Aromatic Substitution

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Unusual *ipso* Substitution of Diaryliodonium Bromides Initiated by a Single-Electron-Transfer Oxidizing Process**

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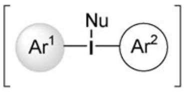
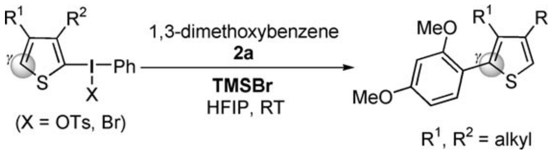


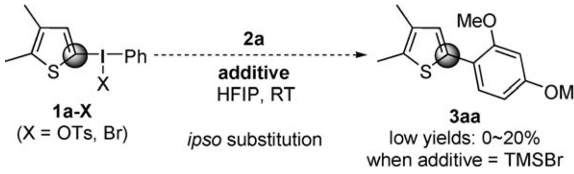
intermediate **A**
(Nu = nucleophile)

The diaryliodonium salts $Ar^1I^+Ar^2X^-$, which have two aryl groups bound to an iodine atom as a ligand, represent one of the most popular classes of hypervalent iodine compounds[1] and they have application as important arylating agents in organic synthesis.[2] In general, the arylation of nucleophiles with these iodonium salts is assumed to involve the tricoordinated intermediate **A** before the final ligand-coupling (LC) steps.[3] Owing to the competition of the two LC pathways of Ar^1 and Nu (LC_{Ar^1}) or Ar^2 and Nu (LC_{Ar^2}) at the iodine atoms in the intermediates, a mixture of two types of arylated products, Ar^1–Nu and Nu–Ar^2, are potentially obtained in the unsymmetrical salts ($Ar^1 \neq Ar^2$) during the aromatic substitution. Previous studies have revealed that the product produced from these pathways should be effected by both electronic and steric factors exerted by the two differential aryl rings of the initial salts—where the nucleophiles would preferentially react with a relatively electron-deficient aryl ring and/or sterically congested *ipso* carbon atom (i.e. the so-called "ortho effect").[4] Therefore, the introduction of nucleophiles to an electron-rich heteroaromatic ring is known to be particularly difficult through typical thermal LC processes, which involve the collapse of the intermediate **A**.[5–7] Despite their rich chemistry, the utility of diaryliodonium salts as a heteroaryl transfer agent in LC processes has been somewhat limited.

Herein, we report a unique single-electron-transfer (SET) oxidizing strategy using diaryliodonium salts as selective heteroaryl transfer agents during *ipso* substitution. Recently, our research group has reported a metal-free C–H coupling method of thiophenes and aromatic compounds using iodonium salts.[8] The method, using TMSBr in hexafluoroisopropanol (HFIP), is useful for the coupling reaction of the thiophene iodonium salts and introduces aromatic nucleophiles to the γ positions of the iodine(III)–carbon bonds [Eq. (1)]. However, this reaction is not suitable for coupling through the *ipso* substitution of the thiophene iodonium salts **1a-X** [X = OTs, Br; Eq. (2)].



(1) Ref. [8]



(2)

To overcome this drawback, screening was undertaken to find a suitable acid additive that accelerated the reaction by activating the thiophene iodonium salt **1a** using the modified reaction conditions shown in Table 1. Among the general acids and typical silicon- and boron-based Lewis acids we examined (Table 1, entries 2–5),[9] the yield of **3aa** was significantly enhanced when TMSOTf was added (Table 1, entry 3). Similarly, a Brønsted acid (TfOH) performed as a good catalyst for the present *ipso*-substitution process (Table 1, entry 6). Other additives, such as trifluoroacetic acid and other analogous superacids (i.e. $HNTf_2$), did not improve the yield of **3aa**. The aromatic nucleophile **2a** did not react with **1a** under the reported conditions. Moreover, other general methods for activating iodonium salts with transition metals were unsuccessful.[10] Pleasingly, our method permitted the formation of the *ipso*-substitution product of the heteroaryl ring. Further optimization using TMSOTf as the acid additive[11] led to a dramatic improvement in the yield of **3aa** (74%; Table 1, entries 7 and 8). The major by-product was 2,3-dimethylthiophene after formal protonolysis.

The unique and selective *ipso* substitution at the heteroaryl ring is a general phenomenon of thienyliodonium

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Table 1: Screening of reaction accelerators,[a] see [Eq. (2)].

Entry	Additive	Yield of **3aa** [%][b]
1	none	0
2	TMSCl	21
3	TMSOTf	46
4	$BF_3 \cdot Et_2O$	32
5	$(c\text{-Hex})_2BOTf$	36
6	TfOH	40
7	TMSOTf[c]	57
8[d]	**TMSOTf**[c]	**74**

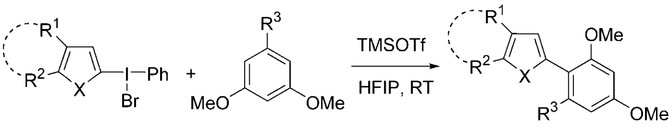
[a] Reactions were performed using **1a-Br** (1 equiv), **2a** (1.5 equiv), and an additive (1 equiv) in HFIP (0.15 M of **2a**) at room temperature in the absence of TMSBr. [b] Yield was determined by GC analysis and was based on the amount of **1a** used. [c] Used TMSOTf (2 equiv). [d] Concentration of **2a** was 0.075 M. c-Hex = cyclohexyl, Tf = trifluoromethanesulfonyl TMS = trimethylsilyl.

bromides, however, no product resulting from phenyl group transfer was observed in all cases shown in Table 2. Under the optimized reaction conditions, the derivatives of **1a** having other alkyl (Table 2, entries 2 and 3), cyclic (Table 2, entry 4), and aryl (Table 2, entry 5) groups on the thiophene rings provided the corresponding heteroaryl-containing biaryl compounds in good yields. The presence of electron-rich aromatic moieties in the iodonium salts slightly affected the yield of the cross-coupling product (Table 2, entry 6). A similar *ipso* substitution occurred in the α-free ($R^2 = H$) thienyliodonium salts **1g** and **1h** (Table 2, entries 7 and 8), and no other regioisomer of **3gb** and **3hb** (such as the 2-arylated thiophenes) were produced. Comparable results were obtained using the other salts **1i** and **1j** based on the exclusive transfer of the furan and pyrrole rings to the aromatic nucleophiles **2** (Table 2, entries 9 and 10). To the best of our knowledge, these results are the first general examples which enable the carbon–carbon bond formation between the *ipso* carbon atom of the heteroaromatic rings in the iodonium salts with unfunctionalized aromatic nucleophiles.[12]

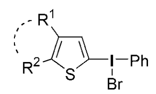
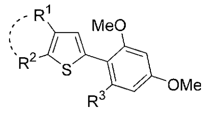
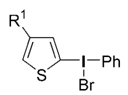
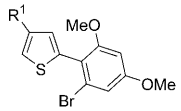
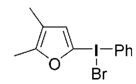
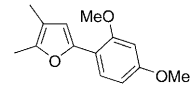
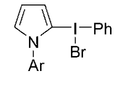
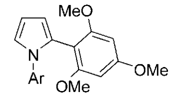
It seems that one cannot assume that the classical intermediates **A** are involved in the observed *ipso*-substitution process because this would result in transfer of the phenyl group. Indeed, we have now succeeded in confirming the SET oxidizing ability of the iodonium **1a-Br** toward electron-rich aromatic compounds (Figure 1). With the aid of TMSOTf, **1a-Br** could generate a stable radical species of 1,4-dimethoxybenzene in HFIP at room temperature; this species was detected by ESR spectroscopy. Based on UV spectroscopic measurements of the reaction solution under the optimized conditions, we concluded that the typically strong absorption band between 400 and 500 nm (the visible region) corresponds to the dimethoxybenzene cation radical **B**.[13–15] The detection of this radical species suggests the involvement of a unique SET reaction mechanism during the course of the reaction. Interestingly, no related cationic radical species were detected by ESR and UV measurements when TMSBr was added instead of TMSOTf.

The substrate **1a-Br** was itself inactive toward the aromatic compound **2a**, and the added TMSOTf played a key role for inducing the SET oxidation process. In our previous studies,[13] we found that the SET oxidation of aromatic compounds by hypervalent iodine atoms should include the preformation of the charge-transfer (CT) complex of the reagents and aromatic rings before inducing the SET. With regard to the role of TMSOTf, it seems to facilitate the initial interaction of **1a** with the aromatic nucleophile **2a**, and

Table 2: Reactions using methoxybenzenes (**2a–c**) as nucleophiles



1 (X=S,O,NAr) **2** **3**

Entry	Iodonium salt **1**	Product **3**	Yield [%][b]
			
1	**1a-Br**, $R^1 = R^2 = Me$	**3aa**, $R^3 = H$	77
2	**1b-Br**, $R^1 = Hex$, $R^2 = Me$	**3ba**, $R^3 = H$	70
3	**1c-Br**, $R^1 = Me$, $R^2 = (CH_2)_5Br$	**3ca**, $R^3 = H$	71
4	**1d-Br**, $R^1R^2 = (CH_2)_4$	**3da**, $R^3 = H$	75
5	**1e-Br**, $R^1 = p\text{-Tol}$, $R^2 = Me$	**3eb**, $R^3 = Br$	81
6	**1f-Br**, $R^1 = p\text{-MeOC}_6H_4$, $R^2 = Me$	**3fb**, $R^3 = Br$	50
			
7	**1g-Br**, $R^1 = Me$	**3gb**, $R^3 = Br$	70
8	**1h-Br**, $R^1 = c\text{-Hex}$	**3hb**, $R^3 = Br$	64
			
9	**1i-Br**	**3ia**, $R^3 = H$	66
			
10	**1j-Br**, $Ar = 4\text{-NO}_2C_6H_4$	**3jc**, $R^3 = OMe$	66

[a] Reactions were performed using **1** (0.2–0.6 mmol) and **2a–c** (3 equiv) for 3 h. [b] Yield of isolated product. Tol = tolyl.

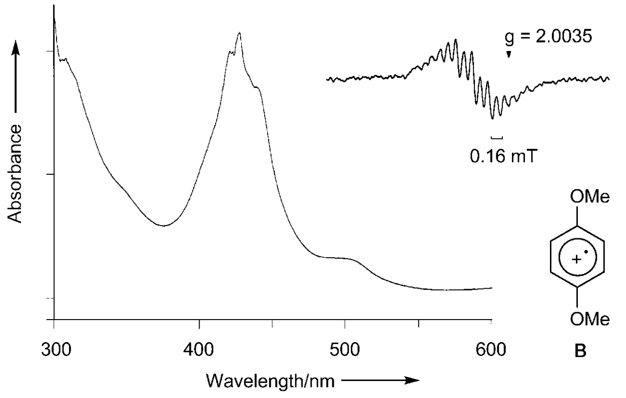
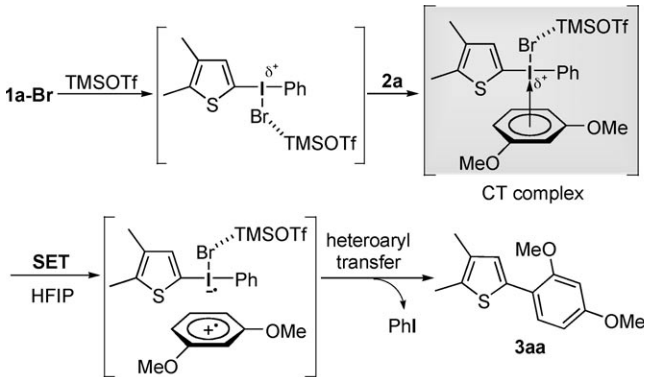


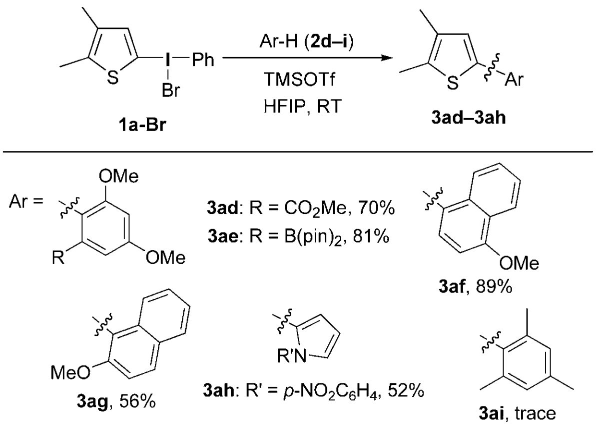
Figure 1. Detection of an aromatic cationic radical formed by SET oxidation with diaryliodonium bromide **1a**.

then forms a CT complex by enhancing the electrophilicity of the iodine atom of **1a** through coordination with the bromo atom, thus assisting in the smooth generation of the cation radicals of **2a** to which the electron-rich heteroaryl ring is transferred (Scheme 1).[16]



Scheme 1. Unique SET reaction pathway through a CT complex of diaryliodonium salt **1a** and aromatic nucleophile **2a**.

Based on the new reaction mechanism, the oxidation potential of the aromatic nucleophiles **2** should be one of the important factors in the determination of the reaction progress. Accordingly, we extended the scope of the nucleophiles **2** by evaluating other electron-rich aromatic compounds, which have oxidation potentials similar to that of dimethoxybenzene **2a** (Scheme 2). It was apparent to us that various aromatic and heteroaromatic compounds **2d**–**h**, which are sensitive to the SET oxidizing processes with hypervalent iodine reagents,[13] except for mesitylene **2i**,[17] exhibit comparable performances with acceptable functional group tolerances in the reactions with **1a** (Scheme 2). Interestingly, the carbon–boron bond was not oxidized in nucleophile **2e**. During this screening, additional strong evidence that accounts for the generation of the cationic radical species of aromatic nucleophiles **2** was also found; the reaction of the 1,2,4-trimethoxybenzene (**2j**) with **1a** resulted in the formation of a radical homocoupling product that incorporated **2j**, that is, 2,2′,4,4′,5,5′-hexamethoxybiphenyl (see the Supporting Information). The expected heteroaryl-transfer product **3aj** was also obtained.



Scheme 2. Use of various aromatic nucleophiles **2d–i** having oxidation potentials similar to that of 1,3-dimethoxybenzene **2a**. pin = pinacol.

In summary, we have discovered uncovered the SET oxidizing ability of the diaryliodonium bromides and have succeeded in carrying out the unusual, although versatile, heteroaryl transfer toward electron-rich aromatic compounds based on the SET mechanism. This new strategy includes an unprecedented formal substitution process at the *ipso* carbon atom of the heteroaryl rings in the diaryliodonium salts, thereby enabling the production of a variety of heteroaryl-containing biaryl compounds under metal-free conditions.

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optimized conditions using TMSOTf. For unique radical reactivities of I^{III}–Br bonds, see: a) T. Dohi, N. Takenaga, A. Goto, A. Maruyama, Y. Kita, *Org. Lett.* **2007**, *9*, 3129; b) T. Dohi, N. Takenaga, A. Goto, H. Fujioka, Y. Kita, *J. Org. Chem.* **2008**, *73*, 7365, and references therein.

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