the unprecedented double cross-coupling reaction between the 2-chloropyridinyl acids and cyclic diaryliodonium salts, in which the carboxylic acids were employed as both traceless directing groups and functional handles, together with the cyclic diaryliodonium salts[20-21] as the bis-electrophile for the cascade reaction (Scheme 1d).

We initiated the investigation by reacting the commercially available 2-chloronicotinic acid **1a** with cyclic diaryliodonium salt **2a** (Table 1). With $Pd(OAc)_2$ as the catalyst, K_2CO_3 as the base and DMSO as the solvent, no desired product **3a** was detected (Table 1, entry 1). By using DMF as the solvent, the product **3a** was isolated in 20% yield (Table 1, entry 2). The yield could be improved to 44% with NMP as the solvent (Table 1, entry 3). However, by changing the reaction temperature (Table 1, entries 4-5), the amounts of the cyclic diaryliodonium salts **2a** (Table 1, entries 6-7) and the base (Table 1, entry 8) there was no any improvement at all. Finally, a catalyst screening was carried out to optimize the yield (Table 1, entries 9-12), and it was found that the desired dibenzo[*f*,*h*]quinoline **3a** could be obtained in 70% yield with $PdCl_2$ (5 mol %) as the catalyst and K_2CO_3 (2.2 equiv) as the base in NMP at 145 °C for 12 h. There is no 1-chlorodibenzo[*f*,*h*]isoquinoline **4** detected, which means that this reaction is highly site selective and no direct C4 pyridine arylation happened as reported by Larrosa.[15]

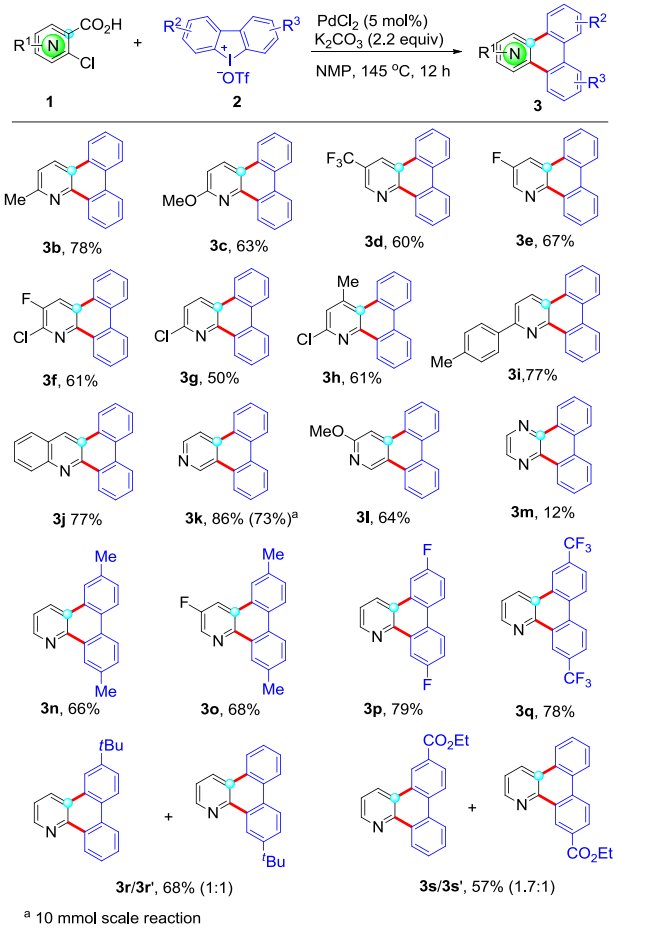
Table 1 Reaction optimization[a]



Entry	Variation from standard conditions	Yield (%)[c]
1	$Pd(OAc)_2$, DMSO	-
2	$Pd(OAc)_2$, DMF	20
3	$Pd(OAc)_2$, NMP	44
4	$Pd(OAc)_2$, 130 °C	10
5	$Pd(OAc)_2$, 160 °C	46
6	**2a** (1.5 equiv), $Pd(OAc)_2$	30
7	**2a** (0.7 equiv), $Pd(OAc)_2$	28
8	$Pd(OAc)_2$, Cs_2CO_3 as base	29
9	CuI as catalyst	-
10	$Pd_2(dba)_3$ as catalyst	53
11	$PdCl_2(dppf)$ as catalyst	45
12	standard	70

With the optimum conditions in hand, we next examined the scopes of this novel decarboxylative cyclization cascade sequence (Scheme 2).

First, we tested various commercially available pyridine carboxylic acid derivatives. The simple 2-chloronicotonic acid derivatives gave the corresponding products in good yields (**3a-b**). The substrates with either strong electron-donating or withdrawing substituents were effective (**3c-d**). Fluorine containing substituents such as F or CF_3 were compatible with the reaction conditions (**3d-e**). Interestingly, for the polychlorinated substrates only the chlorine next to the carboxylic acid functionality was reacted (**3f-h**), which means our catalytic system can directly utilize carboxylic acids as directing groups for the *ortho* cross coupling reaction in preference to the strong coordination of the pyridine nitrogen.[15] The site selectivity makes the intact chlorine as a potential functional handle for the further transformations. For the substrate with a phenyl group next to the nitrogen, surprisingly the pyridine directed arene C — H functionalization didn't happen. The reaction took place site-selectively to give the dibenzo[*f*,*h*]quinoline **3i** in 77% yield. The 2-chloroquinoline-3-carboxylic acid gave the dibenzo[*a*,*c*]acridine **3j** in 77% yield. The 3-chloroisonicotinic acids worked as well to give the desired dibenzo[*f*,*h*]isoquinolines **3k** and **3l** in 86% and 64% yields respectively. However, the yield of dibenzo[*f*,*h*]isoquinoxaline (**3m**) is quite poor with 3-chloropyrazine-2-carboxylic acid as the substrate probably because of the high Lewis basicity of the sp^2-nitrogen, which often results in side reactions due to the catalyst coordination and poisoning.[15]



[a] 10 mmol scale reaction

Scheme 2 Site-selective synthesis of dibenzo[*f*,*h*]quinolines and derivatives

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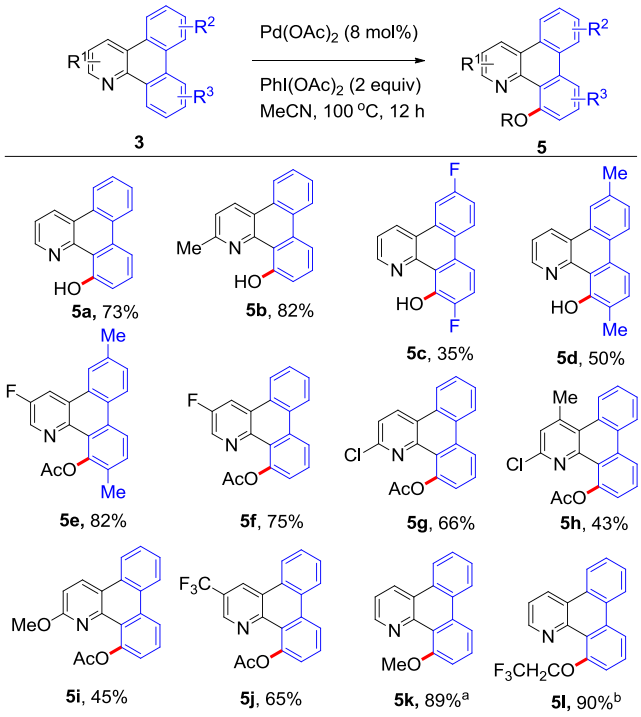
Then a range of substituted cyclic diaryliodonium salts were prepared according to Olofsson's method and subjected to the optimized reaction protocol.[22] For the symmetrical cyclic diaryliodonium salts the reactions gave the corresponding products in good yields (**3n-q**). However, the reaction of 2-chloronicotonic acid with asymmetrical cyclic diaryliodonium salts afforded an inseparable mixture of products (**3r/3r'** and **3s/3s'**).

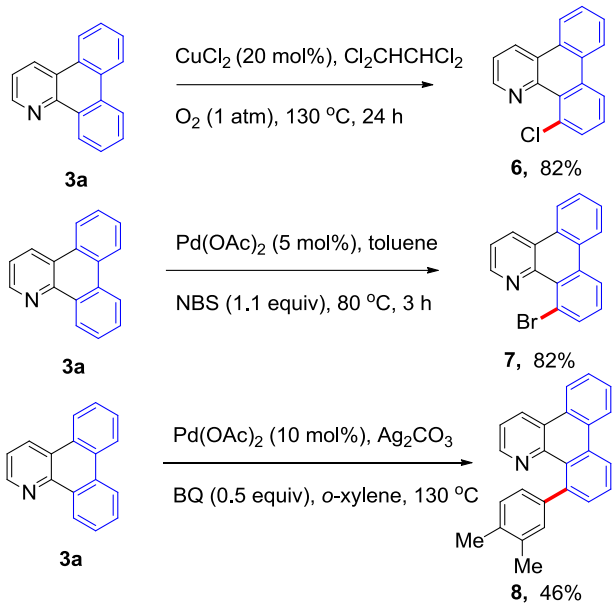
With the dibenzo[*f*,*h*]quinoline products in hand, we would like to demonstrate that they can be further site selectively functionalized by directed Pd-catalyzed C–H activation/functionalization methods (Scheme 3),[23] which would open a door for the rapid access to various dibenzo[*f*,*h*]quinoline derivatives. Although there are some examples for the direct C–H functionalization of PAHs,[24] to our knowledge the direct oxygenation of the dibenzo[*f*,*h*]quinolines has never been reported. Firstly, we would like to introduce a hydroxyl or acetate group to the framework inspired by Sanford's method.[25] With $Pd(OAc)_2$ as the catalyst, $PhI(OAc)_2$ as the oxidant, the simple dibenzo[*f*,*h*]quinolines gave the hydroxylated products in moderate to good yields (**5a-d**). For the other substrates, the acetoxylated products were formed. The halogen groups such as F or Cl were tolerated under the reaction conditions (**5e-h**). The reactions with substrates bearing either strong electron- donating or withdrawing substituents afforded the acetated products in moderate yields (**5i-j**). By changing the solvent to MeOH or CF_3CH_2OH, a methoxy or CF_3CH_2O group could be introduced to the skeleton in 89% and 90% yield respectively (**5k** and **5l**).



[a] $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (1.5 equiv), MeOH, 95 °C, 12 h
[b] $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (1.5 equiv), CF_3CH_2OH, 95 °C, 12 h

Scheme 3 Directed site-selective oxygenation of dibenzo[*f*,*h*]quinolines

In order to demonstrate that our cyclized dibenzo[*f*,*h*]quinoline products could be converted into diversified valuable building blocks, we managed to introduce other functional groups or handles to the framework by site selective direct C–H functionalization (Scheme 4). Treated dibenzo[*f*,*h*]quinoline **3a** with the copper-catalyzed condition with oxygen as the oxidant in tetrachloroethane at 130 °C gave the chlorinated product **6** in 82% yield.[26] With NBS as the oxidant under Pd-catalyzed conditions, a C–Br bond can be constructed in good yield to give product **7**.[27] Finally, by a dehydrogenated cross coupling,[28] the dibenzo[*f*,*h*]quinoline **3a** reacted with *o*-xylene under palladium catalysis affording the arylated product **8** in moderate yield.



Scheme 4 Directed site-selective C–H halogenation and arylation of dibenzoquinolines

In summary, with readily available pyridine carboxylic acids and cyclic diaryliodonium salts as the starting materials we have developed an unprecedented site-selective synthesis of dibenzo[*f*,*h*]quinolines and their derivatives, which can be further functionalized site-selectively to afford diversified building blocks for material chemistry. The key for this novel method is the employment of carboxylic acids as both directing groups and functional handles, together with the cyclic diaryliodonium salts as the **bis-electrophile** for this one-pot double cross-coupling reaction.

Acknowledgements

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Conflicts of interest

There are no conflicts to declare.

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Site-selective Synthesis of Functionalized Dibenzo[*f*,*h*]quinolines and their derivatives involving cyclic diaryliodonium salts **via Decarboxylative Annulation Strategy**

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An unprecedented site-selective synthesis of dibenzo[*f*,*h*]quinolines and their derivatives was reported via an acid directed decarboxylative annulation cascade