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PAPER

Modular Synthesis of Heptaarylindole

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The first synthesis of heptaarylindole (HAI) has been accomplished using a coupling/ring transformation strategy. Four readily prepared modular units (diarylthiophenes, 2-arylaziridines, arylboronic acids, and arylalkynes) were joined together to provide key ynamide intermediates. Subsequent inverse electron-demand intramolecular [4+2] cycloaddition furnished pentaarylindoles (PAIs) regioselectively. This strategy was also applied to the synthesis of tetraarylazaindole with four different aryl substituents. PAIs underwent further arylations at the C2- and N1-positions, providing HAI with seven different aryl substituents with virtually complete regioselectivity.

Introduction

Nitrogen-containing benzoheteroles such as indoles and azaindoles represent privileged structural motifs in functional molecules such as pharmaceuticals, natural products and ligands.[1] In particular, aryl-substituted indoles have often been found in bioactive molecules.[2] To construct these skeletons, cyclization using benzenoid precursors (e.g., Fischer, Larock, and Bartoli indole synthesis) or cross-coupling reaction of halogenated/metallated indoles have been used as conventional and reliable methods.[3] Recently, direct C–H arylations of benzoheteroles have been extensively developed, and regioselective C–H arylations of indoles have been achieved at all positions through transition metal catalysis.[4] Even when taking into consideration these notable advancements, regioselective synthesis of multiply arylated indoles remains challenging.

In related work, our group has recently developed a programmed synthesis of multiply arylated aromatics by a coupling/ring transformation approach (Figure 1a).[5] Tetraarylthiophene *S*-oxides, prepared by regioselective C–H arylations and cross-couplings followed by oxidation of the thiophene, underwent [4+2] cycloaddition with various dienophiles to provide hexaarylbenzenes (HABs),[5a] pentaarylpyridines (PAPs),[5a,b] octaarylnaphthalenes (OANs)[5c] and octaarylanthracenes (OAAs)[5c] in a programmed manner. Motivated by a challenge to synthesize multiply arylated indoles, we decided to tackle the synthesis of fully arylated indole, heptaarylindole (HAI), which has not been achieved so far. Based on our synthesis of multiply arylated aromatics, we envisioned that a coupling/ring transformation strategy would also be effective for the synthesis of HAI (a retrosynthetic analysis is shown in Figure 1b). HAI would be generated from pentaarylindole (PAI) by appendage of two aromatic units at C2 and N1 (coupling reactions). In turn, PAI can be produced by an inverse electron-demand intramolecular [4+2] cycloaddition between thiophene *S*,*S*-dioxide and ynamide moieties *via* ring transformation.[6,7,8]

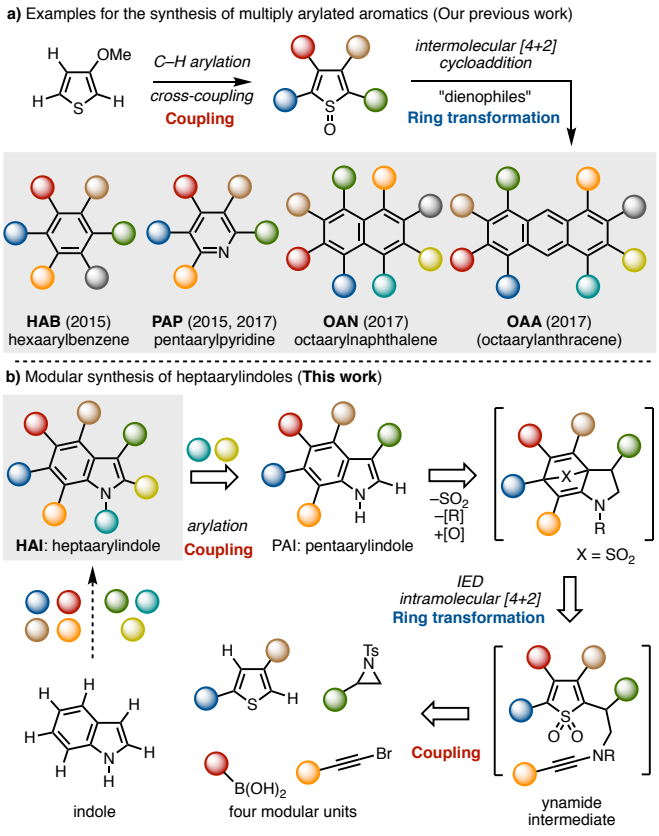

Figure 1. a) Examples for the synthesis of multiply arylated aromatics. b) Modular synthesis of heptaarylindoles.

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The ynamide intermediate would be formed by connecting four modular units: diarylthiophenes, 2-arylaziridines, arylboronic acids, and arylalkynes. Herein, we report the first modular synthesis of HAI.

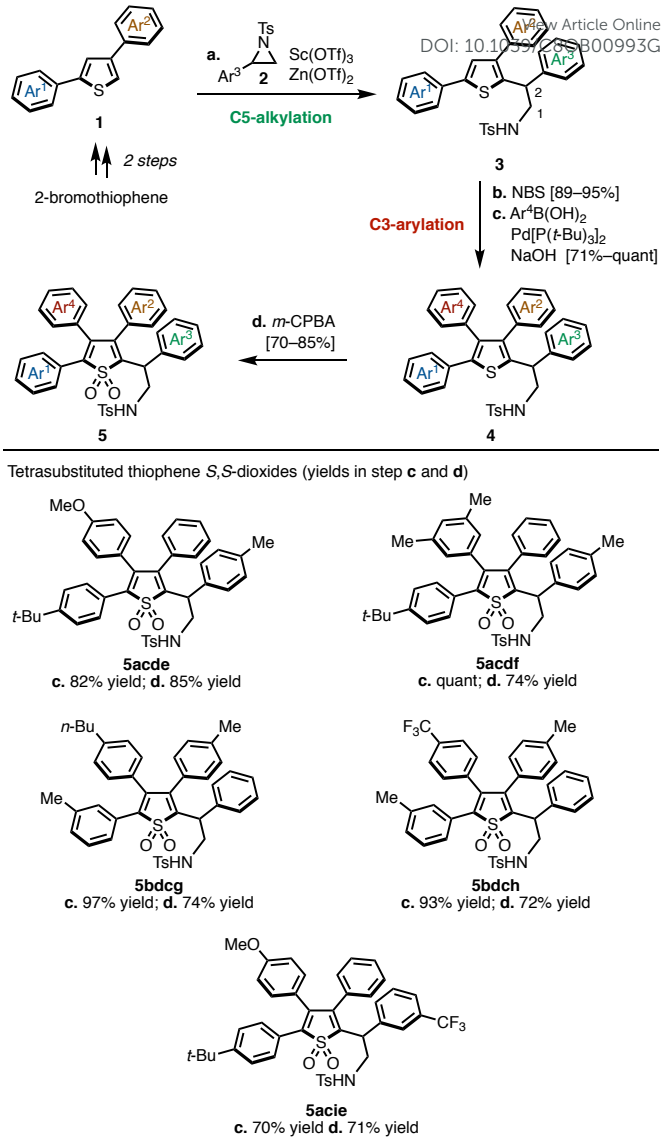
Results and discussion

Synthesis of tetrasubstituted thiophene *S*,*S*-dioxide

Firstly, we synthesized tetrasubstituted thiophene *S*,*S*-dioxide **5** (Scheme 1). The synthesis commenced from 2,4-diarylthiophenes **1**, which were readily prepared by our two-step protocol involving cross-coupling and β-selective C–H arylation of 2-bromothiophene.[9] To achieve a C5-alkylation of **1**, 2-aryl-*N*-tosylaziridines **2** (**2a**: *p*-tolyl, **2b**: phenyl) were reacted with 1.5 equiv of **1** in the presence of a catalytic amount of $Sc(OTf)_3$ and $Zn(OTf)_2$ in dichloroethane to afford C5-alkylated thiophenes **3** in 79% yield (**3acd** from **1ac**) and 62% yield (**3bdc** from **1bd**) as major isomers, containing small amounts of undesired C3-alkylated thiophenes (7:1 to 9:1 ratio).[10] Unfortunately, when electron-deficient aziridine **2** such as 2-(3-(trifluoromethyl)phenyl)-*N*-tosylaziridine (**2i**) was used, the desired products **3aci** was obtained from **1ac** with decreased regioselectivity (8:3). Although this reaction required a small excess of thiophenes **1** to give high yields of **3**, unreacted thiophenes **1** were recovered. Subsequent C3-arylations of **3acd**, **3bdc** and **3aci** were achieved by sequential bromination/Suzuki–Miyaura cross-coupling with arylboronic acids to furnish tetrasubstituted thiophenes **4** in excellent yields (**4acde**, 82%; **4acdf**, quant.; **4bdcg**, 97%; **4bdch**, 93%; **4acie**: 70%) with virtually complete isomeric purities. Then, to enhance the reactivity of the thiophene moiety as a diene, oxidation of thiophenes **4** into thiophene *S*,*S*-dioxides **5** was carried out. Treatment of **4** with *m*-chloroperoxybenzoic acid (*m*-CPBA) successfully provided the corresponding thiophene *S*,*S*-dioxides **5** in good yields.

Synthesis of ynamides and pentaarylindoles (PAIs)

With fully substituted thiophene *S*,*S*-dioxides **5** in hand, we examined the synthesis of ynamide intermediate **6** and pentaarylindoles (PAIs) **9** (Scheme 2a and 2b). After extensive screening of *N*-alkynylations of **5**,[11] we found that a copper-catalyzed alkynylation of sulfonamides with bromoalkynes **7** is effective.[11c] To our delight, upon forming ynamide **6**, intramolecular [4+2] cycloaddition between thiophene *S*,*S*-dioxide and ynamide moieties spontaneously proceeded, providing indolines **8** as single isomers.[12] Since a catalytic amount of $CuSO_4$/phenanthroline (phen) was less effective for *N*-alkynylation, use of 50 mol% $CuSO_4$ and 100 mol% of phen was needed for optimal results (see Table S1). With these optimized conditions, thiophene *S*,*S*-dioxides **5** were reacted with bromoalkynes **7** in the presence of $CuSO_4 \cdot 5H_2O$/phen and K_3PO_4 in toluene at 80 °C to afford the corresponding indolines **8** in moderate yields, along with recovery of unreacted thiophene *S*,*S*-dioxides **5**.



Scheme 1. Synthesis of tetrasubstituted thiophene *S*,*S*-dioxides **5**. Reaction conditions: a) **1** (1.5 equiv), arylaziridines **2** (1.0 equiv), $Sc(OTf)_3$ (5 mol%), $Zn(OTf)_2$ (5 mol%), DCE, RT, 16 h, 79% (9:1, **3acd**), 62% (7:1, **3bdc**); 67% (8:3, **3aci**); b) NBS (1.1–1.2 equiv), $CHCl_3$, RT, 24 h, 89% (**Br-3acd**), 95% (**Br-3bdc**); c) $ArB(OH)_2$ (3.0 equiv), $Pd_2(dba)_3 \cdot CHCl_3$ (2.5 mol%), P(*t*-Bu)$_3 \cdot HBPh_4$ (5 mol%), NaOH (2.0 equiv), THF, reflux, 24 h, 82% (**4acde**), quant. (**4acdf**), 97% (**4bdcg**), 93% (**4bdch**)[b]; 70% (**4acie**); d) *m*-CPBA (2.2–2.5 equiv), CH_2Cl_2, 0 °C to RT, 24h, 85% (**5acde**), 74% (**5acdf**), 74% (**5bdcg**), 72% (**5bdch**) 70% (**5acie**). [b]48 h.

The synthesis of indolines **8** was accomplished for bromoalkynes **7** with a variety of functional aryl groups [4-ethyl (**7A**), 3-thienyl (**7B**), 3-pyridyl (**7C**), 2,6-xylyl (**7D**), 6-methoxynaphthyl (**7E**), 3-methyl (**7F**), 3,5-xylyl (**7G**), 2-thienyl (**7H**), 4-trifluoromethyl (**7I**), 4-methoxy (**7J**), 4-*tert*-butyl (**7K**), 4-fluoro (**7L**, and 4-ethylphenyl (**7M**)]. Then, indolines **8** were converted to PAI **9** bearing five different aryl groups. Although the oxidation of **8** was attempted using various oxidants such as MnO_2, DDQ and DDQ/$FeCl_3$,[13] this only gave starting materials or complex mixtures. In contrast, after removal of the tosyl group, oxidation of the resulting NH-indoline smoothly provided PAI **9**.

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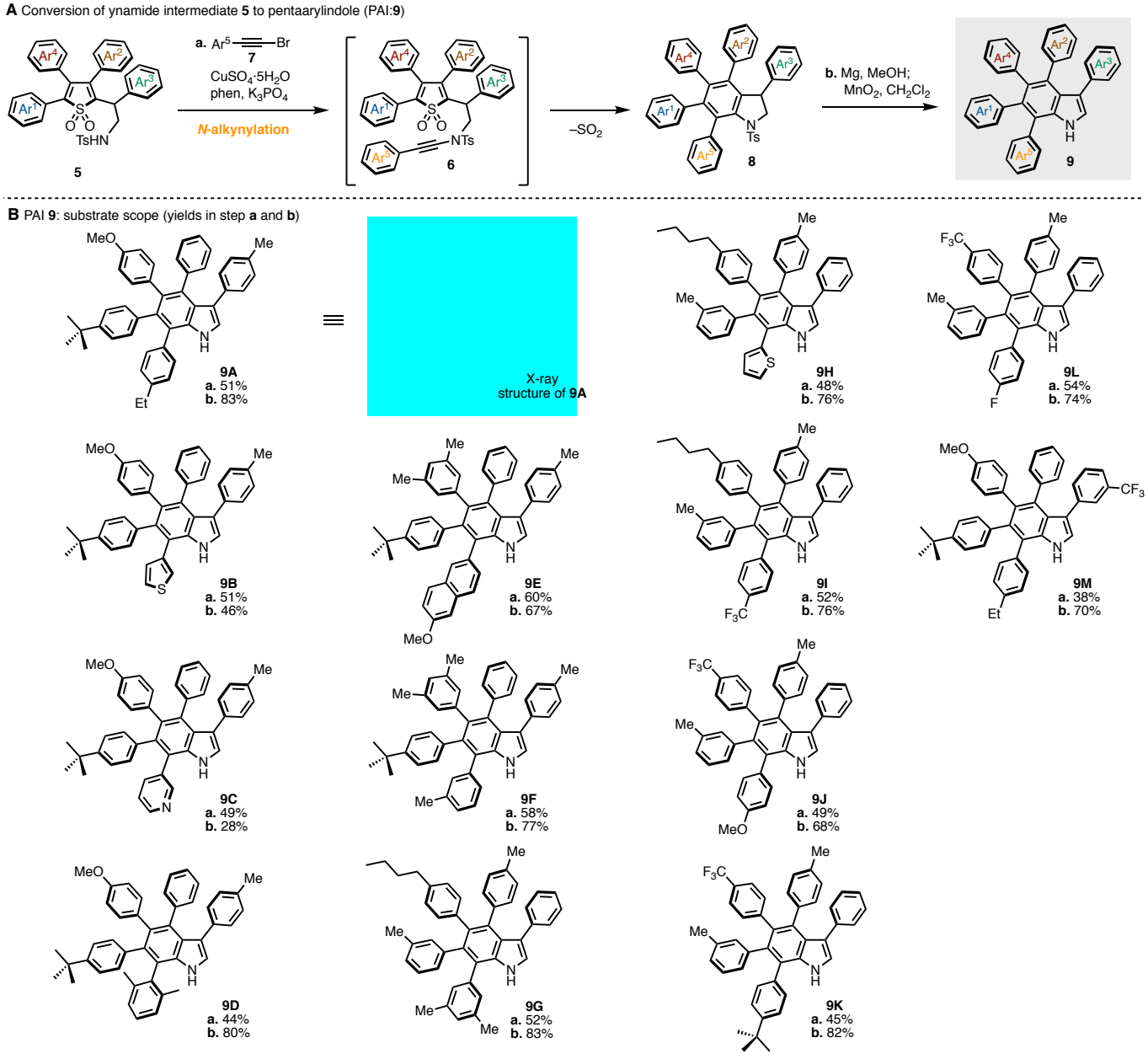

Scheme 2. A) Synthesis of pentaarylindoles **9**. B) Substrate scope. Reaction conditions: a) bromoalkynes **7** (1.2 equiv), $CuSO_4 \cdot 5H_2O$ (0.5 equiv), phen (1.0 equiv), K_3PO_4 (2.0 equiv), toluene, 80 °C, 16 h; b) Mg (60 equiv), MeOH, THF, reflux, 24 h, then MnO_2 (20 equiv), CH_2Cl_2, RT, 30 min. phen = phenanthroline. In the ORTEP drawing of pentaarylindole **9A**, hydrogen atoms are omitted for clarity and thermal ellipsoids are drawn at 50% probability.

To this end, treatment of **8** with Mg turnings in MeOH/THF afforded the detosylated products, which were immediately oxidized with MnO_2, providing PAIs **9** in moderate to good yields (over two steps). PAI **9A** was crystallized from chloroform/pentane and the structure of **9A** was unambiguously confirmed by X-ray crystallographic analysis. The present method afforded PAIs **9A–9M** with five different aryl groups in a predictable and programmed manner.

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Computational studies to elucidate the reaction mechanism of intramolecular [4+2] cycloaddition

To gain insight into the reaction mechanism of intramolecular [4+2] cycloaddition between thiophene *S*,*S*-dioxide and ynamide moieties, DFT calculations of ynamide **Ph-6** were carried out (Figure 2). DFT calculations (B3LYP/6-31G(d)) suggested that the HOMO of **Ph-6** is delocalized over the ynamide moiety. On the other hand, the LUMO is delocalized over the thiophene *S*,*S*-dioxide moiety, indicating that the reaction proceeds via an inverse electron-demand Diels–Alder reaction.[14]

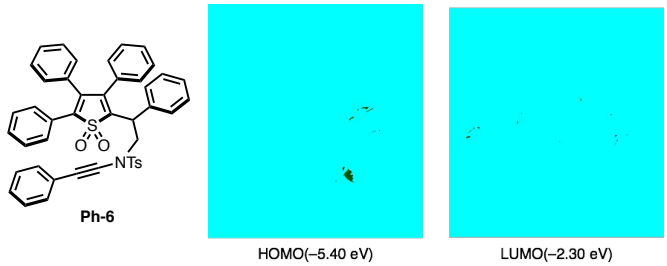
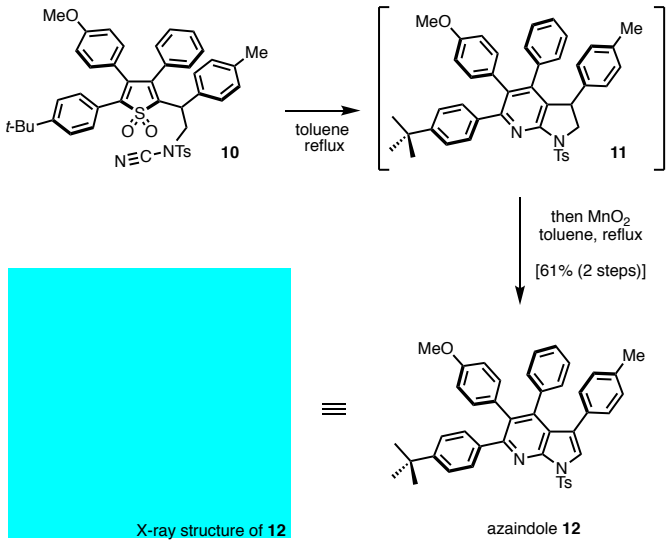


Figure 2. Frontier orbitals of ynamide **Ph-6**.

Synthesis of multiply arylated 7-azaindoles

We applied this protocol to the synthesis of 7-azaindoles **12** using cyanamide instead of ynamide (Scheme 3). Cyanamide intermediate **10**, which was prepared from **4acde** in 6 steps, was refluxed in toluene to furnish 7-azaindolines **11**. Subsequently, treatment of **11** with MnO_2 afforded 7-azaindole **12** in 61% yield (two steps in one pot). The structure of **12** was also confirmed by X-ray crystallographic analysis.



Scheme 3. Synthesis of azaindoles **12**. Reaction conditions: toluene, reflux, 24 h; MnO_2 (60 equiv), reflux, 24 h, 61% (one-pot). ORTEP drawing of **12** with 50% thermal ellipsoid. All hydrogen atoms are omitted for clarity.

Dimerization of pentaarylindoles (PAIs)

As another form of derivatization of PAIs, the synthesis of decaarylated 2,2'-bis-indoles was attempted. It was envisaged that an oxidative dimerization of pentaarylindoles (**9**: PAIs) would directly produce decaarylated 2,2'-bis-indoles **13** (Scheme 4A). Although the trifluoroacetic acid-induced dimerization of 3-substituted indoles reported by Vranken and coworkers was applied to PAI **9A**, the desired dimer **13** was not obtained.[15] After extensive screening of oxidant, treatment of **9A** with copper(II) trifluoroacetate in a dichloroethane / trifluoroacetic acid (TFA) mixture provided unexpected dimer **14** in 69% yield instead of **13**. To our delight, **14** was crystallized from toluene/pentane, and its structure was unambiguously confirmed by X-ray crystallographic analysis. The X-ray crystal structure of **14** revealed that not only a dimerization of **9A**, but also an additional carbon–carbon bond formation occurred. Based on the mechanism of the previously reported thallium(III)-promoted oxidative dimerization of indoles, a plausible reaction mechanism was proposed (Scheme 4B).[16] Initially, one-electron transfer from electron-rich indole **9A** to copper(II) generates an indole radical cation species. Subsequent electrophilic substitution with another indole **9A**, followed by oxidative aromatization, provides the 2,2'-bis-indole **13**. Furthermore, the indole dimer, which is more electron-rich than the monomer, easily undergoes further oxidation to promote an intramolecular electrophilic substitution with the *p*-tolyl group at the C3-position of indole. Finally, an oxidative aromatization of the resulting radical cation species furnishes unexpected dimer **14**. Although the over-oxidation could not be suppressed for indole **9A**, a 2,2'-bis-indole was successfully obtained by changing the aryl group on the C3-position of indole. Indeed, indole **9M**, which has an electron-deficient aryl group (*m*-$CF_3C_6H_4$) at the C3-position, was dimerized under the same conditions to afford bis-indole **15** in 53% yield.

Synthesis of heptaarylindole (HAI)

Next, we proceeded onto the final challenge of synthesizing heptaarylindoles (HAIs), which are fully arylated forms of indole (Scheme 5). Although C2-arylation of **9A** by C–H functionalization was attempted,[4a,4b] this did not provide any C2-arylated products. Therefore, we resorted to a "one-pot C–H arylation method", which consists of a sequence of bromination of **9** and Suzuki–Miyaura cross-coupling reaction with arylboronic acids. To this end, **9A** was reacted with *N*-bromosuccinimide (NBS) in THF at 0 °C to afford C2-bromoindole, which was coupled with 3-thienylboronic acid in the presence of $Pd_2(dba)_3$/P(*t*-Bu)$_3$ catalyst and potassium fluoride to furnish hexaarylindole **16** in 90% yield. Finally, *N*-arylation of **16** was achieved by S_NAr reaction with aryl fluoride: hexaarylindole **16** was deprotonated with potassium hydride in DMF, followed by treatment with 1-fluoro-2,4-dinitrobenzene to provide HAI **17A** in 63% yield. X-ray crystallographic analysis confirmed the structure of **17A**, in which the indole core was fully substituted by seven different

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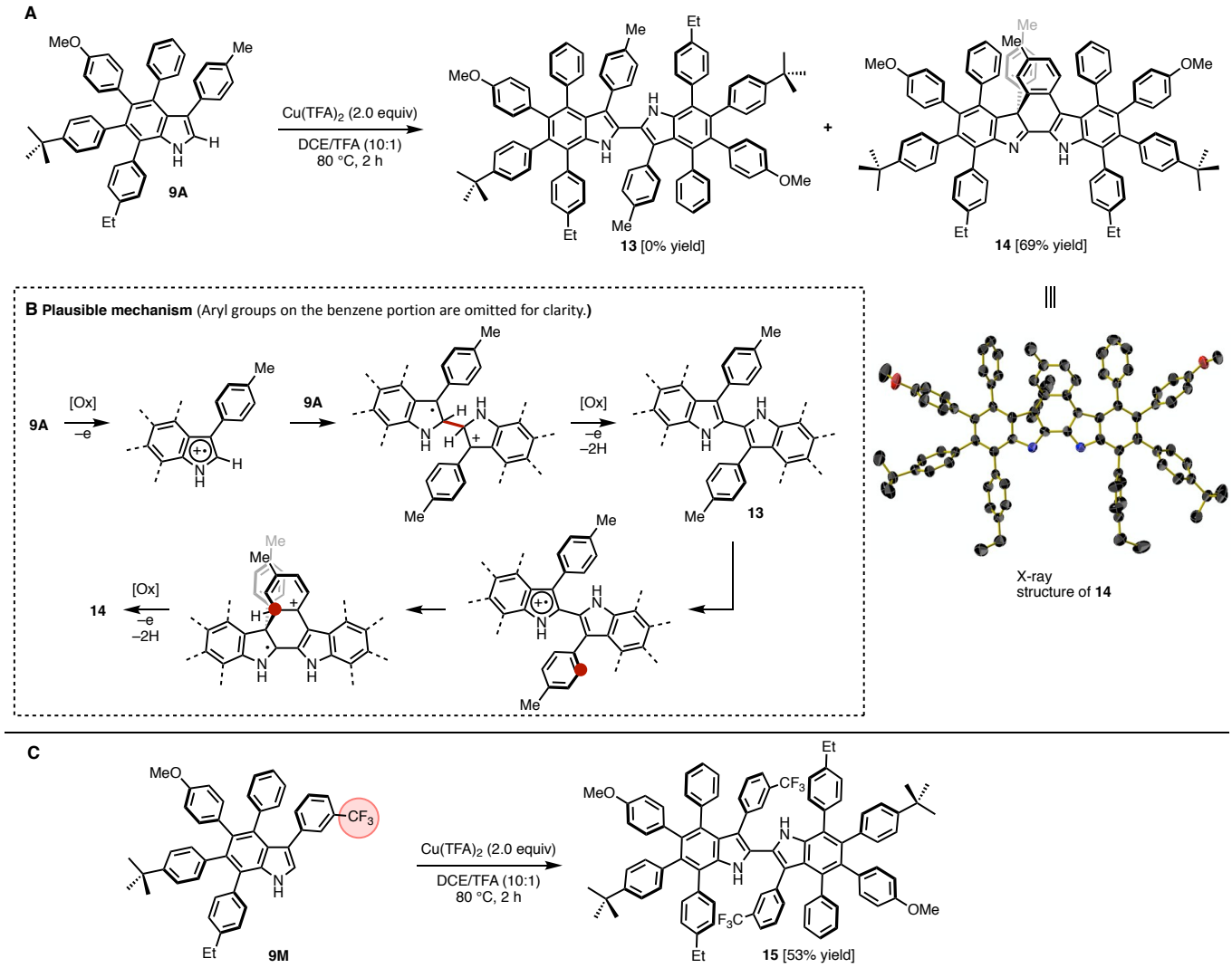


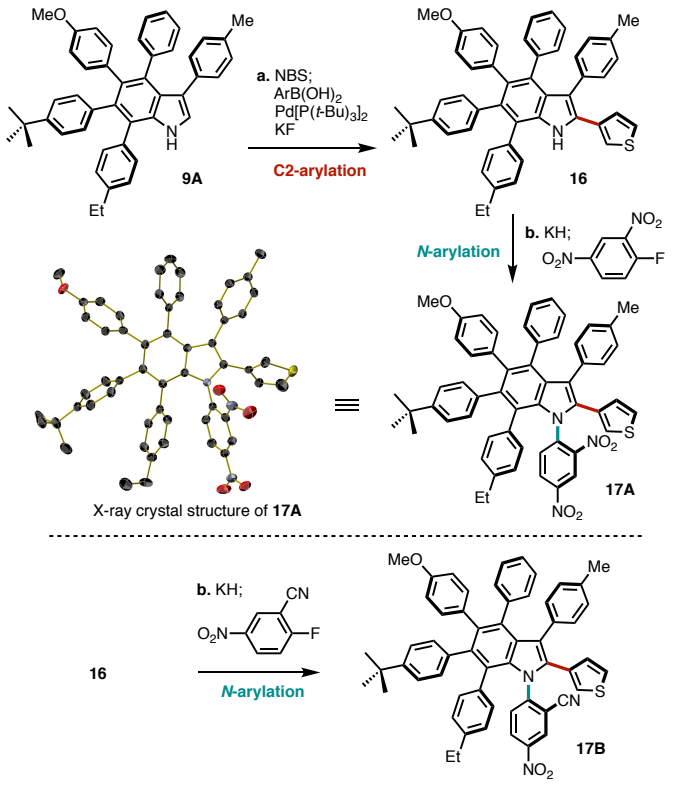
Scheme 4. A) Oxidative dimerization of PAI **9A**; ORTEP drawing of **14** with 50% thermal ellipsoid. All hydrogen atoms are omitted for clarity. B) Plausible mechanism of oxidative dimerization of PAI **9A**. C) Oxidative dimerization of PAI **9M**.

aryl substituents. Lastly, a different aryl fluoride reagent was used to give heptaarylindole **17B**.

Conclusions

In conclusion, we have developed a modular synthesis of multiply arylated indoles. Inverse electron-demand intramolecular [4+2] cycloaddition of fully substituted thiophene *S*,*S*-dioxides with ynamide/cyanamide enabled the synthesis of pentaarylindoles (PAIs) and tetraaryl-7-azaindoles with perfect regioselectivity. Additionally, the oxidative dimerization of PAI successfully led to the corresponding bis-indole. By employing further arylation reactions, the first synthesis of heptaarylindole with all different aryl substituents was accomplished (**17A**: 4.8% yield over 10 steps from 2-bromothiophene). Using this coupling/ring transformation strategy, a variety of aryl groups could be installed onto benzenoid cores, which is conventionally difficult to functionalize regioselectively. This chemistry could also be useful for the synthesis of multiply substituted indoles present in bioactive compounds and natural products.[17] Along with this development of a new method for previously unattainable

molecular structures, the discovery of new functional materials can be expected.



Scheme 5. The synthesis of fully arylated indoles**.** Reaction conditions: a) NBS (1.05 equiv), THF, 0 °C, 1 h, then $ArB(OH)_2$ (3.0 equiv), $Pd_2(dba)_3{\cdot}CHCl_3$ (10 mol%), $P(t\text{-}Bu)_3{\cdot}HBPh_4$ (20 mol%), KF (3.0 equiv), reflux, 24 h, 90%; b) KH (13 equiv), DMF, 0 °C, 5 min, then aryl fluoride (5.0 equiv), RT, 1 h, 63% (**17A**); 35% (**17B**). ORTEP drawing of **17A** with 50% thermal ellipsoid. All hydrogen atoms are omitted for clarity.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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