

Aryl Dance Reaction of Arylheteroles

Hikaru Nakahara,³ and Junichiro Yamaguchi*^a

We have discovered a 1,2-migration (aryl dance reaction) of the aryl group on heteroles. AlCl₃ can efficiently convert C3-arylheteroles to C2-arylheteroles. Depending on the electron density of the substrate, conversion from C2- to C3-arylheteroles was also possible with catalytic Zn(OTf)₂. A one-pot aryl dance/acylation or bromination, and arylation/aryl dance was also demonstrated.

The transfer of substituents from one position to another on an aromatic ring could lead to a convenient synthesis of a wide variety of aromatic compounds.¹ *Substituent rearrangement reactions* of aromatic compounds can install substituents onto positions that are difficult to introduce by electrophilic or nucleophilic substitution reactions. A representative classic example is the Claisen rearrangement (Fig 1A, left arrow).² Such rearrangements typically leave behind a portion of the original substituent on the original carbon. Meanwhile, *substituent translocation reactions* of aromatic compounds involve the loss of the entire substituent from the original carbon, which is then transferred to another carbon (Fig. 1A, right arrow). A transalkylation reaction is a classic example of aromatic substituent translocations,³ and halogen dance reaction is a practical example often observed in heterocyclic chemistry.⁴ However, these reactions require harsh reaction conditions such as high temperatures and stoichiometric amounts of strong base. Recently, we have developed a catalytic substituent translocation (ester dance reaction) that can perform a [1,2]-transfer of the ester group of aromatic esters in the presence of our group's Pd catalyst.⁵ After the ester is translocated, it can be converted to various functional groups by decarbonylative coupling reactions in one pot.⁶ However, the reaction that could introduce a different arenes was the C–H arylation of 1,3-azoles. Several other dance reactions have been reported, but they are acyl and hetero-functional group dance reactions as well.⁷ In order to control the 1,2-migration of arenes, we focused on the aryl dance reaction in this study.

Aryl dance reaction of aromatics can be observed as a side reaction of the Scholl reaction. For example, 1,2-migration of terphenyls and biphenylenes in the presence of TfOH is known, but the regioselectivity is not controllable (Figure 1B).⁸ The regioselectivity can be controlled with arylheteroles, and an aryl dance from C3- to C2-position has been proposed to occur via a Wheland intermediate in the presence of strong acid.⁹ However,

substrate generality has not been reported, and to the best of our knowledge, no 1,2-translocation reactions from C2- to C3-arylheteroles have been reported. Since heteroles with arylated C-H arylation of heteroles can introduce an aryl group at the C2 or C3 position,¹⁰ we believe that establishing such a 1,2-migration would provide a new synthetic method that could switch the position of arylheteroles.

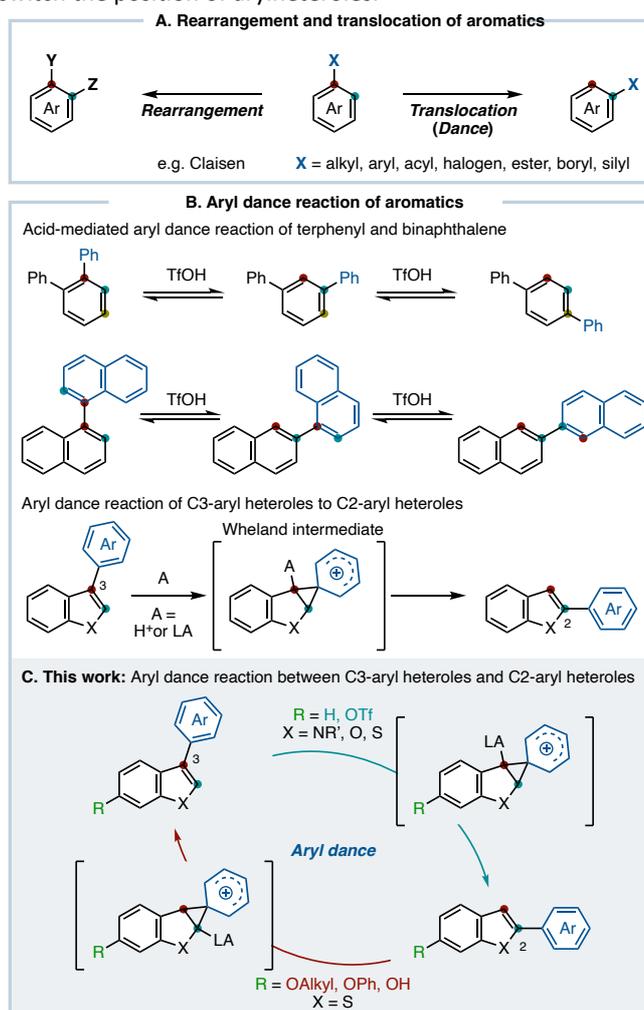


Fig. 1 (A) *Rearrangement vs translocation* of substituents on arenes. (B) Aryl dance reaction of aromatics. (C) Aryl dance reaction between C2-aryl heteroles and α -aryl heteroles.

^b Department of Applied Chemistry, Waseda University, 513, Wasedatsurumakicho, Shinjuku, Tokyo 169-8555, Japan. Email: junyamaguchi@waseda.jp

[†] Footnotes relating to the title and/or authors should appear here.

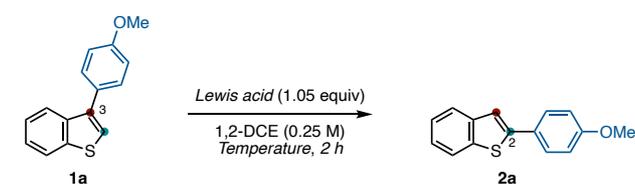
Electronic Supplementary Information (ESI) available: CCDC 2173194 (for **8**). For experimental procedures, spectroscopic data for compounds including ¹H, ¹³C, and ¹⁹F NMR spectra, and crystallographic data in CIF see DOI: 10.1039/x0xx00000x

In this study, we report that aryl groups can be interconverted at the C3 and C2 positions by changing the substrate and reaction conditions (Figure 1C).

We initially examined the dance reaction of C3- to C2-arylheterole using commercially available C3-anisylbenzothiophene **1a**. Although we investigated the use of

transition metal catalysts such as Au or Pt, unfortunately, the reaction did not proceed at all. Then, we focused on acids: To **1a**, several Lewis acids (1.05 equiv) were added with 1,2-DCE as a solvent and heating at 80°C for 2 h (Table 1). Zn(OTf)₂ and B(C₆F₅)₃ were not effective (Entries 1 and 2). When BF₃·OEt₂ was used, the reaction proceeded slightly and C2-anisylbenzothiophene **2a** was obtained in 3% yield (Entry 3). Using GaCl₃, the yield was higher (Entry 4), and using TMSOTf, the yield was increased to 44%, while the recovery of **1a** was also lower (Entry 5). TfOH and AlCl₃ were converted to **2a** in good yields (Entries 6 and 7), but AlCl₃ was selected because the reaction proceeded even when the reaction temperature was 60°C or RT (Entries 8 and 9).

Table 1 Screening of reaction conditions.^a



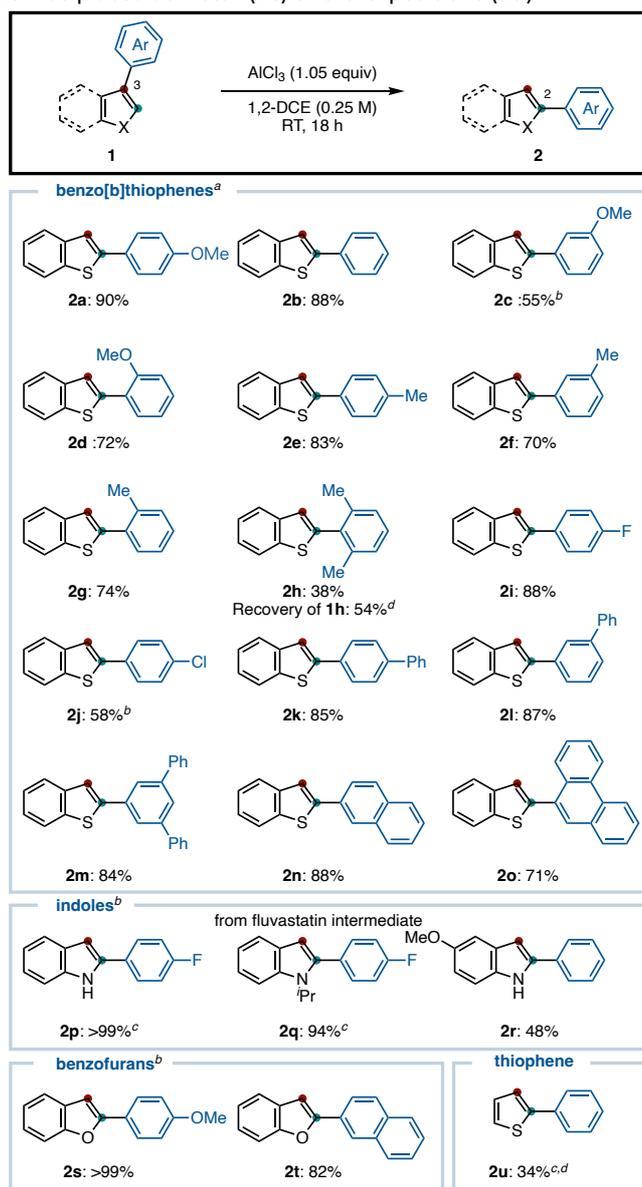
entry	Lewis acid	Temp/ °C	Recovery of 1a / % ^b	Yield of 2a / % ^b
1	Zn(OTf) ₂	80	100	0
2	B(C ₆ F ₅) ₃	80	72	0
3	BF ₃ ·OEt ₂	80	97	3
4	GaCl ₃	80	87	13
5	TMSOTf	80	14	44
6	TfOH	80	16	65
7	AlCl ₃	80	8	74
8	AlCl ₃	60	5	66
9	AlCl ₃	RT	18	66
10^c	AlCl₃	RT	8	91
11 ^{c,d}	AlCl ₃	RT	50	33
12 ^{c,e}	AlCl ₃	RT	40	39
13 ^c	AlCl ₃ (0.50 equiv)	60	6	93
14 ^c	AlCl ₃ (0.30 equiv)	60	7	76
15 ^c	AlCl ₃ (0.10 equiv)	60	37	61

^aConditions: **1a** (0.2 mmol), Lewis acid (1.05 equiv), 2h. ^b Recovery of **1a** and yield of **2a** were determined by ¹H NMR analysis. ^c 18 h. ^d CH₂Cl₂ was used instead of 1,2-DCE. ^e Toluene was used instead of 1,2-DCE.

Remarkably, the use of TMSOTf and AlCl₃ gave less than 10% demethylated compound as a byproduct. Finally, changing the reaction time from 2 h to 18 h gave **2a** in 91% yield (Entry 10). The reaction proceeded when the solvent was changed to dichloromethane or toluene, but the yield was decreased (Entries 11 and 12). The reaction did not require stoichiometric amounts of AlCl₃ (1.05 equiv) and proceeded even with substoichiometric (0.5 equiv) amounts (Entry 13). However, the yields were decreased with 0.30 and 0.10 equiv of AlCl₃ (Entries 14 and 15).

Under the optimal reaction conditions, the substrate generality of arylheteroles were investigated (Scheme 1). The reaction proceeded well even without the methoxy group, affording C2-phenylbenzothiophene **2b** in 88% yield. Furthermore, the desired C2-anisylbenzothiophene **2c** and **2d**

were obtained in moderate yields when the methoxy group in **2a** was placed at *meta*- (**1c**) or *ortho*-positions (**1d**).



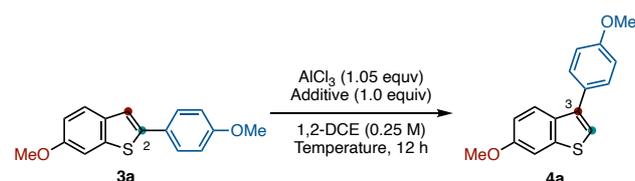
Scheme 1 Substrate scope. ^a**1** (0.20 mmol), AlCl₃ (1.05 equiv), 1,2-DCE (0.25 M), RT, 18 h. ^b AlCl₃ (2.0 equiv), Zn(OTf)₂ (0.50 equiv) was used at 60 °C, 12 h. ^c 80 °C. ^d Yields were determined by ¹H NMR analysis.

The methoxy group was changed to a methyl group, and the corresponding C2-tolylbenzothiophenes **2e–2g** were obtained in similar yields with the methyl group in the *para*- (**1e**), *meta*- (**1f**), and *ortho*-positions (**1g**). Benzothiophene with a xylyl group (**1h**) reacted slowly, presumably due to steric hindrance, and product **2h** was afforded in 38% yield with recovered starting material **1h** (54% yield). Surprisingly, even C3-arylbenzothiophenes with halogens such as fluorine and chlorine on the aryl group gave the corresponding C2-arylbenzothiophenes **2i** and **2j** in moderate to good yields. Benzothiophenes with biphenyl (**1k** and **1l**) or terphenyl (**1m**) also gave the corresponding C2-arylbenzothiophenes **2k–2m** in good yields, and no translocation of the phenyl group was observed. Benzothiophenes with naphthyl or phenanthrenyl groups were also applicable (**2n** and **2o**). Regarding C3-

arylindoles, the desired C2-arylindoles with a *para*-fluorophenyl group **2p** and **2q** were obtained. The reaction also proceeded with C3-arylindoles with a methoxy group on the indole portion (**2r**). Indole is unstable in acidic conditions, and therefore the yields tended to be higher with electron-withdrawing substituents in the form of aryl groups such as **2p** and **2q**. C3-Arylbenzofurans were also applicable to afford C2-arylbenzofurans (**2s** and **2t**) in excellent yields. C3-Phenylthiophene (**1u**) underwent the 1,2-translocation reaction to give C2-phenylthiophene **2u**, albeit in low yield. Note that the addition of Zn(OTf)₂ was effective for some substrates, which is discussed below.

Next, we examined the 1,2-translocation reaction of arylheteroles from the C2- to the C3-position (Table 2). Assuming that the reaction is *via* a Wheland intermediate, we hypothesized that the introduction of an electron-donating group at the 6-position of benzothiophene would improve nucleophilicity at the α -position and that the Lewis acid would react at the C2-position (see Figure 1C). To this end, the reaction with **3a** bearing a methoxy group at the 6-position successfully yielded 31% of C3-anisylbenzothiophene **4a** as expected, and 49% of **3a** was recovered (Entry 1).

Table 2. Screening of reaction conditions. ^a

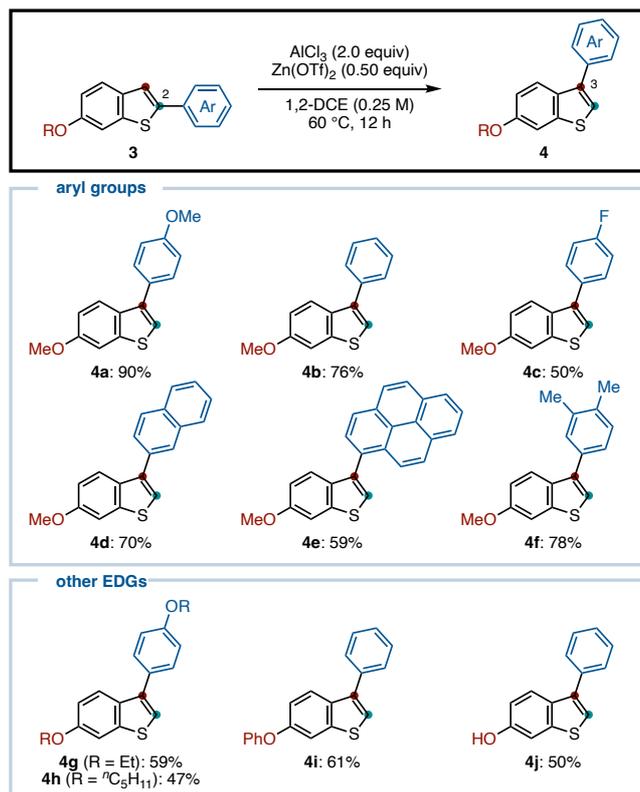


entry	Additive	Temp/ ^o C	Recovery of 3a / % ^b	Yield of 4a / % ^b
1	–	RT	49	31
2	–	50	51	43
3	–	60	48	49
4	–	70	29	41
5 ^c	–	60	44	33
6 ^c	Sc(OTf) ₃	60	24	72
7 ^c	Yb(OTf) ₃	60	13	83
8 ^c	AgOTf	60	40	60
9 ^c	Zn(OTf) ₂	60	27	71
10^c	Zn(OTf)₂ (0.5 equiv)	60	11	89
11	TfOH (w/o AlCl ₃)	60	25	74

Conditions: **3a** (0.2 mmol), AlCl₃ (1.05 equiv), additive (1.0 equiv), 2h. ^b Recovery of **3a** and yield of **4a** were determined by ¹H NMR analysis. ^c AlCl₃ (2.0 equiv) was added.

When the reaction was elevated to 60 °C, the yield of **4a** was improved to 49% yield (Entries 2 and 3), however, demethylation progressed at temperatures over 70 °C (Entry 4). Increasing the amount of AlCl₃ to 2.0 equiv was not beneficial (Entry 5). To avoid this demethylation, we examined additives and found that triflate salts were effective, giving **4a** in the best yield (89%) when 0.5 equiv of Zn(OTf)₂ was added (Entries 6–10). We assumed that TfOH was formed in the reaction and therefore used TfOH, but the yield was slightly lower (Entry 11). Because of these reasons, we decided to use AlCl₃ with Zn(OTf)₂ as the optimal conditions.

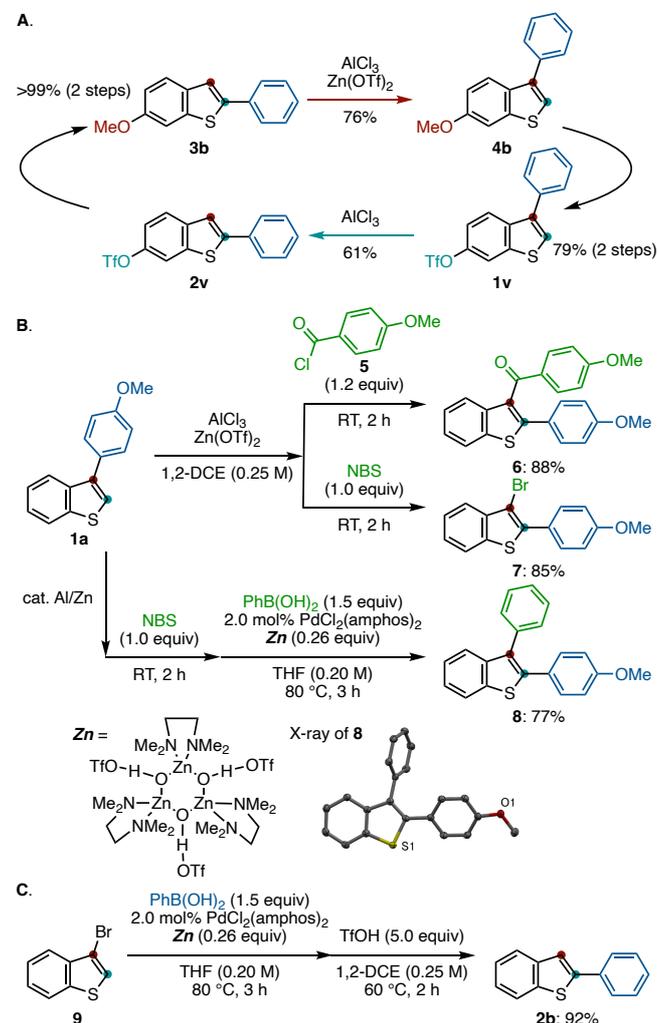
With the optimal conditions in hand, we investigated the generality of the substrate (Scheme 2). Changing the anisyl group to a phenyl group gave the desired C3-phenylbenzothiophene **4b** in high yield. 4-Fluorophenyl (**3c**), naphthyl (**3d**), pyrenyl (**3e**) and xylyl (**3f**) groups could also be derived to C3-arylbenzothiophenes **4c–4f** in moderate yields. Benzothiophene with functional groups instead of methoxy groups was also tried, and these reactions proceeded even in the case of ethoxy (**3g**), pentoxy (**3h**), and phenoxy (**3i**) groups. The hydroxy group (**3j**) also gave the desired C3-arylated compound **4j**, albeit in moderate yield.



Scheme 2 Substrate scope. ^a **3** (0.20 mmol), AlCl₃ (2.0 equiv), Zn(OTf)₂ (0.50 equiv), 1,2-DCE (0.25 M), 60 °C, 12 h.

Finally, the synthetic utility of this reaction is shown in Scheme 3. As mentioned above, the phenyl substituent of **3a** can be translocated to **4a** (Scheme 3A). The methoxy group of **4b** was then converted to a triflate in two steps (**1v**): this was done so that the nucleophilicity of the C3 position is increased compared to the C2 position, and thus treatment of **1v** with AlCl₃ can effect a C3 to C2 translocation (**2v**). Since **2v** can be converted to **3b** in two steps, this sequence can be considered as a controllable “aryl dance”, albeit over a number of steps. Such aryl-danced compounds could also be derived into other compounds in one pot (Scheme 3B). For example, after the dance of **1a**, addition of acyl chloride **5** promoted the Friedel–Crafts acylation, giving **6** in 88% yield, and the addition of NBS gave the bromo compound **7** in 85% yield. Furthermore, the addition of phenylboronic acid, palladium catalyst, and zinc catalyst after the addition of NBS allowed the Suzuki–Miyaura coupling reaction to proceed, yielding diarylbenzothiophene

8.¹¹ The obtained **8** had its structure determined by X-ray analysis after recrystallization. It was also possible to react bromobenzothiophene **9** in arylation and aryl dance reactions in a one-pot process (Scheme 3C). Indeed, the Suzuki-Miyaura coupling of **9**, followed by the addition of TfOH, gave the desired α -phenylbenzothiophene **2a** in high yield.



Scheme 3 Synthetic utility of the aryl dance reaction.

In summary, we have developed an aryl dance reaction of arylheteroles. A variety of C3-arylheteroles can be converted to C2-arylheteroles using AlCl_3 . We also succeeded in synthesizing C3-arylbenzothiophenes from C2-arylbenzothiophenes for the first time under an $\text{AlCl}_3/\text{Zn}(\text{OTf})_2$ system by changing the electronic system of the benzothiophene ring. Applications of this reaction other than the aryl group (e.g., alkenes, alkynes) are currently undergoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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