C–H Activation

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Rhodium(III)-Catalyzed *ortho* C–H Heteroarylation of (Hetero)aromatic Carboxylic Acids: A Rapid and Concise Access to π-Conjugated Poly-heterocycles**

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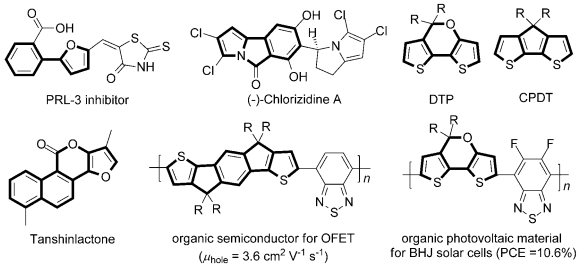
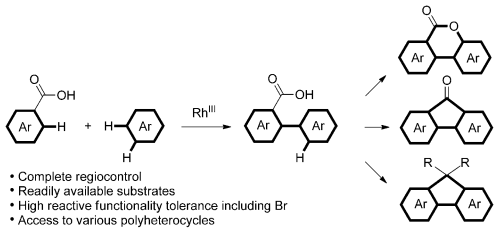
Abstract: *Rh^{III}-catalyzed oxidative C–H/C–H cross-coupling between (hetero)aromatic carboxylic acids and various heteroarenes has been accomplished to construct highly functionalized ortho-carboxy-substituted bi(hetero)aryls. The use of a carboxy group as the directing group obviates tedious steps for installation and removal of extra directing groups, and enables a facile one-step synthesis of ortho-carboxy bi(hetero)aryls. The method provides opportunities for rapid assembly of a library of important fluorene and coumarin-type poly-heterocycles through intramolecular electrophilic substitution or oxidative lactonization. As illustrative examples, the strategy developed herein greatly streamlines accesses to a variety of appealing polyheterocycles such as DTPO (5H-dithieno[3,2-b:2′,3′-d]pyran-5-one), CPDTO (cyclopentadithiophen-4-one), and indenothiophenes.*

Ortho-carboxy-substituted bi(hetero)aryls and their polycyclic derivatives are ubiquitous in synthetic building blocks, natural products, pharmaceuticals, and organic functional materials (Scheme 1).[1] In particular, π-conjugated fluorene and coumarin-type frameworks are well known as excellent structural units for various photoelectronic materials such as organic photovoltaic (OPV) and organic field-effect transistor (OFET) materials.[1,2] For example, in OPV material fields, both cyclopentadithiophene (CPDT) and 5*H*-dithieno[3,2-*b*:2′,3′-*d*]pyran (DTP) are among the most efficient donors. More than 1000 publications and patents associated with the CPDT structure can be retrieved from SciFinder. Because of the lack of rapid, general synthetic routes to *ortho*-carboxy bi(hetero)aryls, the present syntheses



Scheme 1. Selected examples of *ortho*-carboxy-substituted bi(hetero)aryls and their π-conjugated polycyclic derivatives.

of such poly-heterocycles usually necessitate a multistep process, which hinders the exploration of organic optoelectronic materials. Once a concise and reliable pathway toward *ortho*-carboxy bi(hetero)aryls has been established, it would provide opportunities for rapid construction of a large library of polycyclic fluorene and coumarin-like frameworks through intramolecular electrophilic substitution or oxidative lactonization (Scheme 2).



Scheme 2. Synthesis of π-conjugated polyheterocycles through oxidative *ortho* C–H heteroarylation of (hetero)aromatic carboxylic acids.

The existing synthesis of *ortho*-carboxy-substituted bi(hetero)aryls mainly relies on traditional substitution reactions and transition-metal-catalyzed C–X/C–M couplings.[3] Despite the reliability, these methods generally suffer from disadvantages such as tedious multistep synthesis and purification, inaccessible synthetic precursors, and poor substrate generality, which to a certain extent limits rapid diversification of *ortho*-carboxy bi(hetero)aryls. The development of straightforward accesses to highly functionalized molecules starting from readily available substrates through C–H activation is an appealing, yet challenging task.[4] Given that (hetero)aromatic carboxylic acids are one of the most wide-

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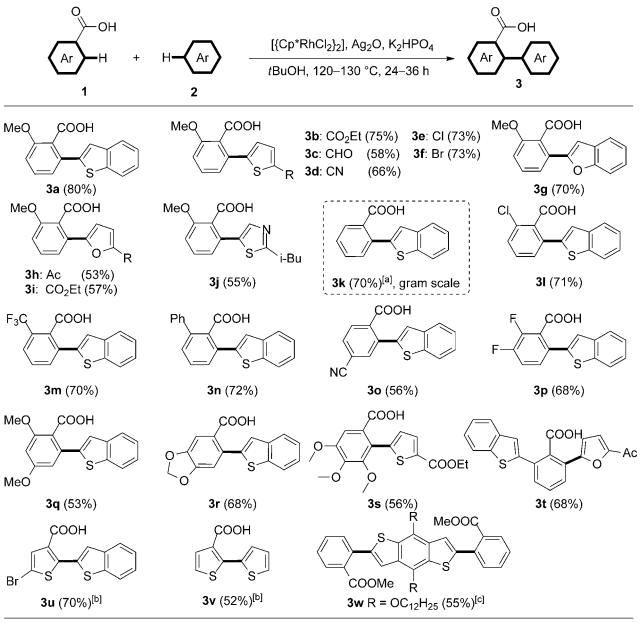
spread compounds, their oxidative C–H/C–H cross-coupling reactions with various heteroarenes would doubtless offer a new, straightforward pathway to diverse *ortho*-carboxy-substituted bi(hetero)aryls through the direct use of the naturally occurring carboxy group as the directing group to selectively activate the *ortho* C–H bond, thus avoiding tedious steps for installation and removal of an extra directing group. Despite a number of successful examples of carboxy-directed *ortho* C–H functionalizations of arenes,[5,6] the direct oxidative *ortho* C–H (hetero)arylation of (hetero)aromatic carboxylic acids to construct diverse *ortho*-carboxy-substituted bi(hetero)aryls through double C–H activation still remain unsolved. To achieve these transformations, several obstacles need to be faced: 1) (Hetero)aromatic carboxylic acids have a tendency to undergo protodecarboxylation, decarboxylative *ipso*-heteroarylation, and homocouplings;[7] and 2) heteroarenes are easily subjected to homocoupling and decomposition.[8]

To evaluate the feasibility of the double C–H activation strategy, we initiated our investigation by using the cross-coupling between 2-methoxybenzoic acid (**1a**) and benzothiophene (**2a**) as a model reaction. After screening several parameters (catalyst, oxidant, additive, solvent, etc.), the cross-coupling proceeded well when 5 mol% of $[\{Cp^*RhCl_2\}_2]$ (Cp^* = pentamethyl cyclopentadienyl) was employed in combination with K_2HPO_4 (2.0 equiv) and Ag_2O (2.0 equiv) in *t*BuOH at 130 °C for 24 hours (see entry 7 in Table S3 of the Supporting Information).

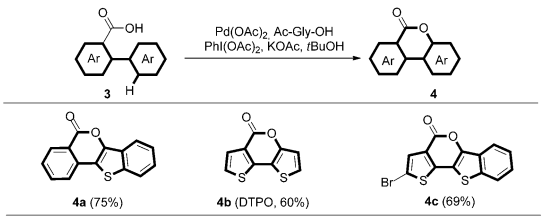
With the optimized reaction conditions in hand, we first evaluated the substrate scope (Scheme 3). It was found that this coupling reaction could tolerate a wide range of heteroarene substrates including thiophenes, furans, and azoles to deliver *ortho*-carboxy bi(hetero)aryls in satisfactory yields (**3a–j**). Carboxylic acids with both electron-rich and electron-poor substituents reacted with various heteroarenes in acceptable yields (**3k–t**). It is emphasized that 2-(benzo[*b*]-thiophen-2-yl)benzoic acid (**3k**) could be obtained without problem on a gram scale in 70% yield, thus providing a bench-scale preparation. **3k** could also react further with 1-(furan-2-yl)ethanone to deliver the biheteroarylated benzoic acid **3t** in 68% yield. More importantly, thiophene-3-carboxylic acids were capable of reacting with thiophenes to yield the important *ortho*-carboxy bithiophenes **3u** and **3v** in synthetically useful yields. **3v** is the key intermediate for the preparation of CPDT and DTP. Diarylation smoothly occurred to afford **3w** in a moderate yield given the two possible reaction sites on the benzodithiophene. Notably, this type of oxidative cross-coupling reaction could tolerate a wide variety of reactive functional groups such as ester, aldehyde, acetyl, cyano, methoxy, chloride, and even the more challenging bromide.



Scheme 3. *ortho*-Heteroarylation of (hetero)aromatic carboxylic acids. Reaction conditions: (hetero)aromatic carboxylic acid (0.25 mmol), heteroarene (3.0 equiv), $[\{Cp^*RhCl_2\}_2]$ (5.0 mol%), Ag_2O (2.0 equiv), and K_2HPO_4 (2.0 equiv) in *t*BuOH (2.0 mL) at 130 °C for 24 h. [a] Benzoic acid (10.0 mmol) in *t*BuOH (10.0 mL) at 130 °C for 36 h. [b] 120 °C for 36 h. [c] 130 °C for 48 h, then K_2CO_3, CH_3I, and DMF at RT. DMF = *N*,*N*-dimethylformamide.

To elucidate whether the C–H activation of the aromatic carboxylic acid foreran the C–H activation of heteroarene or vice versa, deuterium-labeling experiments of benzoic acid (**1b**) and benzothiophene (**2a**) were conducted alone (see Eqs S1 and S2). The exposure of benzoic acid to the catalytic conditions in CD_3OD for 1 hour at 130 °C led to a significant deuterium incorporation at the *ortho*-position (44% D), whereas the H/D exchange ratio of benzothiophene (**2a**) was less than 5%. These observations suggested that the cross-coupling reaction might start from the cyclometalation of benzoic acid.[9] Next, kinetic isotope effects (KIE) were studied with regard to the C–H/D bonds for both coupling partners. The parallel reactions were performed by the use of 2,3,4,5,6-pentadeuteriobenzoic acid and 2-deuterio-benzothiophene under the optimized reaction conditions (see Eqs S3 and S4). The KIE values of 3.9 and 1.1 were observed for 2,3,4,5,6-pentadeuteriobenzoic acid and 2-deuteriobenzothiophene, respectively. These results indicated that the C–H bond breaking of benzoic acid might be the rate-limiting step.[10] Thus, a plausible mechanism could consist of 1) the coordination of the carboxylate oxygen atom to $[Cp^*Rh^{III}]$ and subsequent *ortho*-C–H activation of the arene, 2) the reaction of the resulting rhodacycle intermediate with a heteroarene to give the key aryl-Rh^{III}-heteroaryl, and 3) the reductive elimination to deliver the *ortho*-heteroarylated product.[11]

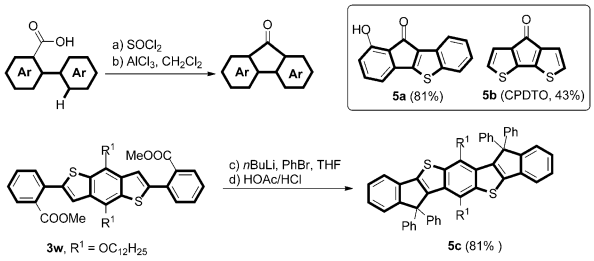
The development of construction strategies for π-conjugated polyheterocycles through C–H activation is becoming a hot topic in the field of organic functional materials.[12] Traditional synthetic accesses to CPDTO (**5b**; see Scheme 5) and DTPO (**4b**; see Scheme 4), the key intermediates for CPDT and DTP, respectively, are hampered by multistep processes and harsh reaction conditions, thus always resulting in erratic and unfavorably low yields (for example, for DTPO, nine steps and 7% yield; for CPDTO, eight steps and 23% yield).[13] The complete build-up strategies developed herein could greatly streamline accesses to such poly-heterocycles. With the *ortho*-carboxy bi(hetero)aryls in hand, we first



Scheme 4. The construction of coumarin-type polycyclic structures. Reaction conditions: **3** (0.25 mmol), $Pd(OAc)_2$ (10 mol%), Ac-Gly-OH (20 mol%), $PhI(OAc)_2$ (2.0 equiv), and KOAc (2.0 equiv) in *t*BuOH (2 mL) at 120°C for 24 h. Ac-Gly-OH = *N*-acetylglycine.

investigated the ring fusion to construct coumarin-type polycyclic structures (**4**) by direct intramolecular oxidative C–H/O–H lactonization (Scheme 4). Although the lactonizations of arenes with carboxylic acids have been reported,[14] the oxidative lactonization of heteroarenes with carboxylic acids is still unexplored so far. It was found that the lactonization could be performed to afford the polycyclic **4** in 60–75% yield by using $Pd(OAc)_2$ as a catalyst. It is noteworthy that the important scaffold DTPO (**4b**) could be readily obtained in 60% yield. Moreover, the bromo group on aromatic rings could be tolerated in the catalytic cycle, and is very useful for further synthetic transformations in the construction of organic conjugated materials (**4c**).

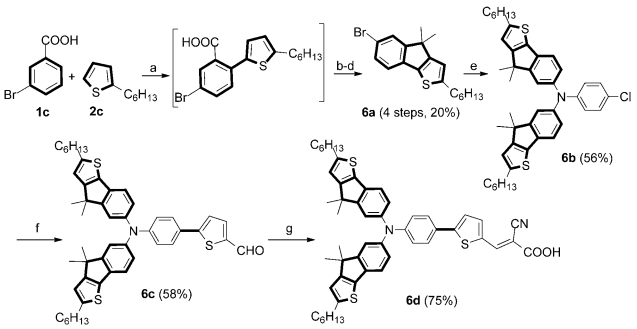
To further illuminate the synthetic utility of our protocol, a variety of transformations of *ortho*-carboxy bi(hetero)aryls into cyclopentadiene derivatives (**5**) were investigated (Scheme 5). The compound **3a** could be easily transformed into the corresponding polyheterocycle **5a** through the Friedel–Crafts acylation and simultaneous demethylation.



Scheme 5. Transformations of *ortho*-carboxy-substituted bi(hetero)aryls into various cyclopentadiene derivatives (**5**). THF = tetrahydrofuran.

The compound **3v** was an extremely useful synthetic handle for CPDTO (**5b**). The twofold oxidative C–H activation strategy in combination with the intramolecular Friedel–Crafts-type cyclization also provided us a concise approach to seven-ringed bis(styryl)benzene **5c**, which is a new member of the family of phenylenevinylene-based ladder molecules, and may be a promising scaffold for organic electronic devices.[15]

Given that the oxidative protocol developed herein can tolerate the reactive bromide, the direct use of bromo-substituted carboxylic acids as a starting material could avoid the late-stage bromination of resulting poly-heterocycles and would greatly streamline synthetic routes. As an illustrative example, a more step-economical pathway for the construction of the indenothiophene-based metal-free organic sensitizer **6d** was developed (Scheme 6). The existing synthetic method of the key bromo-substituted 4,4-dimethyl-4*H*-indeno[1,2-*b*]thiophene (**6a**) involves a seven-step process



Scheme 6. Synthesis of the sensitizer **6d**. Reaction conditions: a) $[\{Cp^*RhCl_2\}_2]$, Ag_2O, K_2HPO_4, and *t*BuOH; b) K_2CO_3, CH_3I and DMF; c) MeMgBr and THF. d) $BF_3{\cdot}Et_2O$ and CH_2Cl_2; e) 4-chloroaniline, *t*BuONa, $[Pd_2(dba)_3]$, XPhos, and toluene; f) thiophene-2-carbaldehyde, $Pd(OAc)_2$, PivOH, $Cy_3P{\cdot}HBF_4$, Cs_2CO_3, and toluene; g) cyanoacetic acid, piperidine, and $CHCl_3$. See the Supporting Information for more details. dba = dibenzylideneacetone.

starting from methyl 5-bromo-2-iodobenzoate and 2-hexylthiophene,[16] and an extra three-step process for preparing methyl 5-bromo-2-iodobenzoate.[17] Based on the construction strategy for poly-heterocycles developed herein, it just needed four steps to access **6a** starting from readily available substrates. Subsequently, the consecutive three-step procedure involving Ullmann reaction, direct C–H arylation of thiophene-2-carbaldehyde, and Knoevenagel condensation afforded the target **6d**. The absorption spectra of **6d** in EtOH solution and on TiO_2 film show a broad absorption band in the range of $\lambda = 300$-650 nm (see Figure S4 and Part IX in the Supporting Information for detailed photophysical and electrochemical data). Under simulated AM 1.5G irradiation, the photocurrent-voltage (*J*-*V*) plots exhibited a conversion efficiency (η) of 6.15% for the **6d**-based DSSC ($J_{sc} = 12.97$ mA/cm^2, $V_{oc} = 0.697$ V and FF = 0.681), and is close to N719 with an efficiency of 7.14% ($J_{sc} = 16.84$ mA/cm^2, $V_{oc} = 0.693$ V and FF = 0.612) under the same fabrication conditions (see Figure S4), thus suggesting that indenothiophene may be an ideal donor candidate for organic sensitizers.

In conclusion, a highly regioselective rhodium(III)-catalyzed oxidative C–H/C–H *ortho* heteroarylation of (hetero)-aromatic carboxylic acids with various heteroarenes (e.g., thiophenes, furans, and azoles) has been developed, and enables a variety of *ortho*-carboxy bi(hetero)aryls with wide reactive functional-group tolerance. The construction strategy developed herein greatly streamlines access to a variety of appealing polyheterocycles such as CPDTO, DTPO, and indenothiophenes. Starting from readily available substrates, DTPO, CPDTO, and bromo-substituted indenothiophene are readily obtained in two or four steps, whereas the previously reported synthetic pathways require eight, nine, and ten steps, respectively. This highly efficient route to diverse poly-

heterocycles has highlighted the appeal of C–H activation in the construction of organic optoelectronic materials.

Keywords: C–H activation · conjugation · cross-coupling · heterocycles · rhodium

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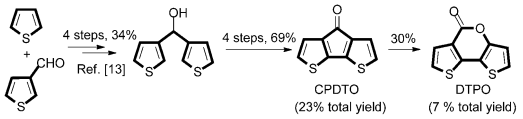

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