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Regiodivergent Synthesis of Brominated Pyridylthiophenes by Overriding the Inherent Substrate Bias

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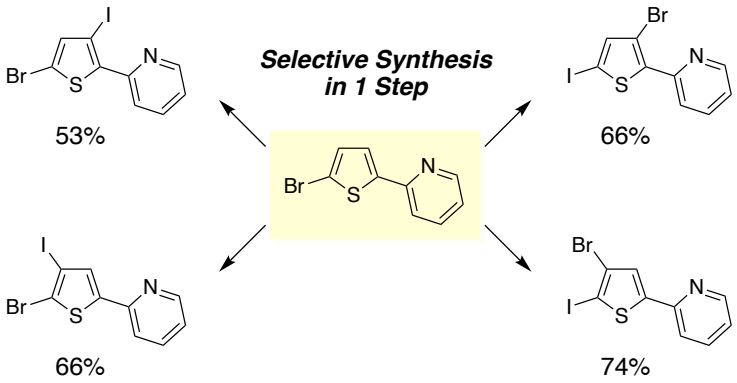

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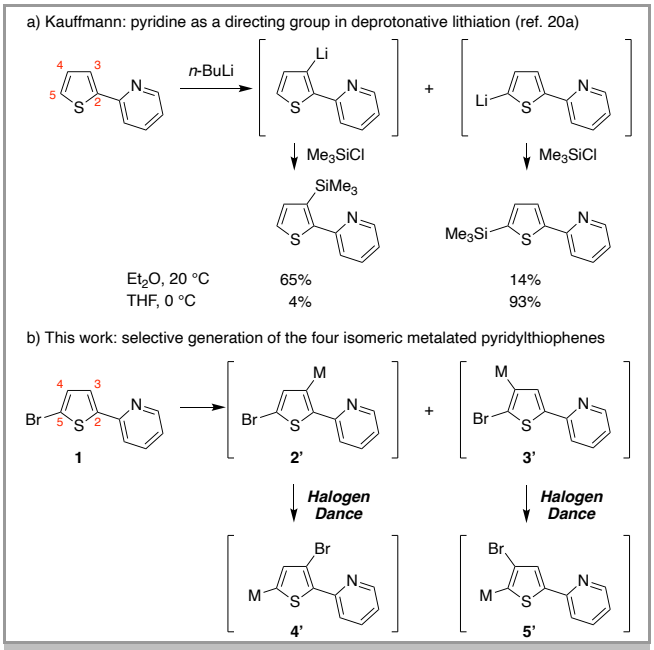
Abstract Regiocontrolled functionalization of a pyridylthiophene scaffold was accomplished. Regioselectivity for deprotonation of pyridylthiophene was switched by the reaction conditions, including metal amide base and solvent. Subsequently, in situ transmetalation and halogen dance on the corresponding organometallic species were controlled by additives and the reaction temperature as well as the above reaction conditions. This method successfully enabled the synthesis of four iodinated constitutional isomers from a single starting material, 2-(5-bromothiophen-2-yl)pyridine.

Key words deprotonation, halogen dance, halogens, in situ transmetalation, organometallic reagents, pyridines, regioselectivity, thiophenes

Thiophene has high application potential as biologically active substances[1] and electronic materials.[2] Oxidation of thiophene provides synthetic intermediates of multiply functionalized benzene derivatives[3] and tools for chemical biology investigations.[4] In particular, the pyridylthiophene scaffold is attractive among biaryl compounds, which can be applied to a broad range of materials, such as pharmaceuticals,[5] α-helix or β-strand mimics,[6] metal chelators,[7,8] photochromic compounds,[9] and fluorescent compounds.[10] To stimulate the wide application of pyridylthiophene, regiodivergent synthesis of constitutional isomers has been intensively investigated. Thiophene is traditionally functionalized using electrophilic aromatic substitution,[11] deprotonation,[12] or cross-coupling reactions.[13] C–H activation can also introduce a variety of functional groups.[14] Our research group has focused on applying halogen dance reactions, which involve the migration of a bromo or iodo group on the aromatic ring through successive intermolecular halogen–metal exchanges,[15,16] leading to the synthesis of multiply functionalized thiophenes. The halogen dance is considered to occur via halogen–metal exchange,[15,17] and aromatic rings can be functionalized without losing the halogen group, which can be used for further functionalization. However, the position of deprotonation is kinetically and thermodynamically governed by the electric and steric nature of aromatic rings and substituents,[18] and the halogen dance generally occurs as a result of the driving force that shifts the position of deprotonation to a thermodynamically more stable position.

Pyridine is a powerful directing group in the functionalization of pyridylthiophene, and transition metal-catalyzed reactions have been reported to proceed regioselectively at the position adjacent to pyridine (the 3-position of thiophene).[19] Pyridylthiophene can be deprotonated at the 3- or 5-position using Et_2O or THF as a solvent, respectively (Scheme 1a).[20] Our recent study also revealed that the position of deprotonation on thiophene changes depending on the incorporated directing group, and the position of the halogen dance changes correspondingly.[16b,16e] These studies indicate that functionalization at the 4-position of pyridylthiophene is challenging owing to the inherent substrate bias originating in the directing effect of pyridine, which has to be overridden. Deprotonative metalation of readily available 2-(5-bromothiophen-2-yl)pyridine (**1**) provides two possible β-metalated pyridylthiophenes **2'** and **3'**, which undergo the halogen dance reaction and are converted into α-metalated pyridylthiophenes **4'** and **5'**, respectively (Scheme 1b). These thienylmetal species can be functionalized by electrophilic trapping to give the corresponding constitutional isomers. In another study, we successfully suppressed the halogen dance reaction of heteroaromatic compounds by using zinc halide diamine complexes.[21] This method provides direct access to each constitutional isomer selectively by choosing appropriate zinc complexes. If the position of deprotonation can be switched by the reaction conditions, it will be possible to synthesize a broad range of functionalized isomers. Herein, we report the control of regioselective deprotonation and subsequent halogen dance reactions on a pyridylthiophene scaffold by reaction conditions, including metal amide base,

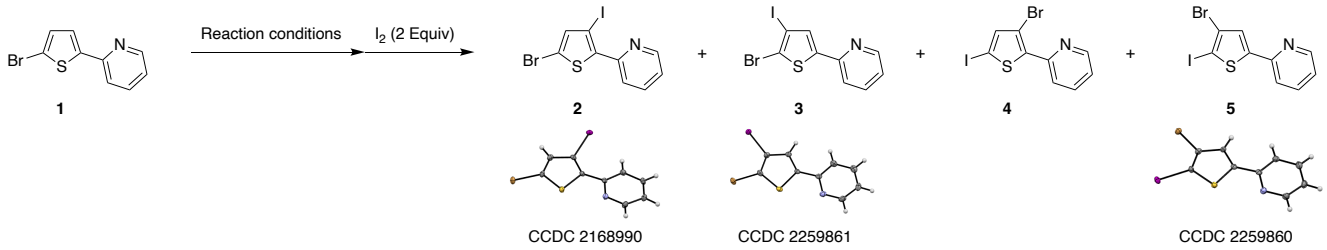
solvent, additives, and reaction temperature, and the synthesis of four iodinated isomers from a single starting material, brominated pyridylthiophene **1**.



Scheme 1 Approaches to generate isomeric metalated pyridylthiophenes.

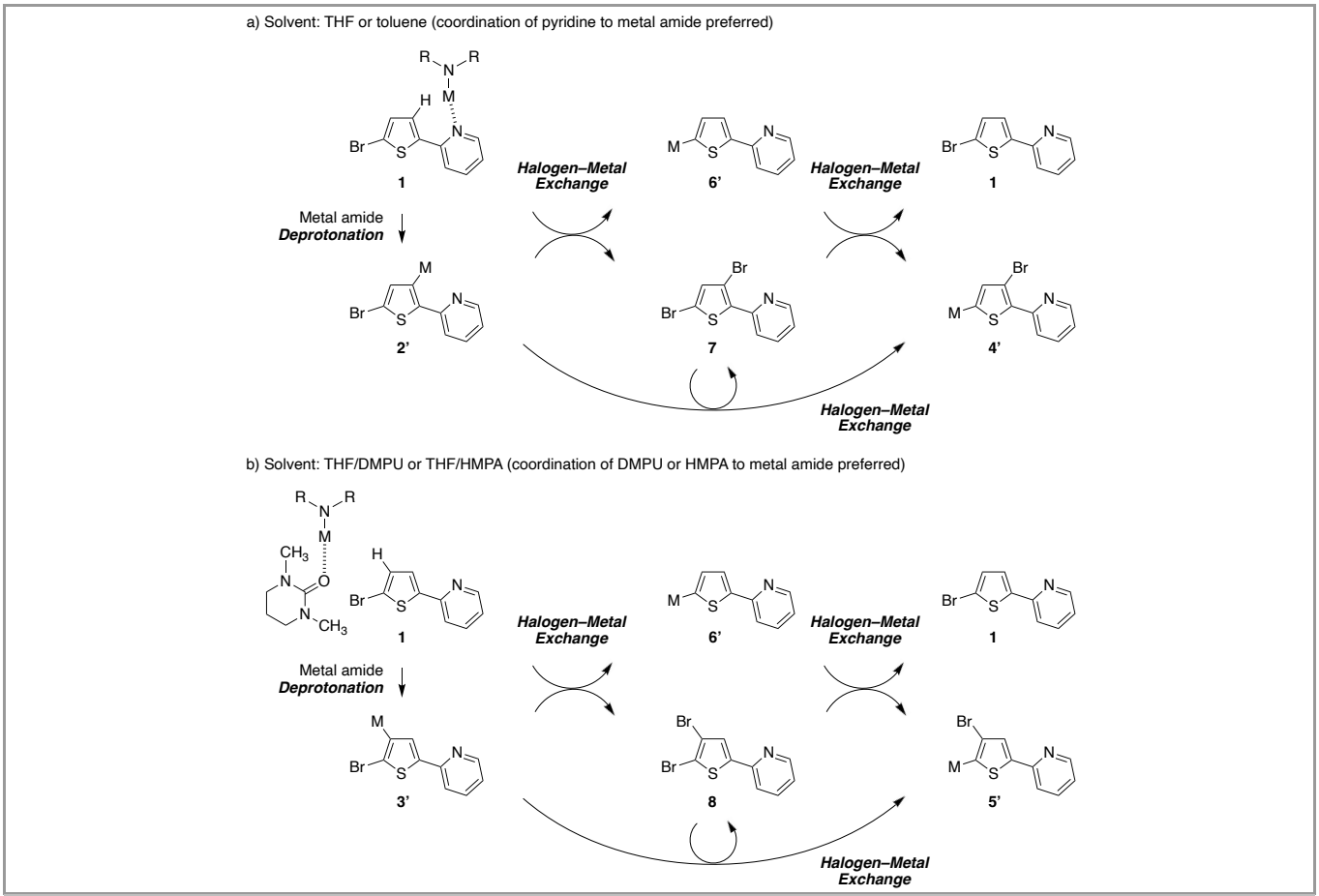
Our study commenced with the halogen dance reaction of 2-(5-bromothiophen-2-yl)pyridine (**1**) using lithium diisopropylamide (LDA), which is based on a literature precedent.[15,16] The reaction was quenched with I_2, and the selectivity was evaluated using the NMR yields of iodinated pyridylthiophenes **2**–**5**, whose structures were determined by X-ray crystallography[22] (Table 1). Upon treatment with LDA in THF at −78 °C, the halogen dance reaction proceeded to give iodinated pyridylthiophenes **4** and **5** in 48% and 13% yields, respectively (entry 1). This result indicated that the 2-pyridyl moiety functioned as a directing group in the deprotonation step, favoring 1,3-migration of the bromo group.[16b,16e] On the basis of the report by Kauffmann,[20a] less polar toluene was used instead of THF to increase the coordination of pyridine nitrogen to LDA, leading to the exclusive formation of pyridylthiophene **4** in 70% yield (entry 2).[23] By eliminating THF with Lewis basicity, coordination of pyridine nitrogen to lithium was relatively reinforced (Scheme 2a). As a result, selective deprotonation took place at the 3 position to generate lithiated thiophene **2'**. Subsequent halogen–lithium exchange with another molecule of bromothiophene **1** provided α-lithiated thiophene **6'** and dibromothiophene **7**. The second halogen–lithium exchange afforded lithiated pyridylthiophene **4'** with regeneration of starting bromothiophene **1**. As another possible reaction pathway, β-lithiated thiophene **2'** was directly transformed into α-lithiated thiophene **4'** by dibromothiophene **7** as a catalyst. Considering these results, we expected that using a Lewis base stronger than pyridine, such as *N*,*N*′-dimethylpropyleneurea[24] (DMPU), would result in weaker coordination of pyridine nitrogen to lithium, leading to switching of the selectivity of deprotonation (Scheme 2b). Thus, deprotonation at the 4 position of pyridylthiophene **1** gives lithiated bromothiophene **3'**, and the halogen dance reaction provides lithiated pyridylthiophene **5'** via α-lithiated thiophene **6'** and dibromothiophene **8** in a similar manner. When the reaction was performed in THF/DMPU (1:1, v/v), the selectivity was drastically changed to provide pyridylthiophene **5** as a major product, albeit in moderate yield (entry 3). Decreasing the amount of DMPU (THF/DMPU = 4:1, v/v) improved the yield of pyridylthiophene **5** by up to 76% (entry 4).[25] The use of hexamethylphosphoric triamide (HMPA) did not give satisfactory results (entry 5). Having found the optimal reaction conditions to generate lithiated pyridylthiophenes **4'** and **5'**, we then turned our attention to the selective trapping of metalated pyridylthiophenes **2'** and **3'**. To suppress the halogen dance reaction, $ZnCl_2$·TMEDA (TMEDA: tetramethylethylenediamine) was added to enable in situ transmetalation, and thus the organolithium species generated after deprotonation was converted into a relatively stable organozinc species (entry 6).[21,26] These reaction conditions provided iodinated pyridylthiophenes **2** and **3** in 74% and 13% yields, respectively. The ratio was attributed to the selectivity in the deprotonation of brominated pyridylthiophene **1**, which was almost consistent with the ratio of the yields of pyridylthiophenes **4** and **5** in entry 1. After extensive screening of the reaction conditions, including metal amide base, solvent, additive, and reaction temperature, we used the Knochel–Hauser base[27] to generate pyridylthiophene **2** as a single isomer in 67% yield (entry 7).[28] The exclusive formation of magnesiated pyridylthiophene **2'**, which was stable even at 60 °C (entry 8), likely originated in the relatively strong coordination between pyridine nitrogen and magnesium. We next attempted to obtain iodinated pyridylthiophene **3** using a combination of the solvent effect of DMPU (entry 4) and in situ transmetalation with $ZnCl_2$·TMEDA (entry 6). To a THF/DMPU (1:1, v/v) solution of brominated pyridylthiophene **1** was added LDA at −78 °C. After stirring at the same temperature for 1 h, the reaction mixture was treated with iodine. Contrary to our expectations, the halogen dance reaction was not suppressed with recovery of starting material **1** (entry 9). This result indicated that 50 vol% of DMPU in THF increased the reactivity of both organolithium species and LDA, which promoted the halogen dance reaction over in situ transmetalation. On the basis of this consideration, the ratio of DMPU was decreased. When 20 vol% of DMPU in THF was used as a solvent in the presence of $ZnCl_2$·TMEDA, the halogen dance reaction was effectively terminated by in situ transmetalation to give iodinated pyridylthiophene **3** as a major product (entry 10). Increasing the reaction temperature to −50 °C further improved the efficacy of in situ transmetalation, although the selectivity of deprotonation slightly decreased and the residual of starting material **1** increased (entry 11). To consume starting material **1**, the amounts of reagents and solvents were increased twice (entry 12). These reaction conditions predominantly gave iodinated pyridylthiophene **3** in 68% yield with complete consumption of starting material **1**.[29] From the above investigations, the four iodinated constitutional isomers were successfully obtained from a single starting material **1**, in one step by optimizing the reaction conditions. In addition to direct electrophilic functionalization of metalated pyridylthiophenes **2'**–**5'**, further functionalization of iodinated bromothiophenes **2**–**5** as substrates is possible by discriminating iodo and bromo groups.[30]

Table 1 Screening of reaction conditions to obtain the four constitutional isomers.



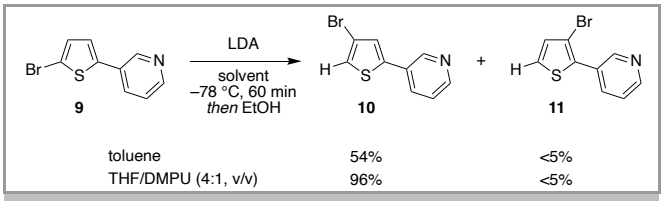
Entry	Reagent	Solvent	Temp.	Time	Yield of **2** (%)[a]	Yield of **3** (%)[a]	Yield of **4** (%)[a]	Yield of **5** (%)[a]
1	LDA (1.5 Equiv)	THF[b]	−78 °C	1.0 h	–[c]	–[c]	48	13
2	LDA (1.5 Equiv)	Toluene[b]	−78 °C	1.5 h	–[c]	–[c]	70 (66[d])	–[c]
3	LDA (1.5 Equiv)	THF/DMPU (1:1, v/v)[b]	−78 °C	1.0 h	–[c]	–[c]	7	60
4	LDA (1.5 Equiv)	THF/DMPU (4:1, v/v)[b]	−78 °C	1.0 h	–[c]	–[c]	16	76 (74[d])
5	LDA (1.5 Equiv)	THF/HMPA (4:1, v/v)[b]	−78 °C	1.0 h	–[c]	–[c]	24	27
6	$ZnCl_2$·TMEDA (1.5 Equiv) then LDA (1.5 Equiv)	THF[b]	−78 °C	1.0 h	74	13	–[c]	–[c]
7	(TMP)MgCl·LiCl (2.0 Equiv)	THF[b]	r.t.	2.5 h	67 (53[d])	–[c]	–[c]	–[c]
8	(TMP)MgCl·LiCl (2.0 Equiv)	THF[b]	60 °C	2.0 h	50	–[c]	–[c]	–[c]
9[e]	$ZnCl_2$·TMEDA (1.5 Equiv) then LDA (1.5 Equiv)	THF/DMPU (1:1, v/v)[b]	−78 °C	1.0 h	–[c]	8	<5	39
10[f]	$ZnCl_2$·TMEDA (1.5 Equiv) then LDA (1.5 Equiv)	THF/DMPU (4:1, v/v)[b]	−78 °C	1.0 h	17	48	<5	18
11[g]	$ZnCl_2$·TMEDA (1.5 Equiv) then LDA (1.5 Equiv)	THF/DMPU (4:1, v/v)[b]	−50 °C	1.0 h	21	42	<5	5
12[h]	$ZnCl_2$·TMEDA (3.0 Equiv) then LDA (3.0 Equiv)	THF/DMPU (4:1, v/v)[i]	−50 °C	1.0 h	22	68 (66[d])	<5	8

[a] Yield was determined by ^{1}H NMR spectrum of the crude product with 1,1,2,2-tetrachloroethane as an internal standard. [b] Concentration of a solution of **1**: 0.2 M. [c] Not detected in the ^{1}H NMR spectrum of the crude product. [d] Isolated yield. [e] Recovery of pyridylthiophene **1** (45%). [f] Recovery of pyridylthiophene **1** (14%). [g] Recovery of pyridylthiophene **1** (32%). [h] Four equivalents of iodine were used. [i] Concentration of a solution of **1**: 0.1 M



Scheme 2 Rationale for the solvent effect on the regioselective formation of the thienylmetal species in the halogen dance reaction.

To confirm the viability of the position of pyridine nitrogen, 3-(5-bromothiophen-2-yl)pyridine (**9**) was subjected to the halogen dance reaction in toluene or THF/DMPU, which was quenched with EtOH. Unlike in the case of pyridylthiophene **1**, 4-bromothiophene **10**[31] was obtained as a major product in both cases with less than 5% of 3-bromothiophene **11**.[32] In terms of regioselectivity in the halogen dance reaction, the 3-pyridyl moiety behaved more like a phenyl group[33] than a directing group, such as the 2-pyridyl moiety.



Scheme 3 Effect of the position of pyridine nitrogen.

In summary, the position of deprotonation of brominated pyridylthiophene was successfully switched by adding DMPU as the Lewis base. This finding enabled the regioselective deprotonation of each proton on thiophene. The subsequent halogen dance of the two metalated pyridylthiophenes was controlled to provide the four iodinated isomers from a single starting material, 2-(5-bromothiophen-2-yl)pyridine (**1**), in one step. The developed method is suitable for the synthesis of a variety of substituted pyridylthiophene derivatives.

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Supporting Information

YES

Primary Data

NO

Conflict of Interest

The authors declare no conflict of interest.

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(22) CCDC 2168990, 2259861, and 2259860 contain the supplementary crystallographic data for compounds **2**, **3**, and **5**, respectively. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures. The crystallographic data for compound **4** was less accurate, but the substitution positions of the bromo and iodo groups were unambiguously confirmed.

(23) **Experimental procedures and characterization data**. A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 2-(5-bromothiophen-2-yl)pyridine (**1**) (200.4 mg, 0.835 mmol, 1.0 equiv) and toluene (4.0 mL). The resulting solution was cooled to −78 °C and changed into the slurry. LDA (2.0 M, 0.62 mL, 1.2 mmol, 1.5 equiv) was added to the Schlenk tube at −78 °C. After stirring at −78 °C for 90 min, the dissolution of the precipitation was confirmed, and iodine (422.8 mg, 1.666 mmol, 2.0 equiv) was added to the reaction mixture in one portion (the septum was removed temporarily). The reaction mixture was warmed to room temperature and stirred at room temperature for 30 min. The reaction mixture was treated with diethyl ether (20 mL) and saturated aqueous sodium thiosulfate (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (20 mL). Each of the organic layers was washed with water (20 mL). The combined organic extracts were concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (hexane/diethyl ether = 20:1) to provide 2-(3-bromo-5-iodothiophen-yl)pyridine (**4**) as a pale yellow solid (200.6 mg, 0.548 mmol, 66%). R_f = 0.37 (hexane/diethyl ether = 9:1); Mp 66.8–67.7 °C; IR (ATR, cm^{-1}): 1582, 1567, 1518, 1460, 1435, 1423, 1305, 1154, 994, 975, 821, 776, 738, 713, 659; ^1H NMR (400 MHz, $CDCl_3$): δ 8.57 (d, 1H, *J* = 4.8 Hz), 8.25 (d, 1H, *J* = 8.4 Hz), 7.76 (ddd, 1H, *J* = 7.8, 7.8, 1.6 Hz), 7.23 (ddd, 1H, *J* = 7.8, 4.8, 1.2 Hz), 7.20 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 150.7, 149.7, 145.2, 141.3, 136.7, 123.0, 120.3, 107.3, 77.0; HRMS (EI$^+$) *m/z*: calcd. for $C_9H_5{}^{79}BrINS$, 364.8365 $[M]^+$; found 364.8373.

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(25) **Experimental procedures and characterization data**. A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 2-(5-bromothiophen-2-yl)pyridine (**1**) (100.3 mg, 0.418 mmol, 1.0 equiv), THF (1.6 mL), and DMPU (0.4 mL). The resulting solution was cooled to −78 °C. LDA (2.0 M, 0.32 mL, 0.64 mmol, 1.5 equiv) was added to the Schlenk tube at −78 °C. After stirring at −78 °C for 60 min, iodine (211.4 mg, 0.833 mmol, 2.0 equiv) was added to the reaction mixture in one portion (the septum was removed temporarily). The reaction mixture was warmed to room temperature and stirred at room temperature for 30 min. The reaction mixture was treated with diethyl ether (10 mL) and saturated aqueous sodium thiosulfate (10 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (10 mL). Each of the organic layers was washed with water (10 mL). The combined organic extracts were concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (hexane/diethyl ether = 20:1) to provide 2-(4-bromo-5-iodothiophen-2-yl)pyridine (**5**) as a pale yellow solid (112.6 mg, 0.308 mmol, 74%). R_f = 0.23 (hexane/diethyl ether = 9:1); Mp 101.3–103.0 °C; IR (ATR, cm^{-1}): 1584, 1564, 1461, 1433, 1408, 1321, 1289, 994, 979, 813, 772; ^1H NMR (400 MHz, $CDCl_3$): δ 8.56–8.53 (m, 1H), 7.71 (ddd, 1H, *J* = 7.8, 7.8, 1.2 Hz), 7.57–7.53 (m, 1H), 7.32 (s, 1H), 7.19 (ddd, 1H, *J* = 7.8, 4.8, 1.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 150.80, 150.78, 149.8, 137.1, 126.7, 123.0, 120.9, 118.3, 80.3; $^{13}C\{^1H\}$ NMR (100 MHz, CD_3CN): δ 152.0, 151.2, 150.4, 138.3, 127.8, 124.2, 121.4, 119.3, 81.5; HRMS (EI$^+$) *m/z*: calcd. for $C_9H_5{}^{79}BrINS$, 364.8365 $[M]^+$; found 364.8374.

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(28) **Experimental procedures and characterization data**. A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 2-(5-bromothiophen-2-yl)pyridine (**1**) (100.0 mg, 0.416 mmol, 1.0 equiv) and THF (1.0 mL). TMPMgCl·LiCl (1.0 M, 0.83 mL, 0.83 mmol, 2.0 equiv) was added to the Schlenk tube at room temperature. After stirring at room temperature for 150 min, iodine (211.9 mg, 0.835 mmol, 2.0 equiv) was added to the reaction mixture in one portion (the septum was removed temporarily). After stirring at room temperature for 30 min, the reaction mixture was treated with diethyl ether (10 mL) and saturated aqueous sodium thiosulfate (10 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (5 mL). Each of the organic layers was washed with water (5 mL). The combined organic extracts were concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (hexane/diethyl ether = 9:1) to provide 2-(5-bromo-3-iodothiophen-2-yl)pyridine (**2**) as a pale yellow solid (80.9 mg, 0.221 mmol, 53%). R_f = 0.33 (hexane/diethyl ether = 9:1); Mp 45.7–46.9 °C; IR (ATR, cm^{-1}): 1583, 1567, 1509, 1460, 1435, 1424, 994, 985, 819, 802, 775, 738, 661; ^1H NMR (400 MHz, $CDCl_3$): δ 8.60–8.57 (m, 1H), 8.28–8.24 (m, 1H), 7.77 (ddd, 1H, *J* = 7.6, 7.6, 1.6 Hz), 7.25 (ddd, 1H, *J* = 7.6, 5.0, 0.8 Hz), 7.13 (s, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 151.4, 149.7, 144.5, 139.8, 136.5, 123.1, 120.4, 116.6, 75.6; HRMS (EI$^+$) *m/z*: calcd. for $C_9H_5{}^{79}BrINS$, 364.8365 $[M]^+$; found 364.8370.

(29) **Experimental procedures and characterization data**. A flame-dried 20-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum under argon was charged with 2-(5-bromothiophen-2-yl)pyridine (**1**) (100.0 mg, 0.416 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (315.5 mg, 1.250 mmol, 3.0 equiv), THF (3.2 mL), and DMPU (0.8 mL). The resulting solution was cooled to −50 °C. LDA (2.0 M, 0.62 mL, 1.2 mmol, 3.0 equiv) was added to the Schlenk tube at −50 °C. After stirring at −50 °C for 60 min, iodine (422.8 mg, 1.666 mmol, 4.0 equiv) was added to the reaction mixture in one portion (the septum was removed temporarily). The reaction mixture was warmed to room temperature and stirred at room temperature for 30 min. The reaction mixture was treated with diethyl ether (20 mL) and saturated aqueous sodium thiosulfate (20 mL). After being partitioned, the aqueous layer was extracted with diethyl ether (10 mL). Each of the organic layers was washed with water (10

mL). The combined organic extracts were concentrated under reduced pressure to give a crude product. The crude product was purified by silica gel column chromatography (hexane/diethyl ether = 20:1) to provide 2-(5-bromo-4-iodothiophen-2-yl)pyridine (**3**) as a pale yellow solid (101.1 mg, 0.276 mmol, 66%). R_f = 0.27 (hexane/diethyl ether = 9:1); Mp 93.0–93.4 °C; IR (ATR, cm^{-1}): 1582, 1564, 1461, 1432, 1410, 1315, 1288, 1158, 995, 771; ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, 1H, *J* = 4.8 Hz), 7.69 (ddd, 1H, *J* = 7.6, 7.6, 1.6 Hz), 7.54 (d, 1H, *J* = 7.6 Hz), 7.37 (s, 1H), 7.18 (ddd, 1H, *J* = 7.6, 4.8, 1.2 Hz); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 150.7, 149.8, 147.6, 137.0, 131.6, 122.9, 119.6, 118.3, 86.4; HRMS (EI^+) *m/z*: calcd. for $C_9H_5{}^{79}BrINS$, 364.8365 $[M]^+$; found 364.8374.

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