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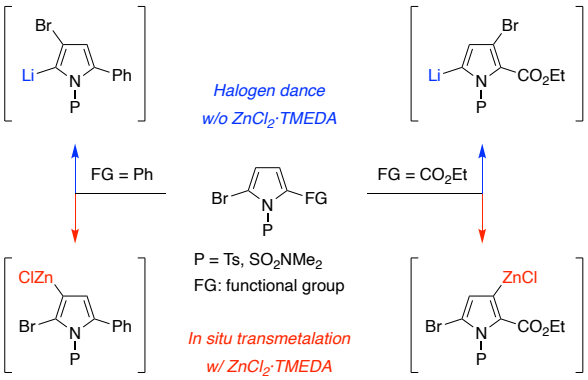

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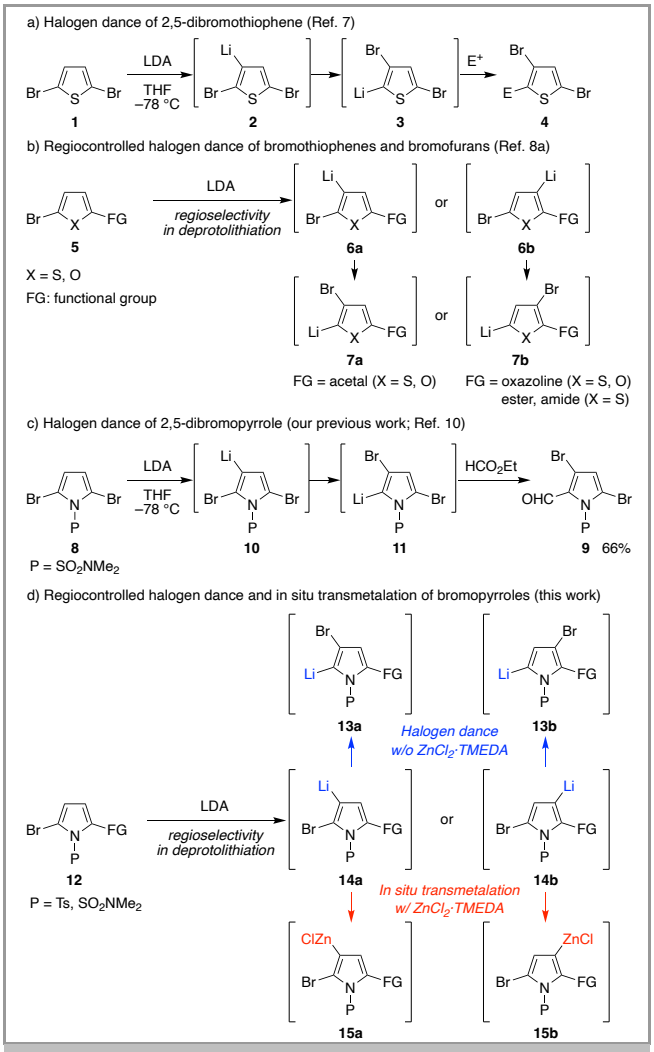
Abstract Multiply substituted pyrroles are found in medicines, natural products, and functional materials. A general method for introducing functionality onto the pyrrole ring is thus required. Herein, a regiocontrolled halogen dance reaction and in situ transmetalation of α-functionalized bromopyrroles are reported. Selective generation of the isomeric pyrrolylmetal species was achieved by using an ethyl ester or a phenyl group at the α position of the pyrrole and by switching the halogen dance reaction and in situ transmetalation. These reactions proceeded smoothly when an *N*,*N*-dimethylsulfamoyl group was attached to the pyrrole nitrogen, providing the corresponding products in 68% to quantitative yields on 1-mmol scales. This method was applicable to the formal synthesis of Kendine 91.

Key words deprotonation, halogen dance, in situ transmetalation, organometallic reagents, pyrroles, regioselectivity

Various pyrroles with multiple substituents are found in medicines, natural products, and functional materials.[1] In addition to the classical Paal–Knorr synthesis, other methods such as cyclization, cycloaddition, and multicomponent reactions have been developed for the construction of the pyrrole skeleton.[2,3] Direct functionalization of pyrrole has also been studied,[4,5] but a general method for synthesizing multiply substituted pyrroles is still required.

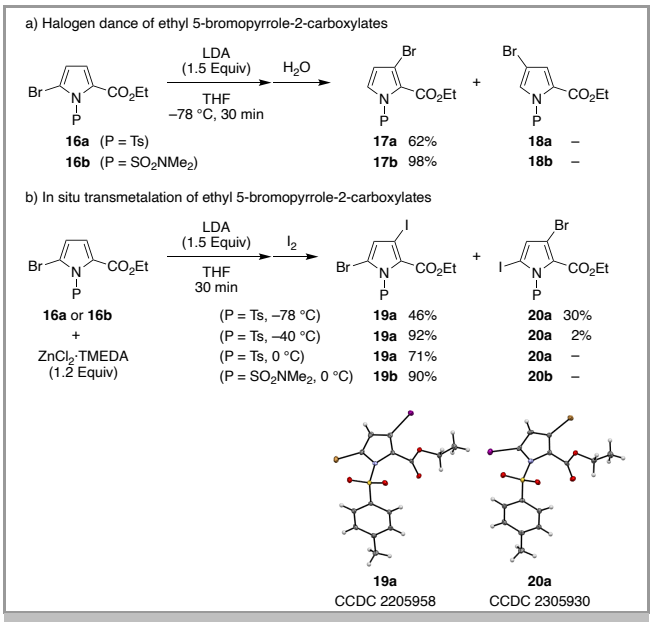
A halogen dance reaction is a formal exchange reaction of a halogen atom and lithium atom on a lithiated heteroaryl halide, and this reaction has been utilized for the synthesis of densely functionalized aromatic rings.[6] Among heteroarenes, bromothiophenes are well known to undergo the halogen dance reaction (Scheme 1a). Deprotonation of 2,5-dibromothiophene (**1**) with LDA generates organolithium **2**. Subsequently, successive intermolecular halogen–lithium exchange reactions occur to produce thermodynamically more stable organolithium species **3**. Treatment with an electrophile leads to the formation of functionalized dibromothiophene **4**, whose α- and β-bromo groups have different reactivities for further transformations.[7]



Scheme 1 Halogen dance of brominated heteroarenes.

Unlike with symmetrical substrates such as dibromothiophene **1**, the use of unsymmetrical substrates introduces a regioselectivity issue for the reaction. We reported that deprotonation of α-bromothiophenes and α-bromofurans **5**, whose regioselectivity was switchable by choosing the appropriate functional group at the α-position, gave two isomeric organolithiums **6a** and **6b**. After treatment with electrophiles, we achieved the regioselective synthesis of bromothiophenes and bromofurans **7a** and **7b** by controlling the 1,2- and 1,3-shift-type migration of the halogen dance reaction (Scheme 1b).[8] To extend the substrate scope of the reaction, we recently investigated the halogen dance reaction of 2,5-dibromopyrrole **8**. The halogen dance reaction was promoted by an electron-withdrawing protective group on the pyrrole nitrogen, particularly by the *N*,*N*-dimethylsulfamoyl group,[9] to form dibromopyrrole **9** via the organolithiums **10** and **11** (Scheme 1c).[10] However, the halogen dance reaction of pyrroles has only been studied for dibromopyrroles[11] and has not been applied to monobromopyrroles. Herein, we report that α-bromopyrrole **12** with the functional group at the α-position also undergoes the halogen dance reaction to give organolithium species **13a** or **13b**, as well as thiophene and furan (Scheme 1d). In another study, an unstable organolithium species in the halogen dance reaction was successfully trapped and converted into the corresponding organozinc species using zinc halide diamine complexes that coexisted during the deprotonation, which is referred to as "in situ transmetalation".[12,13] A combination of the halogen dance reaction and this method would provide selective and direct access to each constitutional isomer. $ZnCl_2$·TMEDA was used to trap the organolithiums **14a** and **14b** before the halogen dance reaction occurred. The generated organozinc species **15a** and **15b** did not undergo the halogen dance reaction. The combination of the halogen dance reaction and in situ transmetalation allowed the utilization of the organometallic species **13a**, **13b**, **15a**, and **15b**. The regiocontrolled reaction was applied to the formal synthesis of Kendine 91.

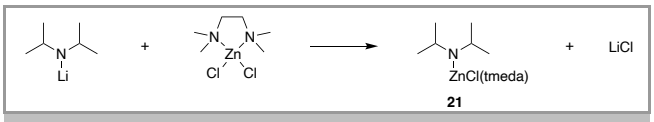
We investigated the halogen dance reaction and in situ transmetalation of bromopyrrole **16** with an ester group (Scheme 2). First, bromopyrroles **16a** and **16b** were treated with LDA followed by water to provide *N*-Ts-3-bromopyrrole **17a** and *N*-sulfamoyl-3-bromopyrrole **17b** in 62% and 98% ^{1}H NMR yields, respectively.[14] The debrominated pyrrole was only obtained as a byproduct in the case of the Ts group. In both cases, the constitutional isomer **18** was not detected. Next, to trap the initially generated organolithium, a THF solution of a mixture of bromopyrrole **16** and $ZnCl_2$·TMEDA was treated with LDA followed by iodine. Bromopyrrole **16a** was converted into the corresponding 5-bromo-3-iodopyrrole **19a** in 46% yield at −78 °C with concomitant generation of iodopyrrole **20a** through the halogen dance reaction. Thus, we expected to promote the trapping of pyrrolyllithium with $ZnCl_2$·TMEDA before the halogen dance reaction, by elevating the reaction temperature. The desired iodopyrrole **19a** was obtained in 92% yield at −40 °C; however, the yield of iodopyrrole **19a** decreased to 71% at 0 °C with recovery of **16a** (19%). The structures of the iodopyrroles **19a** and **20a** were confirmed by X-ray crystallographic analysis.[15]



Scheme 2 Halogen dance and in situ transmetalation of ethyl 5-bromopyrrole-2-carboxylates.

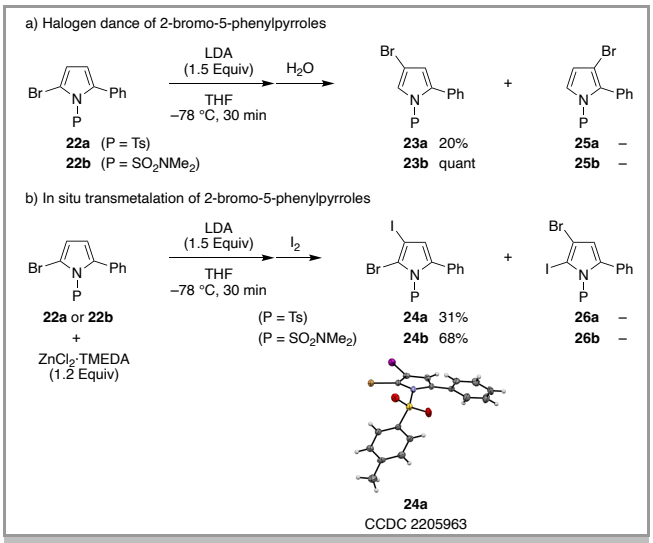
The recovery of the starting material is attributed to the formation of the less basic zinc amide **21** from LDA and $ZnCl_2$·TMEDA (Scheme 3). Because the undesired reaction was

suppressed at −40 °C, the generated pyrrolyllithium was trapped with $ZnCl_2$·TMEDA before the halogen dance reaction to provide iodopyrrole **19a** in 92% yield. Similarly, *N*-sulfamoyl-bromopyrrole **16b** was converted into the corresponding iodopyrrole **19b** in 90% yield at 0 °C.[16] These results indicate that the Ts group or dimethylsulfamoyl group on the pyrrole nitrogen can be used in both the halogen dance reaction and in situ transmetalation of the bromopyrrole bearing the ester moiety.



Scheme 3 The undesired reaction of LDA with $ZnCl_2$·TMEDA.

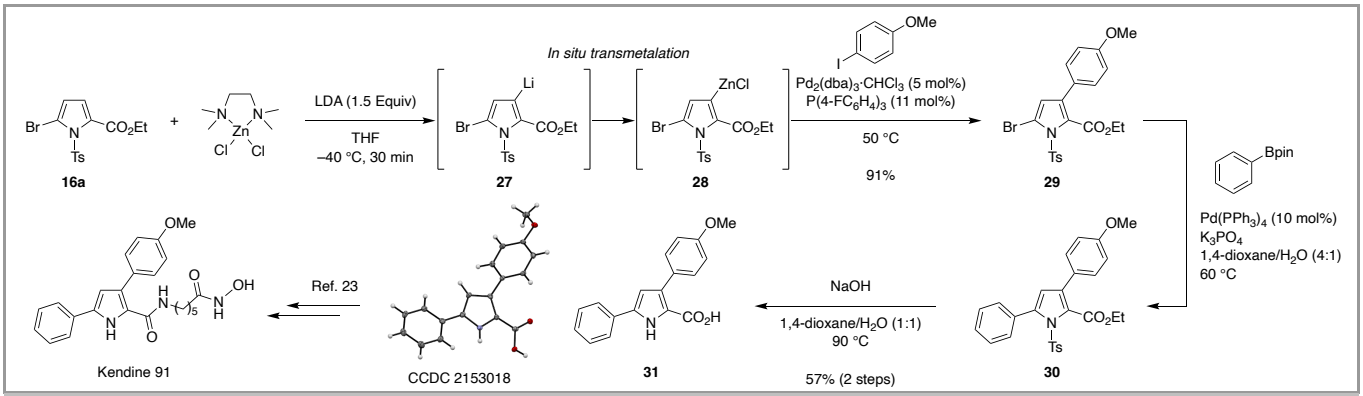
A halogen dance reaction of 2-bromo-5-phenylthiophene proceeds through 1,2-migration of the bromo group.[17] Therefore, we next investigated the halogen dance reaction and in situ transmetalation of bromopyrroles with the phenyl group (Scheme 4). The use of the sulfamoyl group resulted in markedly better yields for both reactions compared with the Ts group, unlike in the case of pyrrole **16** with the ester group. First, *N*-Ts-bromopyrrole **22a** underwent the halogen dance reaction to give product **23a** in 20% yield associated with *N*-Ts-2-phenylpyrrole (42%). Switching the Ts group to the *N*,*N*-dimethylsulfamoyl group significantly improved the yield of 4-bromopyrrole **23b** in quantitative yield at −78 °C.[18] Next, subjecting **22a** to in situ transmetalation followed by iodination provided **24a** in 31% yield with recovery of less than 10% substrate. The structure of **24a** was confirmed by X-ray crystallographic analysis.[15] In contrast to bromopyrrole **16a**, which has the ester group, the halogen dance reaction of bromopyrrole **22a** was completely suppressed, likely owing to the sluggish deprotonation by LDA. The identified byproduct was the benzyl iodide in 21% yield, which was formed through deprotonation followed by iodination of the benzylic proton of the Ts group. In the case of pyrrole **22b**, which has the *N*,*N*-dimethylsulfamoyl group, the in situ transmetalation of the generated pyrrolyllithium proceeded smoothly to provide 2-bromo-3-iodopyrrole **24b** in 68% yield.[19] In both cases, the constitutional isomers **25** and **26** were not detected. These results indicate that phenylpyrrole **22** requires the sulfamoyl group on the nitrogen atom for both reactions.



Scheme 4 Halogen dance and in situ transmetalation of 2-bromo-5-phenylpyrroles.

It is worth noting that, similar to the results of other studies on the halogen dance reaction,[8,17] the position of the deprotonation completely dictates the migratory aptitude of the bromo group. In the case of bromopyrroles **16**, the ester moiety worked as a directing group to promote deprotonation at the position proximal to the ethyl ester. In contrast, 2-bromo-5-phenylpyrroles **22** were deprotonated at the position next to the bromo group because of its inductive effect.

To demonstrate the utility of the newly established method, we synthesized the intermediate of an HDAC inhibitor, Kendine 91,[20] as a multiply substituted pyrrole (Scheme 5). A THF solution of a mixture of bromopyrrole **16a** and $ZnCl_2$·TMEDA was treated with LDA at −40 °C. The in situ transmetalation of pyrrolyllithium **27** proceeded to give pyrrolylzinc species **28**, which underwent Negishi coupling[21] to provide arylated pyrrole **29** in 91% yield without formation of the constitutional isomer produced via pyrrolylzinc species **15a**. Because another possible isomeric arylated pyrrole generated through the halogen dance reaction was not also observed, pyrrolylzinc **28** is considered to be stable at 50 °C. The remaining bromo group was transformed into the phenyl group by Suzuki–Miyaura coupling[22] to provide a mixture of the desired pyrrole **30** and its unprotected pyrrole, which was used for the next reaction without further purification. Finally, hydrolysis of the ethyl ester and removal of the Ts group provided pyrrole carboxylic acid **31**[15] in 57% yield over two steps from **29**, thus achieving the formal synthesis of Kendine 91.[23] This method has the advantage of allowing the two aryl groups to be introduced in a regioselective and stepwise manner, and would be applicable to the synthesis of other Kendine 91 derivatives.



Scheme 5 Formal synthesis of Kendine 91 using in situ transmetalation.

In summary, we have demonstrated the regiocontrolled halogen dance reaction of α-substituted bromopyrroles. The 2-bromopyrroles with the phenyl moiety underwent regioselective 1,2-migration of the bromo group, whereas the ester group worked as the directing group to facilitate 1,3-migration of the bromo group. The combination of the halogen dance reaction and in situ transmetalation achieved selective generation of the isomeric pyrrolylmetal species. In addition, the *N*,*N*-dimethylsulfamoyl group on the pyrrole nitrogen was suitable for a range of substrates, leading to the synthesis of various functionalized bromopyrroles.

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A part of this work was conducted at NAIST, supported by the ARIM Program of the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan. We thank Professor Shigeki Mori and Ms. Rimi Konishi (Ehime University) for the X-ray crystallographic analyses. We thank Edanz (https://jp.edanz.com/ac) for editing a draft of this manuscript.

Supporting Information

YES

Primary Data

NO

Conflict of Interest

The authors declare no conflict of interest.

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(14) **Experimental procedures of the halogen dance reaction and characterization data (17b).** A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with ethyl 5-bromo-1-(*N*,*N*-dimethylsulfamoyl)-1*H*-pyrrole-2-carboxylate (**16b**) (328.2 mg,

1.01 mmol, 1.0 equiv) and THF (10.0 mL). After the solution was cooled to –78 °C, LDA (2.0 M in THF/heptane/ethylbenzene, 0.75 mL, 1.5 mmol, 1.5 equiv) was added to the Schlenk tube and the mixture was stirred at –78 °C for 30 min. The reaction mixture was treated with water (15 mL), and the resulting mixture was extracted with diethyl ether (20 mL) five times. The combined organic extracts were washed with water (50 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yield of 3-bromopyrrole **17b** was determined to be 98% by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane (90.6 mg, 0.540 mmol) as an internal standard by comparing relative values of integration for the peak observed at 6.30 ppm (one proton for **17b**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm. The crude product was purified by silica gel column chromatography (hexane/diethyl ether = 3:2) to provide ethyl 3-bromo-1-(*N*,*N*-dimethylsulfamoyl)-1*H*-pyrrole-2-carboxylate (**17b**) as a colorless oil (238.9 mg, 0.873 mmol, 87%). R_f = 0.45 (hexane/diethyl ether = 1:1); IR (ATR, cm^{-1}): 1737, 1367, 1231, 1216, 1205, 722; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, 1H, *J* = 3.2 Hz), 6.30 (d, 1H, *J* = 3.2 Hz), 4.38 (q, 2H, *J* = 7.2 Hz), 2.97 (s, 6H), 1.40 (t, 3H, *J* = 7.2 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.9, 126.7, 123.8, 114.0, 106.7, 62.0, 38.6, 14.2; HRMS (DART/TOF) *m/z*: [M + H]$^+$ calcd for $C_9H_{14}{}^{79}BrN_2O_4S$, 324.9858; found, 324.9870.

(15) CCDC 2205958, 2305930, 2205963, and 2153018 contain the supplementary crystallographic data for compounds **19a**, **20a**, **24a**, and **31**, respectively. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

(16) **Experimental procedures of in situ transmetalation and characterization data (19b).** A flame-dried 50-mL Schlenk tube equipped with a Teflon-coated magnetic stirring bar and a rubber septum was charged with ethyl 5-bromo-1-(*N*,*N*-dimethylsulfamoyl)-1*H*-pyrrole-2-carboxylate (**16b**) (322.1 mg, 0.991 mmol, 1.0 equiv), $ZnCl_2$·TMEDA (305.4 mg, 1.21 mmol, 1.2 equiv), and THF (10.0 mL). After the solution was cooled, LDA (2.0 M in THF/heptane/ethylbenzene, 0.75 mL, 1.5 mmol, 1.5 equiv) was added to the Schlenk tube and the mixture was stirred for 30 min. The reaction mixture was treated with iodine (500.7 mg, 1.97 mmol, 2.0 equiv). After stirring at 0 °C for 1 h, the reaction mixture was treated with saturated aqueous sodium thiosulfate (10 mL) and saturated aqueous ammonium chloride (10 mL). The mixture was partitioned and the aqueous layer was extracted with diethyl ether (20 mL) five times. The combined organic extracts were washed with brine (50 mL), dried over sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a crude product. The yield of 3-iodopyrrole **19b** was determined to be 90% by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane (69.7 mg, 0.415 mmol) as an internal standard by comparing relative values of integration for the peak observed at 6.44 ppm (one proton for **19b**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm. The crude product was purified by silica gel column chromatography (hexane/diethyl ether = 4:1) to provide ethyl 5-bromo-1-(*N*,*N*-dimethylsulfamoyl)-3-iodo-1*H*-pyrrole-2-carboxylate (**19b**) as a pale yellow solid (333.0 mg, 0.738 mmol, 75%). R_f = 0.49 (hexane/CH_2Cl_2 = 7:3); mp 56–57 °C; IR (ATR, cm^{-1}): 2972, 2922, 1728, 1453, 1390, 1227, 1183, 1155, 1046, 978, 725, 650; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.44 (s, 1H), 4.38 (q, 2H, *J* = 7.0 Hz), 3.07 (s, 6H), 1.39 (t, 3H, *J* = 7.0 Hz); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.3, 133.4, 123.3, 105.0, 68.6, 62.6, 38.6, 14.1; HRMS (DART/TOF) *m/z*: [M + H]$^+$ calcd for $C_9H_{13}{}^{79}BrIN_2O_4S$, 450.8824; found, 450.8827.

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(18) **Characterization data (23b).** Bromopyrrole **23b** was synthesized according to the above experimental procedure of the halogen dance reaction. The yield of bromopyrrole **23b** was determined to be quantitative by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane (65.6 mg, 0.391 mmol) as an internal standard by comparing relative values of integration for the peak observed at 2.43 ppm (six protons for **23b**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm. The title compound was obtained as a colorless solid (244.6 mg, 0.743 mmol, 75%) from 2-bromo-*N*,*N*-dimethyl-5-phenyl-1*H*-pyrrole-1-sulfonamide (**22b**) (325.0 mg, 0.987 mmol). R_f = 0.49 (hexane/CH_2Cl_2 = 1:1); mp 61–62 °C; IR (ATR, cm^{-1}): 1389, 1377, 1168, 1133, 1059, 986, 765, 730, 699; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51–7.44 (m, 2H), 7.41–7.36 (m, 3H), 7.29 (d, 1H, *J* = 2.2 Hz), 6.26 (d, 1H, *J* = 2.2 Hz), 2.43 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 135.5, 131.0, 130.8, 128.9, 128.0, 123.7, 117.0, 98.8, 37.5; HRMS (DART/TOF) *m/z*: [M + H]$^+$ calcd for $C_{12}H_{14}{}^{79}BrN_2O_2S$, 328.9959; found, 328.9960.

(19) **Characterization data (24b).** Iodopyrrole **24b** was synthesized according to the above experimental procedure of in situ transmetalation. The yield of iodopyrrole **24b** was determined to be 68% by ^{1}H NMR analysis using 1,1,2,2- tetrachloroethane (51.0 mg, 0.304 mmol) as an internal standard by comparing relative values of integration for the peak observed at 6.32 ppm (one proton for **24b**) with that of 1,1,2,2-tetrachloroethane observed at 5.96 ppm. The title compound was obtained as a colorless solid (249.5 mg, 0.548 mmol, 55%) from 2-bromo-*N*,*N*-dimethyl-5-phenyl-1*H*-pyrrole-1-sulfonamide (**22b**) (328.1 mg, 0.997 mmol). R_f = 0.44 (hexane/CH_2Cl_2 = 1:1); mp 97–98 °C; IR (ATR, cm^{-1}): 1394, 1174, 763, 738, 727, 651, 637; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41–7.33 (m, 5H), 6.32 (s, 1H), 2.72 (s, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 140.8, 132.5, 130.0, 128.5, 127.6, 121.3, 109.3, 76.7, 38.1; HRMS (DART/TOF) *m/z*: [M + H]$^+$ calcd for $C_{12}H_{13}{}^{79}BrIN_2O_2S$, 454.8926; found, 454.8903.

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