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Synthesis of Tribenzo[*b,d,f*]azepines via Cascade π-Extended Decarboxylative Annulation Involving Cyclic Diaryliodonium Salts

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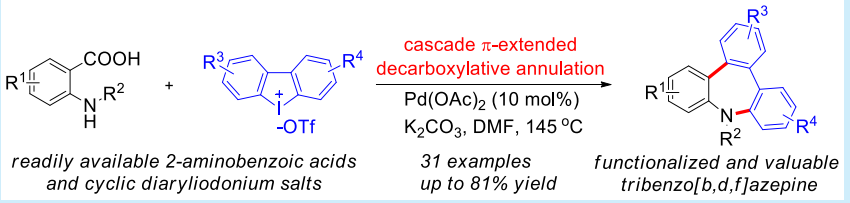
Supporting Information



ABSTRACT: Various functionalized tribenzo[*b,d,f*]azepines were prepared efficiently with the readily available 2-aminobenzoic acids and cyclic hypervalent diaryliodonium reagents as starting materials under Pd(II) catalysis. The key of this step-economical protocol is that the carboxylic acid functionality was employed as both a traceless directing group for the N−H activation/arylation and a functional handle for the tandem π-extended decarboxylative annulation.

Benzoazepine is one of the most important classes of 7-membered nitrogen-containing heterocycles due to its wide prevalence in bioactive natural products such as chilenine and lennoxamine,[1] best-selling drugs such as carbamazepine for the treatment of epilepsy,[2] and functional materials such as organic light-emitting diodes, organic thin-film transistors, and organic photovoltaics (Figure 1).[3] Considerable attention has

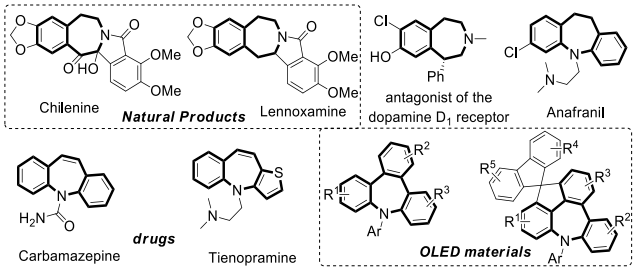
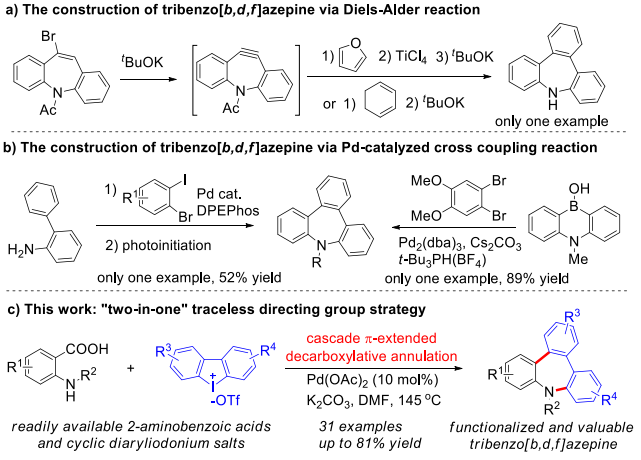


Figure 1. Representative examples of benzoazepines.

been focused on the development of novel methods for their efficient synthesis.[4] However, there are only scarce examples reported for the construction of the tribenzo[*b,d,f*]azepine ring system, which usually requires a multistep sequence with relatively low overall synthetic efficiency. For example, Cann and coworkers reported one example in 1991 about the 9*H*-tribenzo[*b,d,f*]azepine synthesis starting from the brominated dibenzoazepine through a multistep sequence with the Diels−Alder reaction as the key step (Scheme 1a).[5] In 2009, Martin and Rossi et al. reported the 9*H*-tribenzo[*b,d,f*]azepine synthesis through Pd(II)-catalyzed Buchwald−Hartwig reaction followed by photostimulated intramolecular radical nucleophilic substitution (Scheme 1b).[6] In 2014, Taylor and

Scheme 1. Synthetic Strategies for the Construction of Tribenzoazepine Core



coworkers reported another example via a twofold Suzuki−Miyaura coupling of cyclic diarylborinic acids with dibromoarene.[7] Hence, more novel and atom/step-economic methods for tribenzoazepine synthesis need to be developed to explore their chemical space and potential applications in medicinal and material chemistry.

The annulative π-extension (APEX) reaction has been frequently employed for the one- or two-step construction of valuable π-extended and fused aromatic compounds.[8] Although this approach usually requires no prefunctionaliza-

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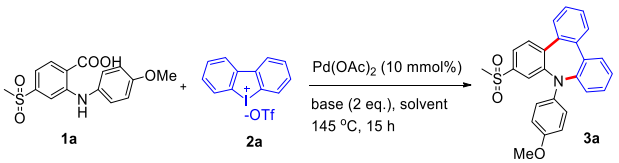
tion of the template arene substrate via direct C−H activation, it still suffers from some limitations such as low yields and limited region diversity.[8b] Also, it may hard to control the site selectivity of C−H activation when multiple C−H bonds exist in the substrates. Furthermore, to the best of our knowledge, currently it can only be employed for the construction of five or six-membered all-carbon aromatic ring. Recently, with diverse benzoic acid and cyclic diaryliodonium salt[9−12] as the starting materials, we reported the one-step synthesis of triphenylenes and dibenzo[*f*,*h*]quinolines via a π-extended decarboxylative annulation (PEDA) strategy.[13] In continuation of our research interest in development of novel methodologies for heterocycle synthesis,[14] we demonstrate that this PEDA strategy can be employed not only for the construction of six-membered all carbon aromatic ring but also for the seven-membered nitrogen containing heterocycle formation. With 2-aminobenzoic acid derivatives as templates and cyclic diaryliodonium salts as π-extending agents, we envisioned that the ring system could be constructed by our PEDA strategy in which the carboxylic acid functionality was employed as both a traceless directing group[15] for the palladium-catalyzed N−H activation/arylation and functional handle for the cascade *ipso*-decarboxylative[16,17] annulation (Scheme 1c). How to selectively achieve the N−H activation/arylation by avoiding the *ortho* C−H activation and protodecarboxylation side reactions and make the consecutive series of reactions proceed smoothly are challenging tasks for this novel double cross-coupling one-pot protocol.

With 2-aminobenzoic carboxylic acid **1a** and cyclic diaryliodonium salt **2a** as model substrates, we initiated the optimization of reaction conditions (Table 1).

We first conducted an intensive screening of metal catalysts (see the Supporting Information). There was no product detected when CuI was used as catalyst (Table 1, entry 1), and the desired product was obtained in 39% yield with $PdCl_2$ as catalyst (Table 1, entry 2). By screening the other palladium catalysts, it was found that $Pd(OAc)_2$ was the optimum catalyst with the yield improved to 68% (Table 1, entry 5). A base screening was then conducted (Table 1, entries 6−9), and it was found the yield can be further improved to 80%. By switching the solvent from DMF to other solvents such as DMA, DMSO, or NMP (Table 1, entries 10−12), decreasing the reaction temperature or amount of catalyst (not shown here), the reaction yields dropped. The reaction was negative in the absence of catalyst or base (Table 1, entries13 and 14, respectively).

Table 1. Optimization of Reaction Conditions[a]

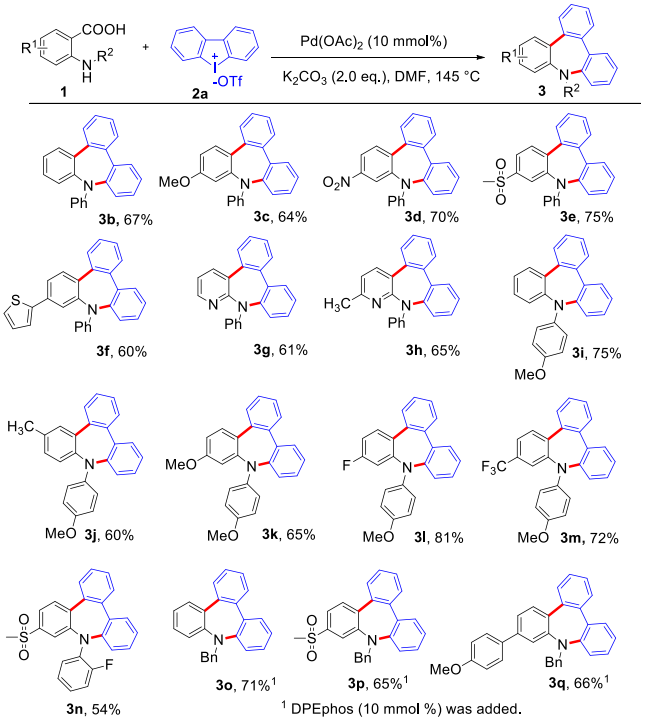


entry	cat (mol %)	base	solvent	yield (%)[b]
1	CuI	Na_2CO_3	DMF	0
2	$PdCl_2$	Na_2CO_3	DMF	39
3	$Pd(PPh_3)_4$	Na_2CO_3	DMF	43
4	$Pd(dba)_2$	Na_2CO_3	DMF	34
5	$Pd(OAc)_2$	Na_2CO_3	DMF	68
6	$Pd(OAc)_2$	K_2CO_3	DMF	80
7	$Pd(OAc)_2$	Cs_2CO_3	DMF	60
8	$Pd(OAc)_2$	NaO^tBu_3	DMF	21
9	$Pd(OAc)_2$	KF	DMF	46
10	$Pd(OAc)_2$	K_2CO_3	DMA	47
11	$Pd(OAc)_2$	K_2CO_3	DMSO	51
12	$Pd(OAc)_2$	K_2CO_3	NMP	64
13		K_2CO_3	DMF	0
14	$Pd(OAc)_2$		DMF	0

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Pd(OAc)_2$ (10 mol %), base (2.2 equiv), solvent (2.0 mL), 15 h, 145 °C, air atmosphere. [b]Isolated yields.

With optimum conditions in hand, the substrate scope of 2-aminobenzoic acid derivatives was first examined (Scheme 2).

Scheme 2. Scope of 2-Aminobenzoic Carboxylic Acids



A range of 2-aminobenzoic acid derivatives with an aryl substituent on nitrogen was prepared and treated under the optimum conditions, and the corresponding tribenzo[*b*,*d*,*f*]-azepine products were obtained successfully in moderate to good yields (**3b**−**3n**), which have potential applications in organic light-emitting devices.[3] Both strong electron donating (**3c**, **3i**−**3m**) and withdrawing (**3d**, **3e**, **3m**, and **3n**) substituents and various functional groups such as nitro (**3d**), thienyl (**3f**), methyl sulfonyl (**3e** and **3n**), and fluorine (**3l** and **3m**) were tolerated under the reaction conditions. The 2-aminopyridinyl carboxylic acids were also effective (**3g** and **3h**). The 2-aminobenzoic acid derivatives with a benzyl substituent on nitrogen also worked well to give the corresponding products in fair yields (**3p** and **3q**).[18]

To fully establish the scope of this π-extended decarboxylative annulation, various substituted cyclic diaryliodonium salts were prepared and subjected to the optimized reaction conditions (Scheme 3).[19] We first tested the symmetrical cyclic diaryliodonium salts (**4a**−**4g**). The cyclic diaryliodonium salts bearing simple methyl substituents on the *para*-position reacted with various 2-aminobenzoic acid derivatives and gave the corresponding products in good yields (**4a** and **4b**) except **4c**.[20] The more torsionally strained cyclic diary-

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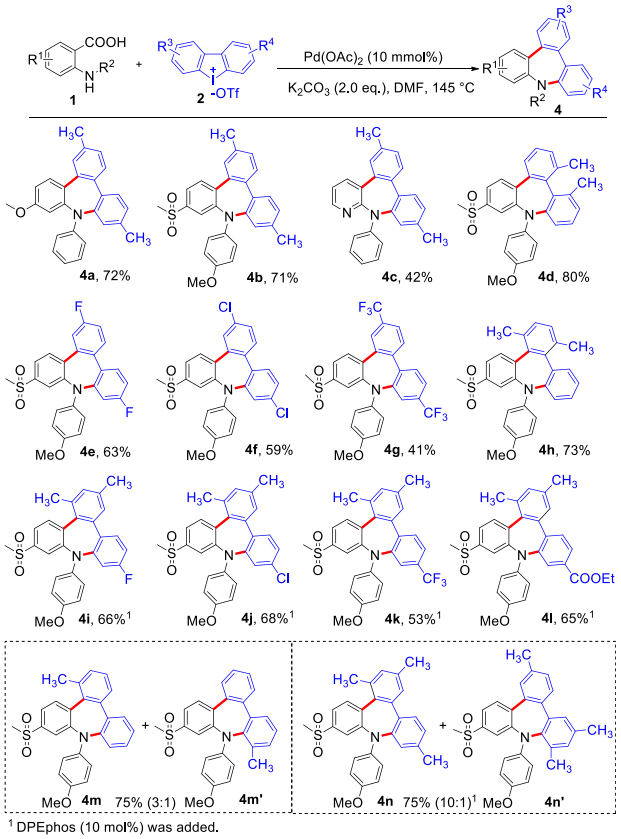
Scheme 3. Scope of Cyclic Diaryliodonium Salts

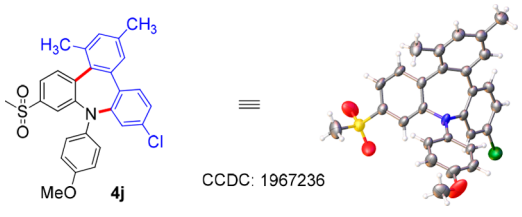


[1] DPEphos (10 mol%) was added.

liodonium salt with two *orthyl* methyl group which was believed to exhibit higher reactivity gave the desired product **4d** in better yield than did **4b**.[21] The symmetric cyclic diaryliodonium salts bearing halogens (F, Cl) were effective under the optimum conditions, affording the corresponding products in fair yields (**4e** and **4f**). However, the cyclic diaryliodonium salt with strong electron-withdrawing groups such as CF_3 gave the product in poor yield (**4g**). The unsymmetrical cyclic diaryliodonium reagents were then examined (**4h**−**4n**). The cyclized products **4h**−**4l** were isolated as single product with the nitrogen attacking from the less hindered and electronic deficient side of the diaryliodonium. However, for the unsymmetrical cyclic diaryliodonium salts without significant steric or electronic differences between the two aryl groups, the reaction gave a mixture of cyclized products in good yields (**4***m*/**4m** and **4***n*/**4n**).

The structure of **4j** was further confirmed by the single-crystal X-ray diffraction analysis (Scheme 4). Because this π-extended decarboxylative annulation involved both C−N and C−C bond formation, the X-ray structure indicated that the *N*-

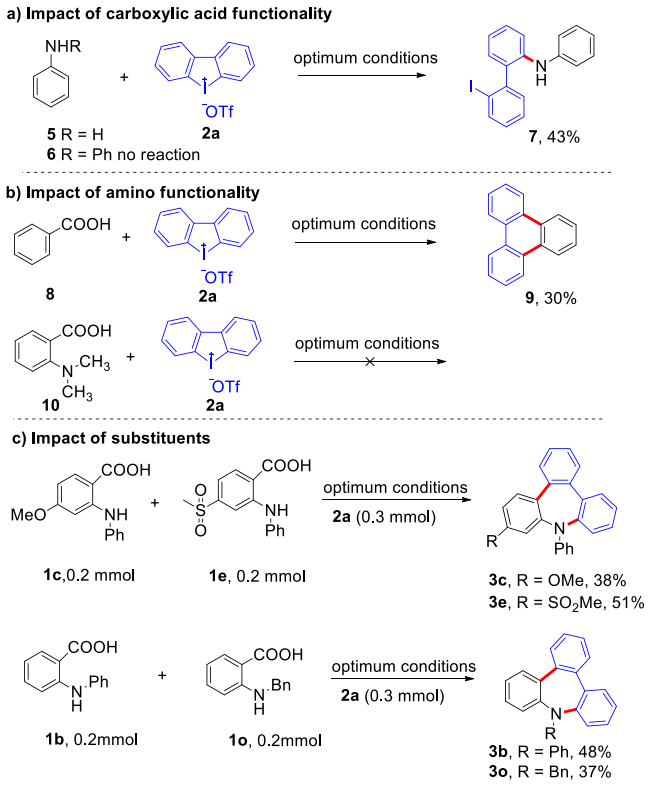
Scheme 4. X-ray Analysis of Product 4j



arylation took place from the less hindered and electron deficient side of the salt, and the C−N bond was constructed before the C−C bond formation.

To further understand this π-extended decarboxylative annulation, the following control experiments were carried out (Scheme 5). First, the impact of the carboxylic functional

Scheme 5. Control Experiments



group was evaluated (Scheme 5a). It was found the linear *N*-arylated product **7** was obtained in 43% yield by reacting aniline **5** with the hypervalent iodine reagent **2a** under the optimum conditions.[22] There was no reaction if diphenyl amine **6** was employed as substrate, which demonstrated the essential directing effect of carboxylic acid. The impact of the amino functionality was then tested (Scheme 5b). The reaction with benzoic acid **8** as substrate gave the triphenylene **9** in 30% yield.[13] There was no reaction with 2-dimethylamino benzoic acid **10** as substrate. Finally, the competition experiments indicated that the benzoic acid **1e** with electron withdrawing substituent on the *para* position of acid functionality reacted faster than the electron-rich counterpart **1c** (Scheme 5c). The acid substrate **1b** with aryl substituent on the nitrogen reacted faster than that **1o** with the benzyl protected group.

A reaction mechanism was proposed based on the above experiments (Scheme 6). First a six-membered palladium(II) complex **A** might formed from the 2-aminobenzoic acid in the presence of $Pd(OAc)_2$ catalyst. The oxidative addition of cyclic diaryliodonium salt **2a** would give the Pd(IV) species **B,** which undergoes reductive elimination and decarboxylation, affording linear intermediate **D**. Another oxidative addition followed by reductive elimination would generate the final cyclized tribenzo[*b*,*d*,*f*]azepine **3b** via the eight-membered Pd(IV) species **E**. The released Pd(II) catalyst goes into the next catalytic cycle.

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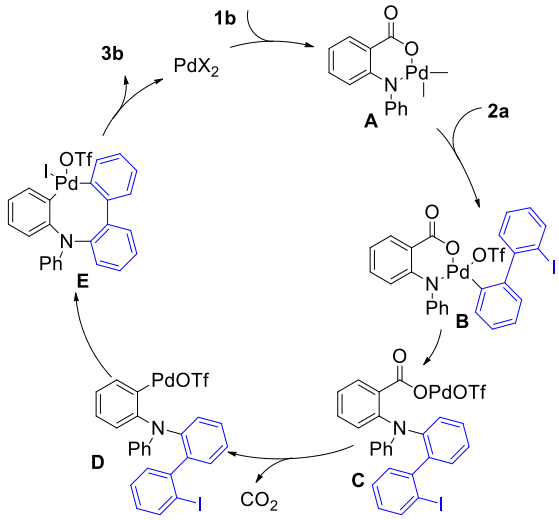
Scheme 6. Proposed Mechanism



In summary, a Pd(II)-catalyzed cascade π-extended decarboxylative annulation was developed successfully for the efficient preparation of various valuable tribenzo[*b*,*d*,*f*]-azepines. The readily available 2-aminobenzocarboxylic acid derivatives and cyclic diaryliodonium salts were used as the starting materials for this one-step double cross coupling protocol. The carboxylic acid functionality was successfully developed as both a traceless directing group for the N−H activation/arylation and a reactive group for the cascade decarboxylative annulation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04269.

Experimental procedures and spectroscopic characterization data (PDF)

Accession Codes

CCDC 1967236 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(18) There was no desired product isolated by using the other 2-aminobenzoic acid derivatives with acyl or Boc group protecting group on nitrogen. Also, it was not successful towards the synthesis of larger rings, tribenzo[*b*,*d*,*f*]oxepine, or tribenzo[*b*,*d*,*f*]thiepine.
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