Refining boron-iodane exchange to access versatile arylation reagents

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Refining boron-iodane exchange to access versatile arylation reagents

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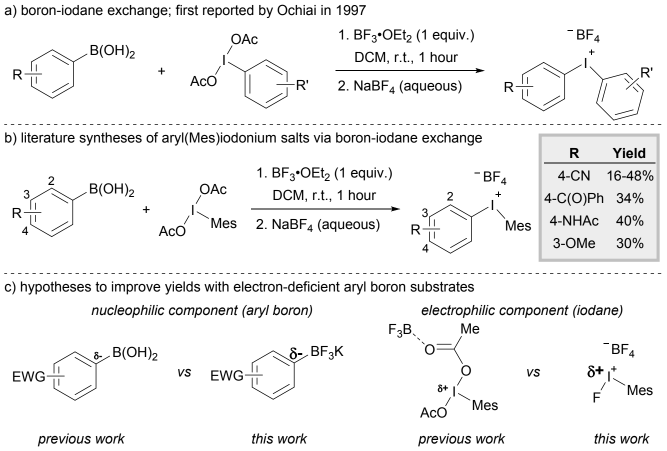
Aryl(Mes)iodonium salts, which are multifaceted aryl transfer reagents, are synthesized via boron-iodane exchange. Modification to both the nucleophilic (aryl boron) and electrophilic (mesityl-λ^3-iodane) reaction components result in improved yield and faster reaction time compared to previous conditions. Mechanistic studies reveal a pathway that is more like transmetallation than S_EAr.

Boron-iodane exchange, originally reported by Ochiai and co-workers,[1] has become a standard method to synthesize symmetrical and unsymmetrical diaryliodonium salts (Scheme 1a).[2] This includes the synthesis of aryl(Mes)iodonium[‡] salts, which are widely used as aryl transfer reagents in metal-catalyzed reactions,[3] metal-free *ipso*-substitution reactions,[4] and as aryne precursors.[5] However, low yielding boron-iodane exchange with electron-deficient arylboronic acids diminishes the impact of this strategy to aryl(Mes)iodonium salts and their eventual use as reagents (Scheme 1b).[3b,c,6] The reduced reactivity of $MesI(OAc)_2$ relative to $PhI(OAc)_2$ (PIDA) may be attributed to increased steric effects. Given our interest in these compounds as aryne precursors,[5] we have considered two distinct approaches to improve the yield of aryl(Mes)iodonium salts, especially from electron-deficient aryl boron compounds: 1) use a more nucleophilic aryl boron source and 2) generate a more electrophilic iodane *in situ* (Scheme 1c). The mechanistic insight gained from competitive Hammett correlation based on the former approach suggests that boron-iodane exchange lies closer to transmetallation than S_EAr on the spectrum of arene functionalization mechanisms.

We selected 4-nitrophenyl (**1a**) boron reagents as representative electron-deficient substrates to test our hypothesis on tuning nucleophilicity by changing the boron group (Table 1).[7] Synthesis of the corresponding aryl(Mes)iodonium salt has not been demonstrated in the literature by this pathway, and so we first tested the original Ochiai conditions. We observed a low yield under previously reported conditions with the arylboronic acid **1a**-$B(OH)_2$, which was increased slightly at longer reaction time (Table 1, entry 1 and 2). Additionally, the less nucleophilic aryl pinacolboronate **1a**-B(pin) resulted in only trace product, but the more nucleophilic **1a**-BF_3K produced **2a** in moderate yield (Table 1, entries 3 and 4).[7] Continuing with **1a**-BF_3K, a similar yield was obtained in MeCN as solvent (52%) and higher temperature increased the yield to 85% (Table 1, entries 5 and 6). Notably, DiMagno[8] and Legault[9] have used potassium aryltrifluoroborates to synthesize other unsymmetrical diaryliodonium salt with electron rich (i.e., methoxy substituted) rings, though we are not aware that this strategy has been used to address low yields with electron withdrawing substituents. Several other Lewis and protic acids were also tested as activators for $MesI(OAc)_2$ though none provided higher yield than BF_3 (Table 1, entries 7 and 8).[10] Two other important features of the conditions developed here are the



Scheme 1. Ochiai reaction to access diaryliodonium salts.

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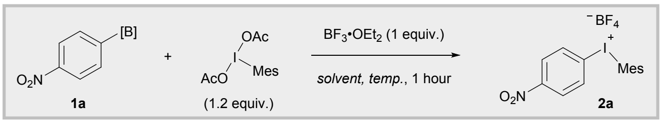
[a] *Address here.*

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Table 1. Screening of reaction conditions.[a]



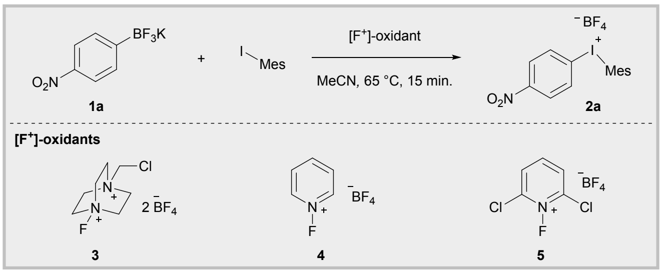
Entry	[B] group	Solvent	Temperature	Yield[b]
1	$B(OH)_2$	DCM	r.t.	11%
2	$B(OH)_2$	DCM	r.t.	21%[c]
3	B(pin)	DCM	r.t.	< 5%
4	BF_3K	DCM	r.t.	56%
5	BF_3K	MeCN	r.t.	52%
6	BF_3K	MeCN	65 °C	85% (70%)[d]
7	BF_3K	MeCN	65 °C	70%[e]
8	BF_3K	MeCN	65 °C	53%[f]

[a]Conditions: **1a** (0.1 mmol, 1 equiv.), $MesI(OAc)_2$ (0.12 mmol, 1.2 equiv.), $BF_3•OEt_2$ (0.1 mmol, 1 equiv.), MeCN (1 mL), see above for temp, 1 hour. [b]Yield determined by ^1H NMR spectroscopy with ethylene carbonate as internal standard. [c]24 hour reaction time. [d]Isolated yield. [e]TMS-OTf used instead of $BF_3•OEt_2$. [f]TfOH used instead of $BF_3•OEt_2$.

replacement of chlorinated solvent, DCM, with greener acetonitrile, and reduction of the reaction time from overnight to one hour or less.

Our hypothesis on the electrophilicity of the iodane component was inspired by Shafir's work on acid activation of phenyliodine dicarboxylates,[11] and reports by Shreeve, DiMagno, Legault, and Gilmour on the use of Selectfluor as an oxidant for aryl iodides.[8,9,12] Specifically, Shafir's work suggests significant lowering of the LUMO for cationic $[PhI(OAc)]^+$ relative to $PhI(OAc)_2•BF_3$, and Gilmour's work suggests a related fluxional acetonitrile solvated $[ArIF]^+$ species is obtained by *in situ* oxidation of ArI with Selectfluor.[11,12b] Therefore, we surveyed reaction conditions for **1a**-BF_3K with mesityl iodide and several F^+-oxidants (Table 2). Indeed, Selectfluor **3** as oxidant provided the product **2a**, though in low yield (6%, Table 2, entry 1). *N*-fluoropyridinium tetrafluoroborate **4** as oxidant did not result in any product formation, consistent with Shreeve's observations with related oxidants (Table 2, entry 2).[12a] However, *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate **5** as oxidant resulted in moderate yield of **2a** (47%, Table 2, entry 3). Given that the putative $[MesIF]^+$ is likely a highly reactive intermediate, we varied the stoichiometry of both the electrophile and nucleophile components in order to more efficiently trap it and form product **2a**. Increasing the equivalents of iodomesitylene and **5** resulted in a slight increase in yield to 61% (Table 2, entry 4). We found that increasing the equivalents of **1a** alone did not result in improved yield of **2a** (Table 2, entry 5 and 6). However, an increase in the equivalents of both **1a** and oxidant **5** resulted in high yield of **2a** (89%, 81% isolated yield, Table 2, entry 7). Consistent with our observations on the original Ochiai reaction, using **1a**-$B(OH)_2$ as the nucleophile resulted in very low yield of **2a** (Table 2, entry 8). Although the highest yield with this approach uses two equivalents of the aryl boron reagent and iodomesitylene as the limiting reagent, the reaction is complete within 15 minutes.

Table 2. Reaction screening with F^+ oxidants.[a]

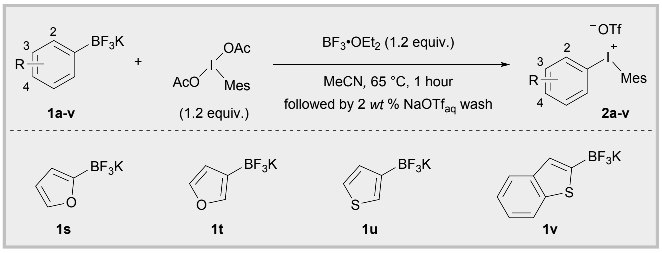


Entry	1a equiv.	Mes-I equiv.	[F+] (equiv.)	Yield[b]
1	1	1	**3** (1.2)	6%
2	1	1	**4** (1.2)	< 5%
3	1	1	**5** (1.2)	47%
4	1	2	**5** (2)	61%
5	1	1	**5** (2)	62%
6	2	1	**5** (1.2)	48%
7	2	1	**5** (2)	89% (81%)[c]
8[d]	2	1	**5** (2)	< 5%

[a]Conditions: **1a** (see Table), **Mes-I** (see Table), F^+-oxidant (see Table), MeCN (1 mL), 65 °C, 15 min, note limiting reagent = 0.1 mmol. [b]Yield determined by crude ^1H NMR spectroscopy with ethylene carbonate as internal standard, based on 0.1 mmol scale of limiting reagent (see Table). [c] Isolated yield of **2a**-OTf on 0.5 mmol scale of Mes-I. [d]Used boronic acid of **1a**.

The scope of the reaction was evaluated for the conditions developed with $MesI(OAc)_2$ because **1** is used as the limiting reagent in this case (Table 3). During our preliminary analysis of scope we found that some aryl(Mes)iodonium tetrafluoroborate salts gave very low isolated yield despite high yield based on crude ^1H NMR spectroscopy. Further analysis revealed that these salts are partially water soluble which was confirmed by low recovery from a liquid-liquid extraction between water and DCM.[13] However, although the aryl(Mes)iodonium tetrafluoroborate salts may be obtained directly without the need for aqueous $NaBF_4$ as described in the original Ochiai reaction, we found that omitting an aqueous extraction resulted in low purity of product. That is, artificially high yield of product was obtained due to inorganic impurities that were invisible by standard analytical characterization techniques (NMR, HRMS) and was only identified when product purity was determined by QNMR. We found that washing the reactions with NaOTf resulted in better recovery and generally higher isolated yields *and* high purity of product (~ 95%). We primarily evaluated the scope with electron-deficient substrates **1**, though several electron-rich substrates and heterocycles were also included (Table 3). In line with our goal, improved yield of aryl(Mes)iodonium salts **2** were achieved in almost all cases where comparison to previous literature yield is possible.[14] For instance, substrates **1b**,**c**,**e**,**g**-**j**,**n**-**p**, which contain electron-withdrawing substituents, lead to formation of the corresponding products **2** in yields ranging from 42-80% yield (62% avg.; Table 3). Conversely, these same products were obtained previously in yields ranging from 16-64% (41% avg; Table 3). In three cases, **1b**,**j**,**n** the yields obtained here and previously are similar (i.e., within 3%), though in many of the

Table 3. Evaluation of scope.[a]

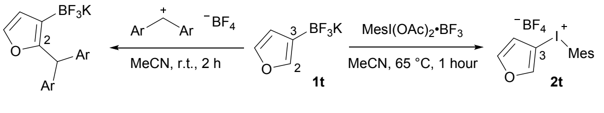


Entry	R-group on **1**	Yield of **2**[b] (NMR)[c]	Purity[d]	Lit yield
1	**1a** (4-NO_2)	70% (85%)	95%	
2	**1b** (4-CN)	42% (82%)	99%	16-44%[3b,6]
3	**1c** (4-SO_2Me)	65% (85%)	93%	35%[3b]
4	**1d** (4-CF_3)	65% (82%)	98%	
5	**1e** (4-CO_2Me)[e]	80% (99%)	99%	64%[4g]
6	**1f** (4-CO_2Bn)	76% (93%)	92%	
7	**1g** (4-Bz)	44% (75%)	99%	30%[3b]
8	**1h** (4-OCF_3)	76% (88%)	99%	33%[4g]
9	**1i** (4-NHAc)	64% (88%)	95%	40%[3d]
10	**1j** (4-Cl)	48% (97%)	91%	45%[3b]
11	**1k** (4-OMe)	89% (98%)	94%	70-85%[3a,b,f,6]
12	**1l** (4-Me)[x]	80% (97%)	99%	70%[3f]
13	**1m** (4-*i*-Bu)	68% (83%)	99%	
14	**1n** (3-CHO)	60% (96%)	94%	57-63%[3d,e]
15	**1o** (3-CO_2Me)	66% (92%)	96%	35%[3b]
16	**1p** (3-OMe)	60% (84%)	99%	30%[3b]
17	**1q** (3-Cl-4-OMe)	53% (84%)	99%	
18	**1r** (R = H)	92% (99%)	97%	64-99%[3b,g,6]
19	**1s**	59% (87%)	93%	
20	**1t**	77% (93%)	98%	90%[3g]
21	**1u**	60% (79%)	96%	68-84%[3c]
22	**1v**	69% (78%)	99%	

[a]Conditions: **1** (0.5 mmol, 1 equiv.), MesI$(OAc)_2$ (0.6 mmol, 1.2 equiv.), BF_3•OEt_2 (0.6 mmol, 1.2 equiv.), MeCN (5 mL), 65 °C, 1 hour. [b]Isolated yield of triflate salt. [c]Yield of tetrafluoroborate salt determined by crude ^1H NMR spectroscopy vs ethylene carbonate as internal standard (on 0.1 mmol scale of **1**). [d]Purity of isolated material determined by QNMR with ethylene carbonate as internal standard. [e]Isolated as BF_4 salt.

other cases the improvement in yield is much greater (14-43% increase; Table 3). This approach also works for **1** with electron-rich substituents, **1k**-**m**,**q**,**r** and heterocyclic substrates **1s**-**v**. Finally, based on QNMR, all products were obtained in high purity (91-99%, 96% avg; Table 3). A limitation of this work, which remains a limitation of other boron-iodane exchange reactions, is that potassium pyridyl trifluoroborate salts resulted in complex mixtures and product could not be isolated.

Aryl boron compounds have been used extensively in both metal-free and metal-catalysed transformations, and their wide availability is an attractive feature. Irrespective of the reaction partner, substitution occurs almost exclusively at the ipso position.[15] However, Knochel and Mayr have discovered that the trifluoroborate group activates remote positions to attack carbocations in some potassium heteroaromatic trifluoroborates.[16] For example, **1t**, which has a trifluoroborate group at the 3-position, reacts as π-nucleophile with benzhydrylium ion at the 2-position (Equ. 1, left).[16] On the other hand, **1t** reacts with iodane electrophile derived from MesI$(OAc)_2$ and BF_3 at the ipso 3-position (Equ. 1, right). These results point toward the possibility of different mechanisms for reaction of **1t** with carbon and iodine derived electrophiles, where in the latter is less reliant on the furan π-system. We further probed the relationship between substituent effects and the reaction mechanism by a one-pot competitive Hammett correlation. Specifically, competition experiments between compounds **1j**-**m** bearing *para*-substituents and unsubstituted **1r** were conducted and the ratio of products **2j**-**m**/**2r** measured by crude ^1H NMR spectroscopy. A negative slope was observed consistent with a faster reaction rate for substrates with electron-donating substituents (i.e., OMe, Me, *i*-Bu) and a slower rate for substrates with electron-withdrawing substituents (i.e., Cl) relative to unsubstituted **1r** (Figure 1). The magnitude of the slope (ρ-value) can also be used to infer the sensitivity of the reaction mechanism to substituent effects and the degree of positive charge build up in the transition state. The ρ-value obtained in this work is -3.4. For comparison, the ρ-values obtained for bromination of simple arenes is -11.4,[17] bromination of arylboronic acids is -4.6,[17] C-H functionalization by Rh,[18] Ir,[18] and Ru[19] are -2.3, -2.7, and -2.4, respectively, and boron-palladium transmetallation is -0.5.[20] At the two extremes of these examples are electrophilic aromatic substitution (S_EAr) and transmetallation which are likely connected by a spectrum of mechanisms that resemble each of these. S_EAr involves breaking of the aromatic π-system and a positively charged Wheland intermediate which aligns with the large negative ρ-value (-11.4),[17] whereas transmetallation involves a σ-bond metathesis with very little positive charge build up on the aromatic ring manifested by a very small negative ρ-value (-0.5).[20] Intermediate between these extremes, though closer to transmetallation, are reactions of arylboron compounds with non-metal electrophiles such as bromine[17] and iodine, as well



(Equ. 1)

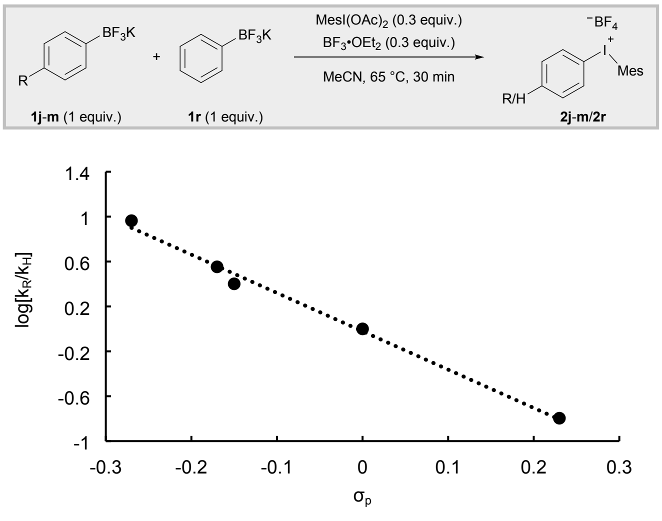


Figure 1. Competitive Hammett correlation.

as C-H functionalization reaction by metal complexes of Rh, Ir, and Ru.[18,19] The C-H functionalization reactions have been proposed to proceed through a σ-bond metathesis-type transition state involving concerted metalation-deprotonation (CMD), which does not involve breaking the aromatic π-system.[18,19] Given the similar value obtained in this work (-3.4) to those obtained for a variety of concerted reactions, we propose that boron-iodane exchange likely proceeds through a mechanism that appears closer to transmetallation than S_EAr.

In conclusion, we have analysed the nucleophilic and electrophilic components of boron-iodane exchange to synthesize aryl(Mes)iodonium salts and significantly improved the yields, especially for electron-deficient substrates. Mechanistic analysis via Hammett correlation suggests a σ-bond metathesis type pathway with relatively little involvement of the aromatic π-system. We plan to use this approach in strategic applications of aryl(Mes)iodonium salts in synthesis.

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Author Contributions

SSK and DRS conceptualized the project. SSK developed the methods and conducted the experiments. SSK and DRS analysed the experimental results. SSK assembled the supplementary information. DRS wrote the manuscript with input from SSK.

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‡ Mes = 2,4,6-trimethylphenyl

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