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Communication

Palladium-catalyzed diarylative dearomatization of indoles with aryl thioesters

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ABSTRACT

We report herein a palladium-catalyzed diarylative dearomatization of indole by employing thioester and arylboronic acid as the aryl electrophiles. The reaction involved a decarbonylation/migratory insertion/terminal Suzuki coupling procedure. Substrates bearing various functional groups are well tolerated in the reaction, affording the diarylated indoline skeletons in moderate to good yields.

Indoline derivatives represent an important class of nitrogen-containing heterocyclic scaffolds, which are commonly found in biologically active natural products and pharmaceuticals [1–3]. Dearomatization of indole is a very attractive tool to construct indoline-based skeletons with fused polycyclic scaffolds [4]. In recent years, transition-metal-catalyzed intramolecular migratory insertion strategies for highly region-and stereoselective dearomatization of indoles have been widely explored (Scheme 1a) [5]. In 2001, Grigg and coworkers reported a seminal work on the palladium-catalyzed dearomatization of indoles *via* a domino Heck-type mechanism [6]. Since then, Lautens, Jia, Liang *et al.* developed Pd- and Ni-catalyzed dearomative difunctionalization of indoles (including arylalkynylation, arylcyanation, aryliodination, arylborylation, arylarylation, arylborylation, arylphosphoylation and hydroarylation) (Scheme 1a) [7,8]. In 2015, Jia and coworkers reported the first Pd-catalyzed enantioselective dearomatization of indoles *via* intramolecular hydroarylation reactions [8a]. Despite of significant advantages, aryl halides are often employed as the aryl electrophile. To further explore the substrate scope, conversion of readily available carboxylic acids derivatives as new aryl electrophiles in dearomatization of indoles would be highly appealing.

Aryl thioesters could be conveniently prepared from aryl carboxylic acids and corresponding thiols. Thioesters are reactive but bench stable, and often act as electrophilic acylating reagent in the macrolactones synthesis and peptides ligation [9]. C(O)–S bonds of thioesters are known to undergo the oxidative addition to low-valent metals including Pd, Ni and Rh, enabling the thioester to be versatile and practical building block in organic synthesis [10]. For example, palladium-catalyzed cross coupling of thioester with organometallic reagents have been widely applied in the ketone synthesis [11]. The Fukuyama reduction with Et_3SiH could facilely and selectively reduce thioesters to the aldehydes [12]. Catellani-type difunctionalization of aryl halide with thioesters has been demonstrated by Gu [13]. Decarbonylative thiolation and borylation of thioesters were successfully achieved by Yamamoto, Wenkert, Kambe, Sanford and Hosoya [14,15]. Very recently, our group reported palladium-catalyzed decarbonylation of aryl thioester to dearomatize indoles *via* an intramolecular reductive Heck reaction (Scheme 1b) [16]. Based on previous work and our continued interest in the construction

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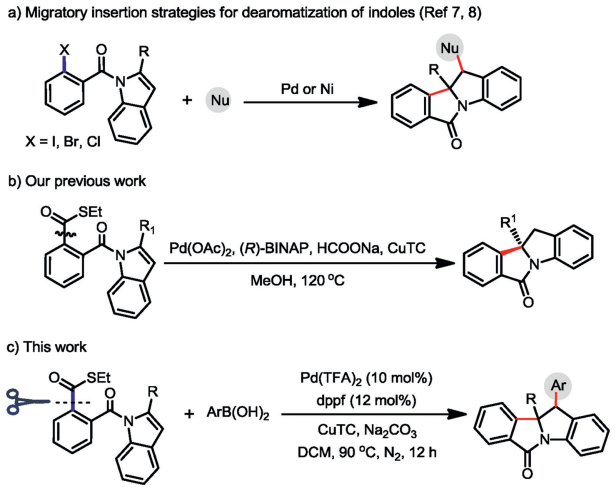
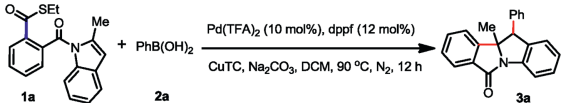


Scheme 1. Transition-metal-catalyzed migratory insertion strategies for dearomatization of indoles.

indoline scaffolds, we report herein the diastereoselective dearomative diarylation of indoles using aryl thioesters and arylboronic acids as the arylation reagents (Scheme 1c). The reaction proceeded *via* a decarbonylation-Heck-Suzuki sequence. Our protocol shows excellent functional group tolerance in both coupling partners, thus allowing for the rapid construction of polycyclic indoline skeletons.

We began our studies by employing *S*-ethyl 2-(2-methylindole-1-carbonyl)benzothioate **1a** and phenylboronic acid **2a** as the model substrates. After carefully screening of various ligands, bases, solvents, copper and palladium salts, ultimately, the desired dearomatization product **3b** was obtained in 61% yield (Table 1, entry 1, see Supporting information for detailed optimization). Phosphine ligands are found to be essential in the reaction (entries 2–7). Among various phosphine ligands, bidentate dppf (1,1'-bis(diphenylphosphino)ferrocene) ligand proved to be most effective. Other mono- and bidentate phophine ligands were also effective, albeit with somewhat lower yields. Copper salts are proposed to scavenge the ethanethiol released over the course of the reaction by forming the strong Cu–S bond, thus facilitating the decarbonylation and migratory insertion process [11]. After screening of copper salts, CuTC was the optimal. When Na_2CO_3 was replaced by $KHCO_3$ and CsF, 45% and 28% yields of product **3a** were obtained (entries 8 and 9). Regarding the solvent employed, DCE afforded 32% yield of product, while toluene gave no dearomatization product (entries 10 and 11). Among various palladium catalysts examined, $Pd(TFA)_2$ proved to be most effective, and other palladium salts afforded lower yields (entries 12–14).

Table 1
Optimization of the reaction conditions.[a]



Entry	Variation from the standard conditions	Yield (%)[b]
1	none	61 (59)[c]
2	BINAP instead of dppf	3
3	dppb instead of dppf	20
4	DPEphos instead of dppf	35
5	dppm instead of dppf	10
6	PCy_3 instead of dppf	7
7	TFP instead of dppf	6
8	$KHCO_3$ instead of Na_2CO_3	45
9	CsF instead of Na_2CO_3	28
10	DCE instead of DCM	32
11	toluene instead of DCM	n.d
12	$Pd(OAc)_2$ instead of $Pd(TFA)_2$	50
13	$PdCl_2$ instead of $Pd(TFA)_2$	55
14	$Pd_2(dba)_3$ instead of $Pd(TFA)_2$	49

BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene, dppb: 1,4-bis(diphenylphosphino)butane, DPEphos: bis[(2-diphenyl-phosphino)phenyl] ether, dppm: bis(diphenylphosphino)methane, TFP: tri(2-furyl)phosphine, CuTC: copper(I) thiophene-2-carboxylate.

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (2.0 equiv.), $Pd(TFA)_2$ (10 mol%), dppf (12 mol%), CuTc (1.5 equiv.), Na_2CO_3 (2 equiv.), DCM (2 mL), 90 °C, under N_2, 12 h.

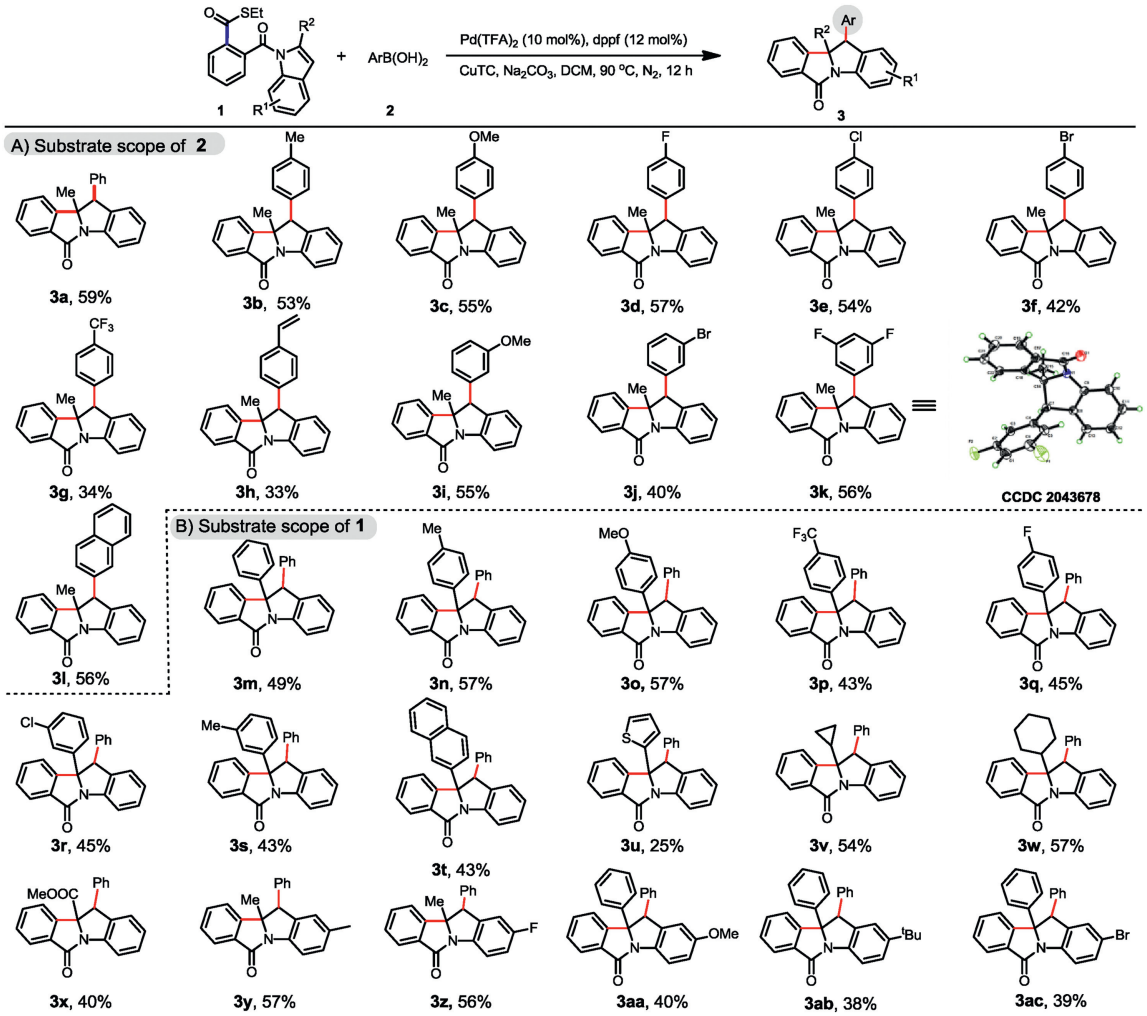
[b] Determined by ^1H NMR using dibromomethane as internal standard.

[c] Isolated yields.

With the optimal reaction conditions in hand, we commenced to explore the substrate scope of dearomatizative diarylation of indole **1a** with various aryl boronic acids **2**. As shown in Scheme 2, under the optimized conditions (10 mol% of $Pd(TFA)_2$, 12 mol% of dppf, 2.0 equiv. of Na_2CO_3, 1.5 equiv. of CuTC, 90 °C, 12 h), aryl boronic acid bearing electron-donating and -withdrawing groups (-Me, -OMe, -F, -Cl, and $-CF_3$) were well tolerated, affording the desired products (**3a**-**3e**, **3g**, **3i**, **3k**) in moderate to good yields. The structure of product **3k** was determined by X-ray analysis. Very sensitive bromide and alkene groups were well tolerated, leaving functional handles for further transformations *via* transition metal-catalyzed cross coupling reaction. 2-Naphthylboronic acid was also suitable substrate, furnishing the dearomatization product **3l** in 56% yield. Next, we investigated the substrate scopes of the *S*-ethyl 2-(2-methylindole-1-carbonyl)arylthioate **1** under the standard conditions. When C2-phenyl-substituted indole **1m** was employed as the substrate, the corresponding product **3m** was obtained in 49% yield. Other electron-rich and -poor aryl groups at C2 position of indole were well tolerated, giving the dearomatization product **3n**-**3t** in 43%–57% yields. To our delight, the protocol could be extended to thiophene-containing substrate, albeit in lower yield (**3u**). The reaction performed well when C2-alkyl- and ester-substituted indole substrates were employed (**3v-3x**). Methyl, methoxyl, *t*-butyl, fluoro, and bromo substituents at other positions of indole were also investigated, giving the desired products **3y**-**3ac** in 38%–57% yields. It is worth noting that *dr* values of > 20:1 are observed for products **3a**-**3ac** based on the NMR analysis of the crude reaction mixture.

Based on experimental results and previous reports [7–10], a plausible mechanism for the Pd(0)-catalyzed ligand-promoted diarylative dearomatization of indoles is illustrated in Scheme 3. The reaction is initiated by the oxidative addition of Pd(0) catalyst into the thioester **1a**, generating the Pd(II) complex **A**. Cu salts coordinate to the sulfur atom to polarize the Pd-S bond. Then the phosphine ligand promote the decarbonylation of thioester to afford arylpalladium **B**. Subsequent intramolecular migratory insertion of arylpalladium into indole ring give the dearomatization intermediate **C**. Transmetallation of intermediate **C** with phenylboronic acid **2a** results in intermediate **D**, which then undergo the reductive elimination to give the final product **3a** with the regeneration of the active Pd(0) species.

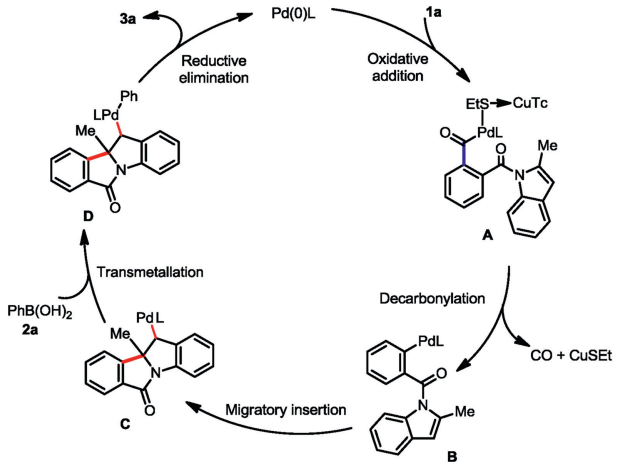
In summary, we have developed a palladium-catalyzed diarylative dearomatization of indole thioester, affording the fused polycyclic indoline skeletons in moderate to good yields. Aryl thioesters were employed as the aryl electrophiles *via* decarbonylation of thioesters. Our protocol shown broad substrate scope, and sensitive -Cl, -Br and alkene groups could be tolerated, leaving a functional handle for further structure diversification.



Scheme 2. Substrates scope for the dearomatization of indoles. Reaction conditions: **1** (0.1 mmol), **2** (2.0 equiv.), $Pd(TFA)_2$ (10 mol%), dppf (12 mol%), CuTc (1.5 equiv.), Na_2CO_3 (2 equiv.), DCM (2 mL), 90 °C, N_2, 12 h.

Declaration of competing interest

The authors report no declarations of interest.



Scheme 3. Proposed mechanism.

Acknowledgments

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2021.02.048.

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