Article

An Admix Approach to Determine Counter Anion Effects on Metal-Free Arylation Reactions with Diaryliodonium Salts

Thomas L. Seidl, and David Ross Stuart

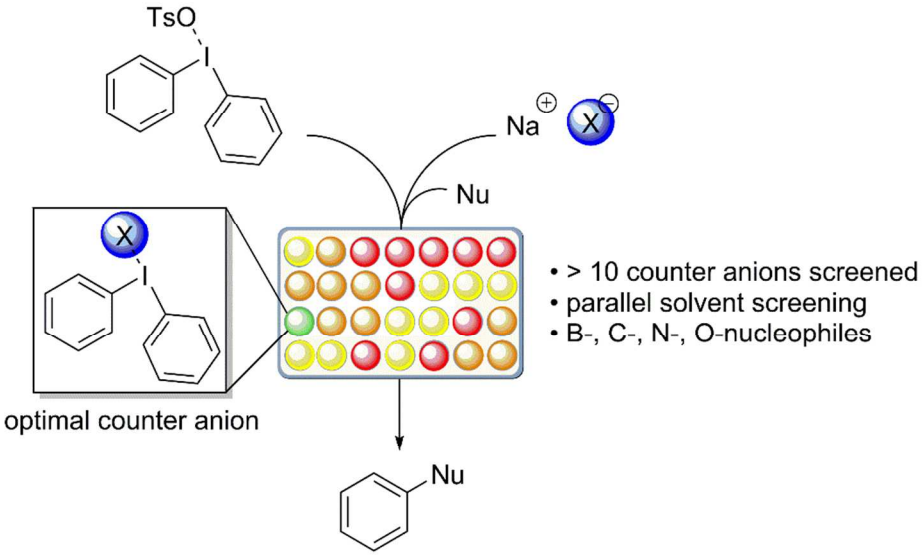
J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b01599 • Publication Date (Web): 11 Aug 2017

An Admix Approach to Determine Counter Anion Effects on Metal-Free Arylation Reactions with Diaryliodonium Salts

Thomas L. Seidl and David R. Stuart*

Department of Chemistry, Portland State University, Portland Oregon 97201, United States

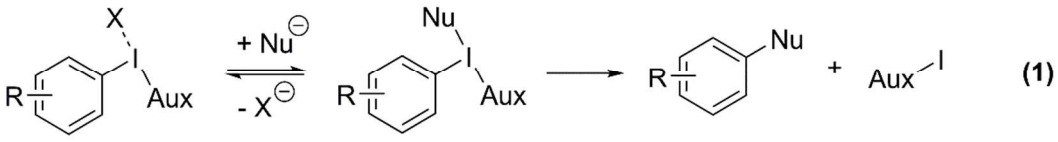
dstuart@pdx.edu



Abstract: A method to determine the effect of counter anions in metal-free arylation reactions of diaryliodonium salts is described. This approach avoids the independent synthesis of individual diaryliodonium salts and potentially enables assessment of a large number of different counter anions, including those that are synthetically challenging to install. Diaryliodonium tosylate salts serve as a general precursor for this approach and an azide arylation reaction was used to develop this strategy. Further optimization and representative scope of azide arylation is demonstrated in yields that range from 74 – 95% (89% average). The use of this method as a screening tool has also been validated with arylation reactions of three different nucleophiles employing diphenyliodonium tosylate.

Introduction

Reaction screening methods that reduce both time and material toward discovery are enabling tools for development of new chemical reactions[1] and synthesis of complex-molecule libraries.[2] Empirical screening[3] is a common and effective approach entrenched within organic synthesis and is particularly important when mechanistic understanding of a reaction variable is limited (e.g., solvent). However, synthesis of the reaction variable of interest is a major practical hurdle to empirical screening and admixing primary components is an attractive approach to circumvent synthesis. While admixing is common place for catalyst screening (metal salt and ligand),[1a-c,j,p-r] it is rarely applied to screening potential reagents. Diaryliodonium salts are novel arylation reagents and undergo reaction with a range of carbon and heteroatom nucleophiles under metal-free conditions.[4] The counter anion of these salts is reversibly displaced by nucleophiles and often exerts a dramatic influence on reactivity; as such, it is a critical variable for screening in reaction discovery and development efforts (eq 1). The optimal counter anion, though, is typically determined by heuristic methods and the need to synthesize individual salts for screening limits, in practice, the range of counter anions typically analyzed. The development of a screening method that avoids the practical obstacle of salt synthesis by admixing primary components (diaryliodonium and target anion) would facilitate a more thorough investigation of the counter anion contribution in reactions of diaryliodonium salts. Herein, we describe the development, validation, and application of a convenient approach for such a screening protocol.

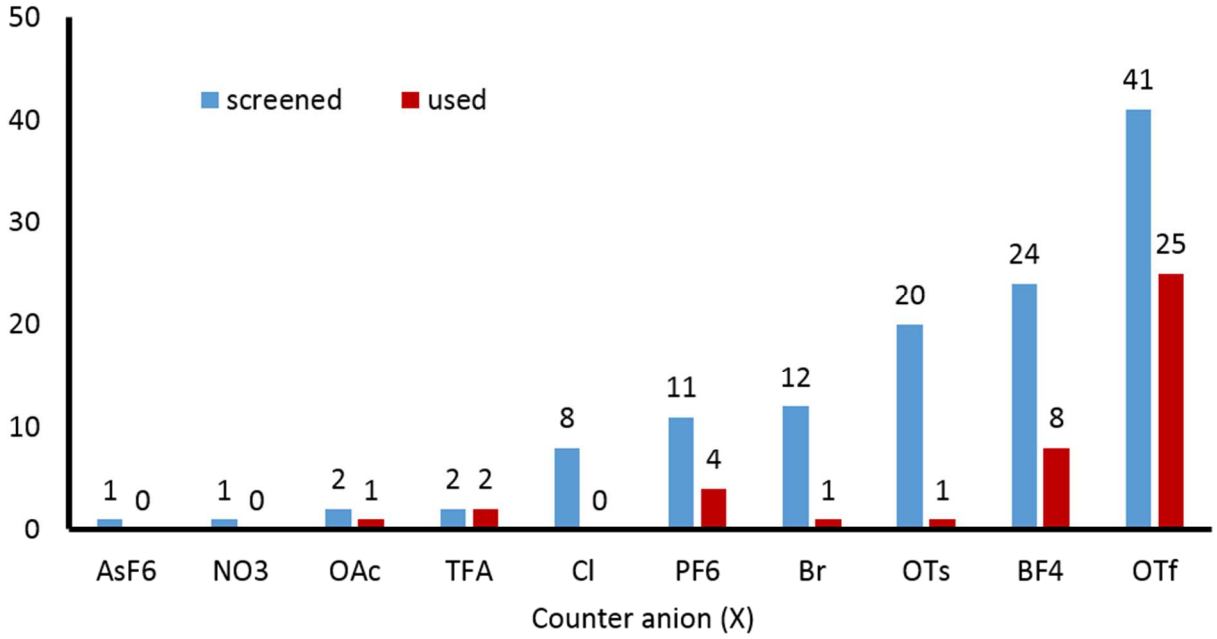


(1)

Results and Discussion

We have analyzed 42 representative metal-free arylation reactions with diaryliodonium salts published between 2011 and 2016 (Figure 1).[5] In total, ten different counter anions were screened within these reports and seven different counter anions were evaluated as "optimal" for the given reaction, which corroborates the breadth of reactivity observed to result from counter anions. The three most commonly screened counter anions in these reports were triflate ($^{-}$OTf), tetrafluoroborate ($^{-}BF_4$), and tosylate ($^{-}$OTs), and we surmise that this is a direct result of well-established methods to access these diaryliodonium salts.[6,7,8] Interestingly, 11 of the literature reports did not describe counter anion screening studies and simply used diaryliodonium triflates as the arylation reagent. On the other hand, our analysis found that between two and five counter anions were typically screened in the majority of these reports with three counter anions being the average and median. Given the importance of counter anion screening indicated by this analysis but the relatively small number of anions assessed (typically three) in reaction development studies we sought to develop an efficient method to elucidate counter anion effects and thereby address this disparity. Here, we demonstrate that the effect of 13 different counter anions may be determined by combination of their sodium salts with a diaryliodonium tosylate in a nucleophile arylation reaction.[9] The minimal synthetic effort required by this approach facilitates multi-dimensional screening with other variables that are amenable to high throughput screening. We have coupled this approach with elucidating potential solvent and aryl group electronic effects on reaction outcome. Additionally, while we have utilized aryl-azide coupling[8e,9,10,11] as a platform for development, we have also recapitulated literature results of counter anion screening studies in *B*-, *O*-, and *C*-arylation reactions with diphenyliodonium tosylate.

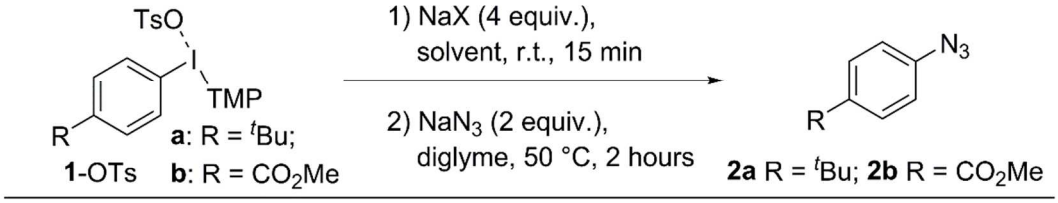
Figure 1. Frequency of counter anions screened in reaction development studies for arylation with diaryliodonium salts.



This approach is supported by our recent finding that unsymmetrical aryl(auxiliary)iodonium tosylate salts readily exchange anions with an excess of NaX (X = Br^-, I^-, TFA^-, ^-OTF, $^-PF_6$, and $^-BF_4$) salts under aqueous conditions when the auxiliary is 2,4,6-trimethoxyphenyl (TMP).[8e] We hypothesized that this facile exchange may be leveraged as an *in situ* technique under non-aqueous conditions to determine the effect of counter anions without having to synthesize each iodonium salt and we envisioned that this may lead to a wider range of anions routinely analyzed. Our approach consists of admixing an appropriate aryl(TMP)iodonium tosylate with NaX for 15 minutes at room temperature prior to addition of the nucleophile and adjustment of the reaction temperature (Scheme 1). In this way, we have analyzed 13 different anions: F^-, Cl^-, Br^-, TFA^-, TCA^- (trichloroacetate), ^-OAc, ^-OTf, TCM^- (trichloromesylate), ^-OMs, ^-OTs, $^-BF_4$, $^-PF_6$, and $^-SbF_6$; and we prepared and used two

electronically different aryl(TMP)iodonium tosylates **1a**-OTs and **1b**-OTs. Aryl azidation[8e,9,10,11] with NaN_3 as nucleophile was used to establish the feasibility for this approach in diglyme, which emerged from an initial solvent screen (Scheme 1).[12] The results in Scheme 1 confirm the success of this approach because they demonstrate a clear counter anion effect; a positive and negative effect relative to tosylate is observed for **1a**-OTs and a negative effect observed for **1b**-OTs. Selection of the optimal counter anion *a priori* is not currently possible and the results from Scheme 1 illustrate that this approach provides insight into which anions are problematic and which ones are worth pursuing further. The results also show several interesting effects of the counter anion and its confluence with the electronic effects of the aryl substituent to impact the yield of **2a** and **2b** (Scheme 1). First, the addition of NaX to these reactions has a wide-ranging influence on reaction yield (min of 0%; max of 70%). Second, as expected, higher yields are obtained with **1b** bearing an electron deficient aryl group relative to **1a** with an electron-rich aryl group; this is consistent across the majority of counter anions screened. Additionally, in general there was a larger variation in yield across the counter anions for reactions of **1a** than for **1b**; that is, there was a larger "counter anion effect" for **1a**. Third, and perhaps most intriguing, is that five anions emerged from this study to provide similar yields with electron-rich **1a** and electron-deficient **1b**. Fluoride, chloride, acetate, mesylate, and tosylate stood out in this regard and suggest that these less commonly used counter anions may provide a general advantage over more commonly used anions (OTf, BF_4) in the solvents tested. This strategy also provides a means to analyse the effect of counter anions that are difficult to install on diaryliodonium salts.[13] For instance, we were unable to obtain pure acetate or fluoride salts **1a**-OAc and **1a**-F, but found that addition of these anions as sodium acetate and sodium fluoride to **1a**-OTs, led to a small but positive counter anion effect.

Scheme 1. Counter anion screening by admixing aryl(TMP)iodonium tosylate and NaX in a metal-free aryl-azide coupling reaction.[a]



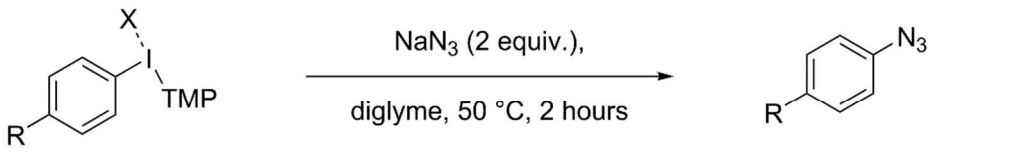
X =	F⁻	Cl⁻	Br⁻	TFA⁻	TCA⁻	AcO⁻	TfO⁻	TCM⁻	MsO⁻	⁻BF₄	⁻PF₆	⁻SbF₆	TsO⁻
1a-OTs	(60%)	(48%)	(0%)	(11%)	(0%)	(54%)	(10%)	(17%)	(59%)	(18%)	(6%)	(6%)	(42%)
1b-OTs	(64%)	(58%)	(16%)	(62%)	(25%)	(60%)	(58%)	(51%)	(44%)	(63%)	(60%)	(44%)	(70%)

[a]*Conditions*: **1**-OTs (0.1 mmol, 1 equiv.), NaX (0.4 mmol, 4 equiv.), solvent (1 mL), r.t., 15 min; NaN_3 (0.2 mmol, 2 equiv.), 50 °C, 2 hours. [b]Yield determined by GCMS vs bromomesitylene as an internal standard. TFA^- = trfluoroacetate, TCA^- = trichloroacetate, TCM^- = trichloromesylate

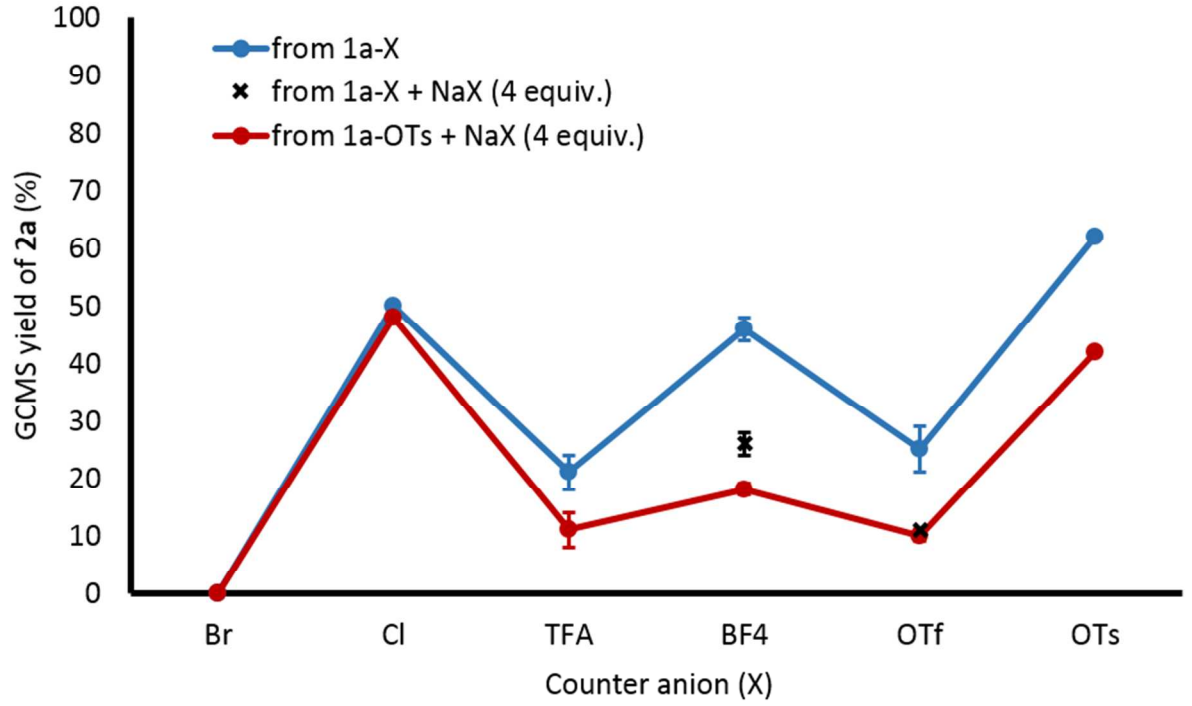
In order to probe our hypothesis that *in situ* anion exchange occurs when diaryliodonium tosylates and sodium salts of potential counter anions are admixed, we directly compared the yields of our screening protocol (**1a**-OTs + NaX and **1b**-OTs + NaX) with those obtained from pre-exchanged salts (**1a**-X and **1b**-X; Scheme 2).[14] We selected counter anions that led to a range of yields and those that led to both similar and disparate yields of **2a** and **2b** for the same counter anion (i.e., Cl^- and TFA^-, respectively). Overall, similar trends in yield were observed when with pre-exchanged salts (blue lines and circles, Scheme 2) and the admix approach (red lines and circles, Scheme 2) were used, and several examples highlight this point. First, when the screening experiment indicated a universally low yield (< 20%) of **2a** and **2b** (such as **1a**-OTs and **1b**-OTs with NaBr) the yield from the pre-exchanged exchanged salts (**1a**-Br and **1b**-Br) was also low.[15] Second, when the screening experiment indicated a moderate yield (~ 50%) of both **2a** and **2b** (such as **1a**-OTs and **1b**-OTs + NaCl) the yield from the pre-exchanged salt (**1a**-Cl and **1b**-Cl) was similar. Third, the yields obtained for **2a** and **2b** in the screening

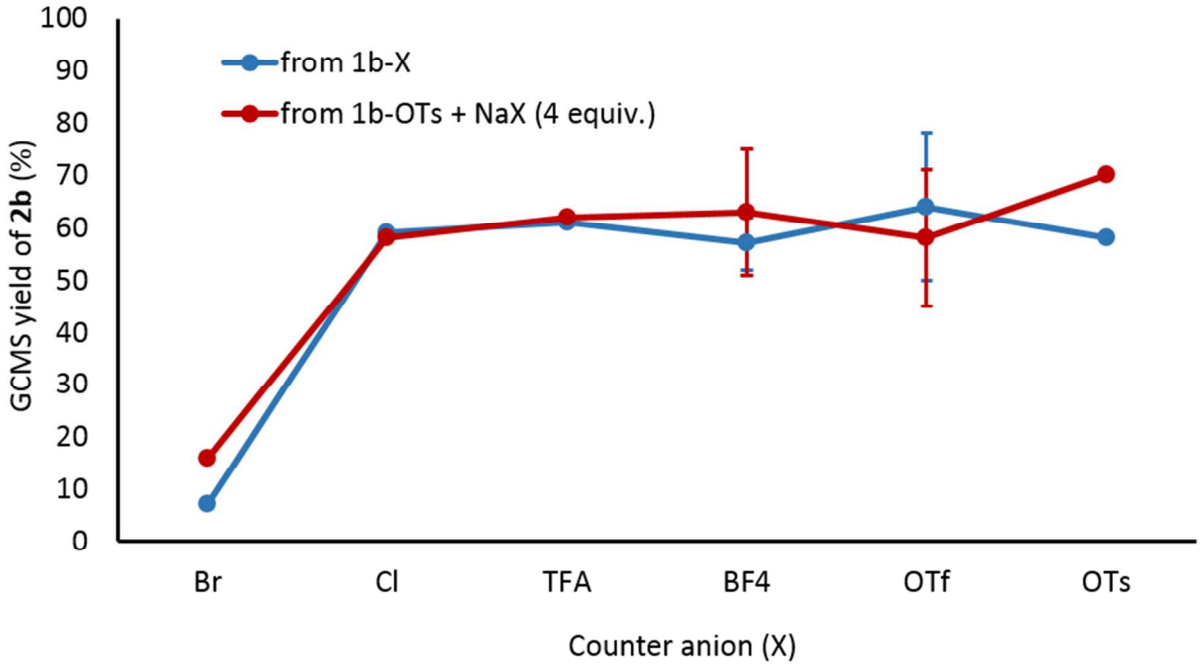
experiment with NaTFA as the additive were 11 and 61%, respectively. This difference in yield for **2a** and **2b** was also observed when the pre-exchanged salts **1a**-TFA and **1b**-TFA were used (Scheme 2). The results with $^{-}BF_4$, ^{-}OTf, and ^{-}OTs as the counter anions and their effect on the yields of **2a** and **2b** with pre-exchanged salts and with admixing warrants further discussion. While the yields of **2b** were uniformly high and similar for pre-exchanged (**1b**-X) and admixed (**1b**-OTs + NaX) salts, there were distinct differences in yields of **2a** for the **1a** series of salts (Scheme 2). An important difference between the admixing experiment and that with the pre-exchanged salts is a four-fold excess of the common ion X^- (from NaX). We assessed the effect of added $NaBF_4$ and NaOTf on reactions of **1a**-BF_4 and **1b**-OTf (black **×**, Scheme 2), respectively, and found that the yield was depressed to the same extent as the admixing reaction when excess NaX was added to **1a**-OTs; this may suggest a common-ion effect influencing the equilibrium in eq. 1.[16] Indeed we have found that when the ratio of total azide: total tosylate is varied the yield of **2a** increases dramatically with ratios greater than 1 and decreases with fractional ratios.[17] The observed trends from Scheme 2 with regard to the yields of **2a** support an anion exchange, but also suggest that due to the excess NaX required for the admixing protocol, follow-up experiments on the top two or three counter anions are strongly suggested for further optimization studies.

Scheme 2. Comparison of pre-exchanged diaryliodonium salts (1a-X and 1b-X, blue) with diaryliodonium tosylates (1a-OTs and 1b-OTs) doped with NaX (red).



1a R = ^{t}Bu; **1b** R = CO_2Me **2a** R = ^{t}Bu; **2b** R = CO_2Me

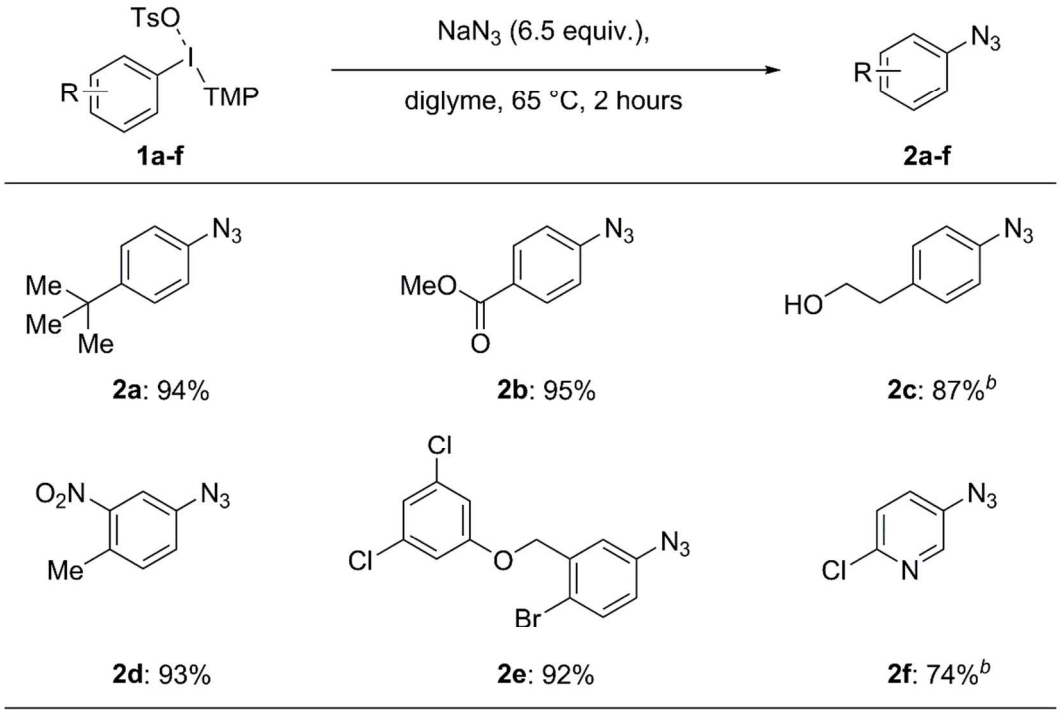




These studies formed the basis of a high-yielding and metal-free aryl-azide coupling reaction (Scheme 4). Aryl azides are often prepared by metal-based methods[10] and very few

methods employing diaryliodonium salts have been reported.[9,11] However, aryl azides represent attractive motifs because they are useful as moieties for bioconjugation,[18] photoaffinity labels,[19] and general precursors to other nitrogen-based functional groups.[20] Based on our initial lead from the counter anion screening experiment (Scheme 1) and the studies with pre-exchanged salts (Scheme 2), we explored the influence of several variables to further optimize the yield of aryl azide products **2** with **1**-OTs salts. The influence of the reaction temperature and stoichiometry of added sodium azide were explored as key variables. We used a full-factorial screening design at two levels to assess the main effects and interaction effects of these variables. In this way the experimental space spanned 1 – 8 equivalents of sodium azide and 25 – 90 °C reaction temperature. All four combinations of the boundaries of the experimental space were investigated as well as multiple runs of a center point (4.5 equivalents of sodium azide and 57.5 °C) to assess reproducibility of the yield. The results of these experiments revealed that temperature had a larger influence on yield of **2a** than the stoichiometry of sodium azide. A response surface on the temperature-azide stoichiometry plane is included in the ESI and shows an increasing yield with both higher temperature and azide equivalents.[17] The optimal conditions (> 90% yield) selected included 6.5 equivalents of sodium azide in diglyme at 65 °C for 2 hours. A representative scope of substrates is presented in Scheme 3 that highlights the utility of this reaction. Both electron-rich and deficient aryl groups undergo coupling in high yield (Scheme 3, **2a** and **2b**, respectively). Free hydroxyl groups are tolerated under the reaction conditions (Scheme 3, **2c**). Finally, the coupling of elaborate aryl groups that warrant the use of an unsymmetrical aryl(auxiliary)iodonium salt are well tolerated (Scheme 3, **2d** and **2e**) as are heterocyclic pyridyl groups (Scheme 3, **2f**).

Scheme 3. Representative scope of aryl azide compounds synthesized.[a]

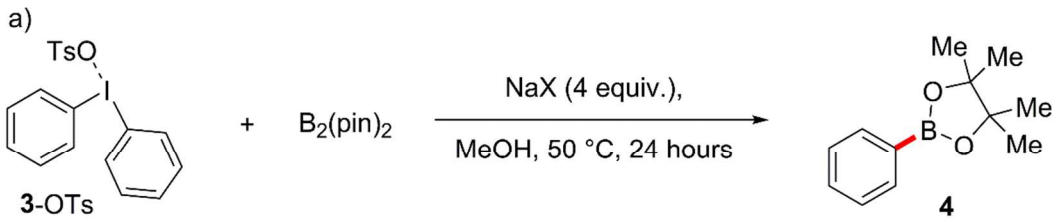


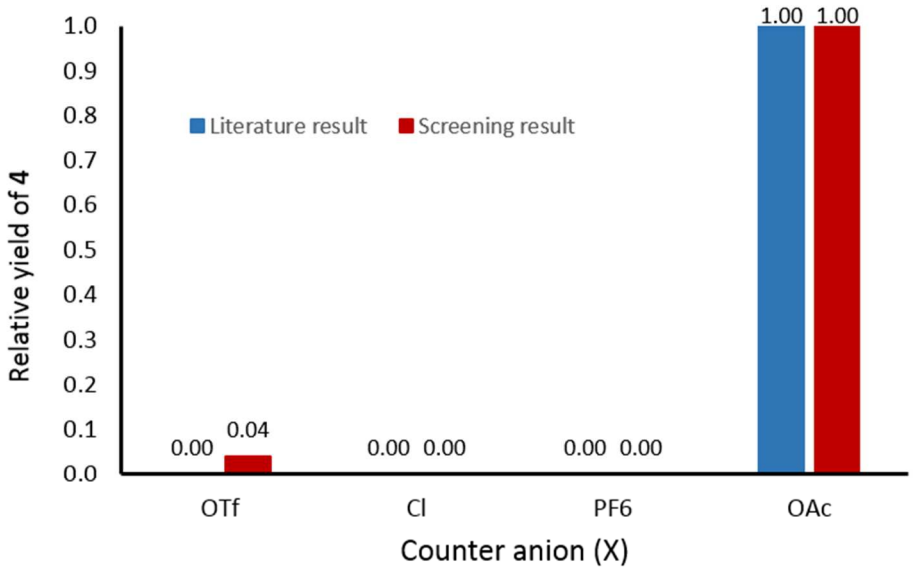
[a]Conditions: 1-OTs (0.1-0.5 mmol, 1 equiv.), NaN_3 (0.65-3.25 mmol, 6.5 equiv.), diglyme (1-5 mL), 65 °C, 2 hours. [b]Reaction performed in acetonitrile as solvent.

We have validated this strategy beyond the reaction of aryl(TMP)iodonium salt electrophiles and azide nucleophiles. Reaction discovery and development with iodonium salts is often conducted with diphenyliodonium **3** and we have applied our admix approach as an anion screening method to several previously reported reactions. We used **3**-OTs as electrophile with three different nucleophiles (*B*-, *C*-, and *O*-nucleophiles), that were reported in three different solvents (MeOH, DMF, and toluene), and where three different counter anions proved to be optimal ($^-$OAc, $^-PF_6$, and $^-BF_4$). In each case, our screening method recapitulated the literature results of counter anion screening with pre-exchanged salts (Scheme 4). A recent example of *C*-*B* bond formation reported Muñiz and co-workers features anion activation of $B_2(pin)_2$ as a means to a nucleophilic boron reagent.[13b] The counter anion effect reported by Muñiz was dramatic in which acetate acts as an “on-switch” for the reaction; no conversion was

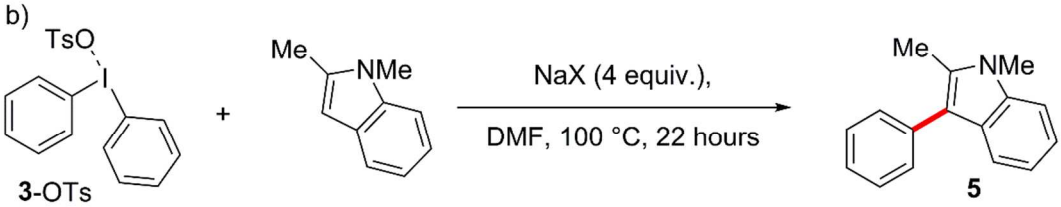
reported for $^{-}$OTf, Cl^{-}, or $^{-}PF_6$ counter anions tested (Scheme 4a). We observed a similar effect when **3**-OTs was used and NaOTf, NaCl, $NaPF_6$, and NaOAc were admixed in MeOH prior to addition of $B_2(pin)_2$. Given our previous observation that $^{-}$OTs/$^{-}$OAc exchange may not be operative, this result indicates that a counter anion effect may still be probed by this method and is particularly relevant for difficult to prepare diaryliodonium salts. Ackermann and co-workers have reported the metal-free arylation of indoles with diphenyliodonium salts in DMF.[21] Six counter anions were screened in the original report, and all except bromide provided high-yield of product **5** (Scheme 4b). We have used **3**-OTs to screen the same six counter anions and the results show that similar yields are obtained (Scheme 4b). Specifically, addition of TFA^{-} and $^{-}PF_6$ improve the yield relative to $^{-}$OTs alone whereas addition of $^{-}BF_4$ and $^{-}$OTf lead to similar yields as $^{-}$OTs and addition of Br^{-} results in no product **5** detected by GCMS. Third, we explored the *C*-*O* coupling reaction of **3**-OTs with benzoic acid/KO^{t}Bu in toluene at 100 °C that has been reported by Olofsson and co-workers (Scheme 4c).[22] In the original work, Br^{-}, $^{-}$OTf, $^{-}$OTs, and $^{-}BF_4$ were screened with $^{-}BF_4$ providing the highest yield of product. Notably, like the original report, the use of Br^{-} does provide a low, but measurable, yield of product **6**. We have obtained similar results with Br^{-}, $^{-}$OTs, and $^{-}BF_4$. However, the relative yield of **6** that we obtained from our screening experiment with $^{-}$OTf was significantly lower than Olofsson's result and may point to the common ion effect of $^{-}$OTf in this case as well; the common ion effect may also have a nucleophile dependence.

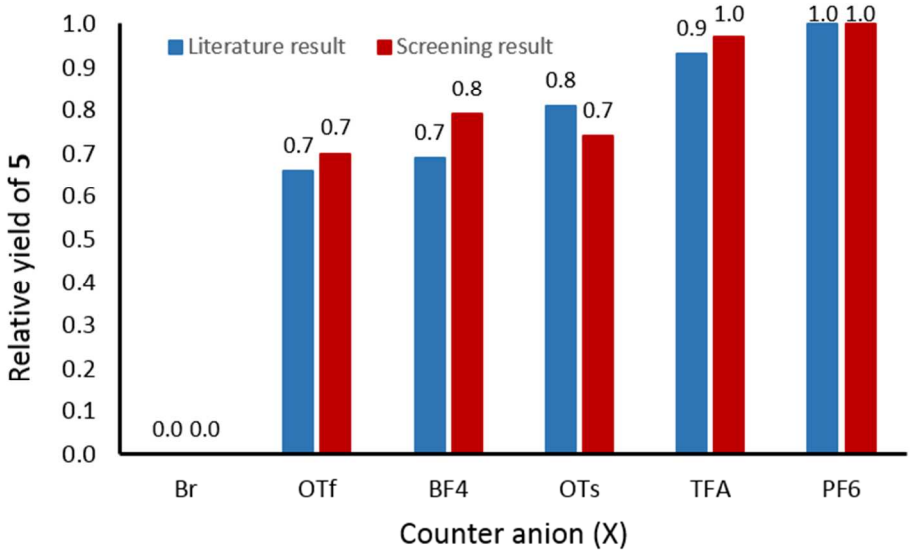
Scheme 4. Comparison of relative yields for literature (blue) and screening (red) result in a) *C*-*B* bond formation; b) *C*-*C* bond formation; c) *C*-*O* bond formation.

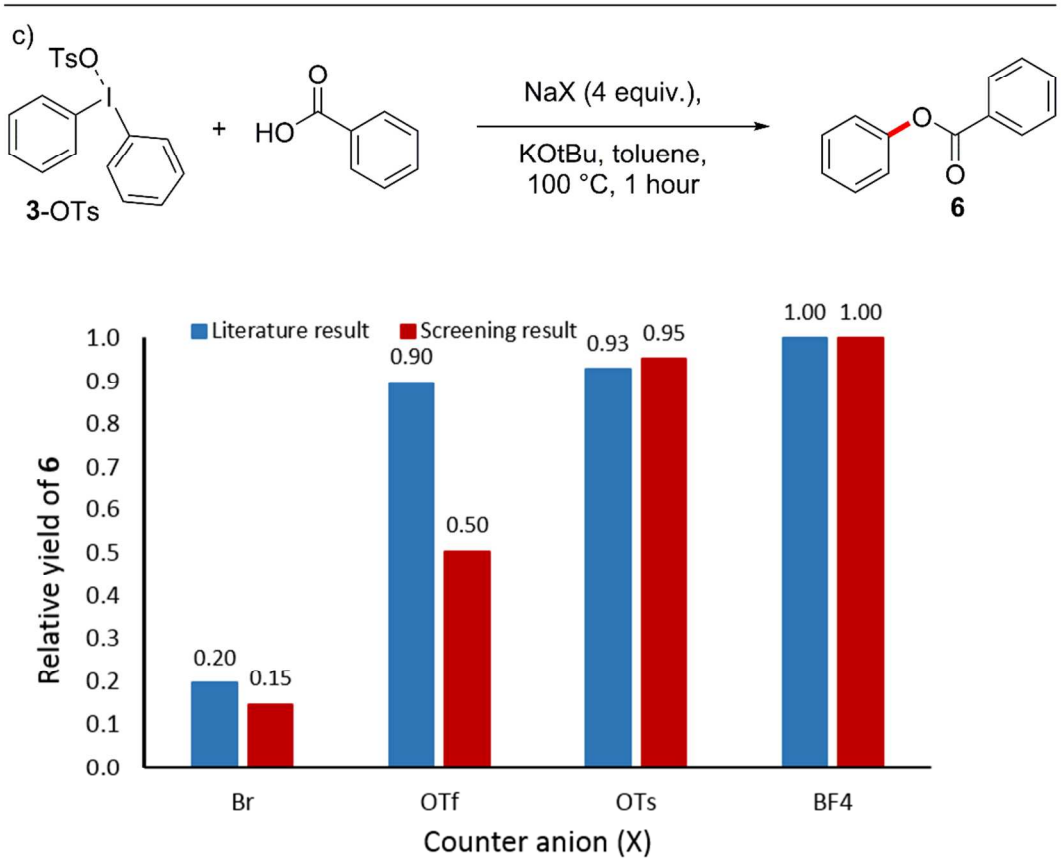



Relative yield of 4
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Literature result
Screening result
0.00
0.04
0.00
0.00
0.00
0.00
1.00
1.00
OTf
Cl
PF6
OAc
Counter anion (X)

b)


TsO
I
3-OTs
+
Me
NMe
NaX (4 equiv.),
DMF, 100 °C, 22 hours
Me
NMe
5


Relative yield of 5
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Literature result
Screening result
0.0
0.0
0.7
0.7
0.7
0.8
0.8
0.7
0.9
1.0
1.0
1.0
Br
OTf
BF4
OTs
TFA
PF6
Counter anion (X)



Conclusion

We have described a straightforward and practical method to efficiently assess the effect of counter anions in metal-free arylation reactions by admixing diaryliodonium tosylate with sodium salts of target anions. This method permits screening a wide variety of counter anions including those that are challenging to install in diaryliodonium salts (i.e., acetate and fluoride). We are continue to explore the extent to which *in situ* anion exchange occurs for different anions by NMR spectroscopy. A by-product of the development of this strategy was a high-yielding method to synthesize aryl azides, which are useful moieties in diverse science disciplines. The method was also validated on several literature examples that include *C*-*B*, *C*-*C*, and *C*-*O* coupling reactions. In a broader sense, the demonstration of this approach may engender related studies of other salt reagents wherein either anion or cation may be screened by admixing, such as reactions of aryl diazo compounds and organotrifluoroborates.

Experimental Section

General Considerations. Commercially available reagents and solvents were used without further purification unless otherwise stated. Compounds **1a**-**f**-OTs,[8e] **1a,b**-TFA,[23] and **3**[8b] were prepared by literature procedures. All other materials were prepared as described in detail below. Crude reaction mixtures were analyzed by ^{1}H NMR spectroscopy, gas chromatography mass spectrometry (GCMS), and thin-layer chromatography (TLC). Crude materials were purified by flash column chromatography on silica gel unless otherwise stated. ^{1}H, ^{13}C{^{1}H} , and ^{19}F{^{1}H} NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 (referenced to tetramethylsilane) on a 400 or 600 MHz spectrometer at 298 K unless otherwise stated. The following notation is used: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets. FTIR spectra were recorded as solutions in DCM or $CDCl_3$. High resolution mass spectrometry (HRMS) data was obtained by electrospray ionization (ESI) with an ion trap mass analyzer or electron impact (EI, 70 eV). Melting points are reported as uncorrected.

General procedure for anion exchange from aryl(TMP)iodonium tosylates (A).[8e] Aryl(TMP)iodonium tosylate (~ 1 g, 1 equiv) is added to 50 mL boiling water. If the iodonium salt does not dissolve after boiling for 1-2 minutes, then methanol is added in small portions until the material is dissolved. While still hot, a salt containing the target anion is added in excess. The exact amount required depends on the exchange salt and the iodonium salt and an excess of 10 or more equivalents is recommended. The resulting solution is allowed to naturally cool to ambient temperature, before chilling further in an ice-bath. The precipitate is isolated by suction filtration and the filter cake washed by slurry filtration with water (3 x 30 mL). The cake is dried under suction for 10 – 20 min and then washed by slurry filtration with ethyl ether (3 x 30 mL). The sample is finally dried under high vacuum to remove residual solvent. If product is

suspected in the aqueous wash then it may be recovered by extraction with dichloromethane or ethyl acetate.

Compound 1a-Br: Prepared from **1a**-OTs according to procedure A on 2 mmol scale, using potassium bromide (12 g, 10 equiv.) and obtained in 95% yield (1.138 g) as a white powder. ^{1}H NMR (600 MHz, DMSO-d_6 & CD_3OD) δ 7.81 (d, J = 7.0 Hz, 2H), 7.43 (d, J = 7.0 Hz, 2H), 6.39 (s, 2H), 3.92 (s, 6H), 3.83 (s, 3H), 1.24 (s, 9H). $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6 & CD_3OD) δ 165.6 , 159.3 , 153.9 , 133.9 , 128.3 , 114.7 , 91.9 , 90.3 , 57.2, 56.1, 34.7, 30.73. FTIR: 3051, 2953, 2868, 2841, 1576, 1458, 1409, 1207, 1121, 814 cm^{-1}. HRMS (ESI$^+$): Calculated for $C_{19}H_{24}IO_3^+$ [M - Br]$^+$: 427.0765; Found: 427.0768. Mp 195 – 196 ˚C.

Compound 1a-Cl: Prepared from **1a**-OTs according to procedure A on 2 mmol scale, using sodium chloride (12.6 g, 100 equiv.) and obtained in 94% (0.873 g) yield as a white powder. ^{1}H NMR (600 MHz, DMSO-d_6 & CD_3OD) δ 7.81 (d, J = 7.6 Hz, 2H), 7.43 (d, J = 7.6 Hz, 2H), 6.40 (s, 2H), 3.92 (s, 6H), 3.84 (s, 3H), 1.23 (s, 9H). $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6 & CD_3OD) δ 166.6, 159.9, 155.0, 134.4, 128.7, 113.4, 92.0, 88.0, 57.1, 56.0, 34.9, 30.7. FT-IR: 3068, 3004, 2955, 2901, 2868, 1586, 1410, 1231, 1119, 1059, 810, 670 cm^{-1}. HRMS (ESI$^+$): Calculated for $C_{19}H_{24}IO_3^+$ [M - Cl]$^+$: 427.0765, Found: 427.0759. Mp 205 – 206 ˚C.

Compound 1a-OTf: Prepared from **1a**-OTs according to procedure A on 2 mmol scale, using sodium triflate (5.0 g, 29 equiv.) and obtained in 92% (1.06 g, 1.8 mmol) yield as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (d, J = 8.7 Hz, 2H), 7.50 (d, J = 8.7 Hz, 2H), 6.48 (s, 2H), 3.96 (d, J = 5.8 Hz, 6H), 3.87 (d, J = 4.7 Hz, 3H), 1.25 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 166.1 , 159.3 , 154.7 , 134.2 , 128.7 , 120.7 (q, J_{C-F} = 322.5 Hz), 112.5 , 92.0 , 86.9, 57.3, 56.1, 34.8, 30.7 . $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6) δ (ppm): −77.7. FT-IR: 3070, 2955, 2870, 2847, 1580, 1471, 1415, 1243, 1210, 1125, 1026, 814, 635 cm^{-1}. HRMS (ESI$^+$): Calculated for $C_{19}H_{24}IO_3^+$ [M - OTf]$^+$: 427.0765, Found: 427.0765. Mp 78 – 79 ˚C.

Compound 1a-BF_4: Prepared from **1a**-OTs according to procedure A on 2 mmol scale, using sodium tetrafluoroborate (22 g, 95 equiv.) and obtained in 91% yield (0.930 g, 1.81 mmol) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.85 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 6.48 (s, 2H), 3.97 (s, 6H), 3.88 (s, 3H), 1.25 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 166.6, 159.9, 155.2, 134.7, 129.2, 113.0, 92.5, 87.4, 57.8, 56.6, 35.3, 31.2. ^{19}F[^{1}H} NMR (376 MHz, DMSO-d_6) δ (ppm): −148.3. FT-IR: 3022, 2903, 2870, 1579, 1462, 1347, 1232, 1126, 1050, 995, 808, 665cm^{-1}. HRMS (ESI$^+$): Calculated for $C_{19}H_{24}IO_3^+$ [M – BF_4]$^+$: 427.0765, Found: 427.0747. Mp 156 – 157 ˚C.

Compound 1b-Br: Prepared from **1b**-OTs according to procedure A on 2 mmol scale, using potassium bromide (12 g, 100 equiv.) and obtained in 85% yield (0.930 g, 1.81 mmol) as a white powder. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.27 – 7.79 (m, 4H), 6.49 (s, 2H), 3.97 (s, 6H), 3.89 – 3.52 (m, 6H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 166.9, 165.6, 159.9, 135.1, 132.7, 132.3, 121.4, 92.6, 87.3, 57.8, 56.6, 53.1. FT-IR: 3086, 2988, 2972, 2901, 1721, 1579, 1279, 1121 cm^{-1}. HRMS (ESI$^+$): Calculated for $C_{17}H_{18}IO_5^+$ [M - Br]$^+$: 429.0193; Found 429.0167. Mp 159 – 160 ˚C.

Compound 1b-Cl: Prepared from **1b**-OTs according to procedure A on 3.25 mmol scale, using sodium chloride (14 g, 74 equiv.) and obtained in 94 % yield (1.42 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6 and CD_3OD) δ 8.03 – 7.83 (m, 4H), 6.37 (s, 2H), 3.90 (s, 6H), 3.82 (s, 3H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6 & CD_3OD) δ 166.4, 165.0, 159.4, 134.0, 132.1, 131.2, 121.1, 91.4, 87.3, 56.4, 55.3, 51.7. FT-IR: 3071, 2988, 2971, 2944, 2901, 1733, 1577, 1280, 1116, 748 cm^{-1}. HRMS (ESI$^+$): Calculated for $C_{17}H_{18}IO_5^+$ [M - Cl]$^+$: 429.0193; Found 429.0170. Mp 164 – 165 ˚C.

Compound 1b-OTf: Prepared from **1b**-OTs by procedure A on 1 mmol scale, using sodium triflate (3 g, 17.5 equiv) and obtained in 84 % yield as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 8.6 Hz, 2H), 7.98 (d, J = 8.6 Hz, 2H), 6.49 (s, 2H), 3.95 (s, 6H),

3.88 (s, 3H), 3.86 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 166.4 , 165.1 , 159.4 , 134.6 , 132.2 , 131.8 , 120.8, 120.7 (q, J_{C-F} = 322.4 Hz), 92.1 , 86.8 , 57.3 , 56.2 , 52.6. $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6) δ -77.7 (s). FTIR: 3107, 2950, 2849, 1732, 1576, 1464, 1352, 1275, 1229, 1159, 1029, 816, 665 cm^{-1}. HRMS (ESI^+): Calculated for $C_{17}H_{18}IO_5^+$ $[M - OTf]^+$: 429.0193; Found 429.0191. Mp 120 – 122 ˚C (decomposition).

Compound 1b-BF_4: Prepared from **1b**-OTs by procedure A on 2 mmol scale, using sodium tetrafluoroborate (11 g, 50 equiv) and obtained in 77 % yield (0.8079 g) as a white powder. The filtrate was not extracted to recover more product. ^{1}H NMR (400 MHz, DMSO-d_6 and CD_3OD) δ 8.61 – 7.78 (m, 4H), 6.49 (s, 2H), 4.01 (s, 6H), 3.92 – 3.78 (m, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6 and CD_3OD) δ 166.9, 165.6, 159.9, 135.1, 132.7, 132.3, 121.4, 92.6, 87.3, 57.8, 56.6, 53.1. $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6 and CD_3OD) δ -148.30 (s). FT-IR: 3089, 2988, 2971, 2901, 1716, 1578, 1549, 1277, 1159, 1115, 1066, 642 cm^{-1}. HRMS (ESI^+): Calculated for $C_{17}H_{18}IO_5^+$ $[M - BF_4]^+$: 429.0193; Found 429.0186. Mp 152 – 153 °C.

General procedure for determining the effect of counter anion by admixing (B). Aryl(TMP)iodonium tosylate (0.1 mmol, 1eq) and is added to a vial with a magnetic stirbar. A sodium salt with the desired anion is added (0.4 mmol, 4 equ), followed by 1 mL of anhydrous diglyme. The mixture is vigorously stirred at room temperature for 15 min. Sodium azide (2 mmol, 2 equiv) is added and the mixture is stirred at 50 °C for two hours and then removed from heat and diluted with 1 mL of aqueous sodium bicarbonate solution. Upon addition of (10 µL, ~1 eq) of internal standard (bromo mesitylene), the reaction is extracted with ethyl acetate, filtered through a celite plug and analyzed by GC/MS.

General procedure for aryl azidation with pre-exchanged diaryliodonium salts (C). Aryl(TMP)iodonium salt (0.1 mmol, 1eq) is added to a vial with a magnetic stirbar. Sodium azide (0.2 mmol, 2 equiv. or 0.65, 6.5 equiv.) is added, followed by 1 mL anhydrous diglyme. The solution is stirred at 50 °C or 65 °C for two hours, removed from heat and diluted with 1 mL

of aqueous bicarbonate solution and extracted with ethyl acetate. The reaction is either analyzed by GCMS (with 10 µL of bromo mesitylene as internal standard) or purified by flash column chromatography.

Compound 2a: Prepared according to procedure C on 0.5 mmol scale (6.5 equivalents of sodium azide and heating at 65 °C) and obtained in 94% (0.0818 g, 0.47 mmol) yield as a pale yellow oil. The crude product was adsorbed onto silica and purified by column chromatography using hexanes as the eluent. The characterization data agree with previously reported values.[24] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.6 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 1.27 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 147.9, 137.2, 126.6, 119.0, 34.5, 31.3 ppm.

Compound 2b: Prepared according to procedure C on 0.1 mmol scale with the following deviations: i) the crude reaction was extracted with pentane and purified by column chromatography on silica using 5% ethyl ether followed by 10% ethyl ether in pentane. The product was obtained in 95% (0.0167 g, 0.095 mmol) yield as a pale yellow solid. The characterization data agree with previously reported values.[25] ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 3.91 (s, 1H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 166.3, 144.8, 131.4, 126.7, 118.8, 52.2 ppm.

Compound 2c: Prepared according to procedure C on 0.1 mmol scale with the following deviations: i) acetonitrile was used as the solvent, ii) the crude reaction was extracted with ethyl ether and purified by column chromatography on silica using ethyl ether in hexanes (1:1) to followed by neat ethyl ether. The product was obtained in 86% (0.014 g, 0.086 mmol) yield as a colorless oil. The characterization data agree with previously reported values.[26] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (d, *J* = 7.6 Hz, 2H), 6.98 (d, *J* = 7.4 Hz, 2H), 3.84 (t, *J* = 6.4 Hz, 2H), 2.84 (t, *J* = 6.4 Hz, 2H), 1.70 (s, 1H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 138.3, 135.5, 130.5, 119.2, 65.9, 38.6 ppm.

Compound 2d: Prepared according to procedure C on 0.5 mmol scale and obtained in 93% (0.0828 g, 0.465 mmol) yield as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 2.4 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.17 (dd, *J* = 8.3, 2.4 Hz, 1H), 2.57 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 149.7, 139.3, 134.1, 130.0, 123.4, 115.2, 20.0. FT-IR: 3081, 2988, 2938, 2901, 2110, 1527, 1303, 1338, 1066, 907, 872, 729 cm^{-1}. HRMS (ESI^+) Calculated for $C_7H_6N_4O_2^+$ $[M - H]^+$: 178.0491; Found 178.0507. Mp 67 - 68 ˚C.

Compound 2e: Prepared according to procedure C on 0.5 mmol scale and obtained in 92% (0.172 g, 0.462 mmol) yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.5 Hz, 1H), 7.17 (d, *J* = 2.7 Hz, 1H), 7.01 (t, *J* = 1.8 Hz, 1H), 6.91 – 6.85 (m, 3H), 5.04 (s, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 159.1, 140.0, 137.0, 135.6, 133.9, 121.9, 120.0, 119.2, 117.2, 114.0, 69.4. FT-IR: 3095, 3055, 2920, 2842, 2115, 2075, 1590, 1572, 1299, 1057, 804, 662 cm^{-1}. HRMS (ESI^+) Calculated for $C_{13}H_8BrCl_2N_3O$ $[M - H]^+$: 370.9228; Found 370.9250. Mp 98 - 99˚C

Compound 2f: Prepared according procedure C on 0.1 mmol scale with the following deviations: i) acetonitrile was used as the solvent. The crude product was purified by column chromatography on silica using 10% ethyl ether in hexanes. The product was obtained in 74% (0.0114 g, 0.074 mmol) yield as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 2.1, 1.5 Hz, 1H), 7.45 – 7.25 (m, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 147.1, 140.7, 136.4, 128.9, 125.0. FT-IR: 3086, 3055, 2131, 2099, 1455, 1299, 824, 565 cm^{-1}. HRMS (ESI^+) Calculated for $C_5H_3ClN_4$ $[M - H]^+$: 154.0046 Found 154.0066. Mp 39 ˚C.

Acknowledgments

We acknowledge Portland State University for financial support of this work. Florian Guillot is thanked for NMR titration experiments. Rory Gallagher is thanked for acquisition of selected melting point data.

Supporting Information. Complete references, details of optimization, and NMR (^{1}H, $^{13}C\{^{1}H\}$, $^{19}F\{^{1}H\}$) spectra for all new compounds.

References

1. (a) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043. (b) Szewczyk, J. W.; Zuckerman, R. L.; Bergman, R. G.; Ellman, J. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 216. (c) Boussie, T. R.; Diamond, G. M.; Goh, C.; Hall, K. A.; LaPointe, A. M.; Leclerc, M.; Lund, C.; Murphy, V.; Shoemaker, J. A.; Tracht, U.; Turner, H.; Zhang, J.; Uno, T.; Rosen, R. K.; Stevens, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 4306. (d) Kanan, M. W.; Rozenman, M. M.; Sakurai, K.; Snyder, T. M.; Liu, D. R. *Nature* **2004**, *431*, 545. (e) Trapp, O.; Weber, S. K.; Bauch, S.; Hofstadt W. *Angew. Chem. Int. Ed.* **2007**, *46*, 7307. (f) Beeler, A. B.; Su, S.; Singleton, C.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2007**, *129*, 1413. (g) Rozenman, M. M.; Kanan, M. W.; Liu, D. R. *J. Am. Chem. Soc.* **2007**, *129*, 14933. (h) Teichert, A.; Pfaltz, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 3360. (i) Müller, C. A.; Phaltz, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 3363. (j) Markert, C.; Rösel, P.; Pfaltz, A. *J. Am. Chem. Soc.* **2008**, *130*, 3234. (k) Kinoshita, H.; Ingham, O. J.; Ong, W. W.; Beeler, A. B.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2010**, *132*, 6413. (l) Robbins, D. W.; Hartwig, J. F. *Science* **2011**, *333*, 1423. (m) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114. (n) Quinton, J.; Kolodych, S.; Chaumonet, M.; Bevilacqua, V.; Nevers, M.-C.; Volland, H.; Gabillet, S.; Thuéry, P.; Créminon, C.; Taran, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 6144. (o) Collins, K. D.; Gensch, T.; Glorius F. *Nat. Chem.* **2014**, *6*, 859. (p) Wolf, E.; Richmond, E.; Moran, J. *Chem. Sci.* **2014**, *6*, 2501. (q) Richmond, E.; Moran, J. *Synlett* **2016**, *27*, 2637. (r) Mannel, D. S.; Ahmed, M. S.; Root, T. W.; Stahl, S. S. *J. Am. Chem. Soc. 2017*, *139*, 1690.

2. Santanilla, A. B.; Regalado, E. L.; Pereira, T.; Shevlin, M.; Bateman, K.; Campeau, L.-C.; Schneeweis, J.; Berritt, S.; Shi, Z.-C.; Nantermet, P.; Liu, Y.; Helmy, R.; Welch, C. J.; Vachal, P.; Davies, I. W.; Cernak, T.; Dreher, S. D. *Science* **2015**, *347*, 6217.
3. For selected and impressive examples where > 100 (and up to as many as 500) reactions were run to identify reagents/conditions, see: (a) Su, S.; Rodriguez, R. A.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 13922. (b) Yining, J.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Nat. Acad. Sci. USA* **2011**, *108*, 14411. (c) Martin, D. B. C.; Vanderwal, C. D. *Chem. Sci.* **2011**, *2*, 649.
4. For reviews and perspectives on organohypervalent iodine chemistry, including diaryliodonium salts, see: (a) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997. (b) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299. (d) Merritt, E. A.; Olofsson, B. *Angew. Chem. Int. Ed.* **2009**, *48,* 9052. (e) Yusbov, M. S.; Maskaev, A. V.; Zhdankin, V. V. *Arkivoc*, **2011**, 370. (f) Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116*, 3328. (g) Olofsson, B. *Top. Curr. Chem.* **2016**, *373*, 135.
5. See the ESI specific references. Disclaimer: these are representative literature references and do not constitute an exhaustive list of metal-free arylation reactions reported with diaryliodonium salts during this time-period.
6. For one-pot reactions to synthesize diaryliodonium triflates, see: (a) Carroll, M. A.; Pike, V. W.; Widdowson, D. A. *Tetrahedron* **2000**, *41*, 5393. (b) Hossain, M. D.; Kitamura, T. *Tetrahedron* **2006**, *62*, 6955. (c) Hossain, M. D.; Ikegami, Y.; Kitamura, T. *J. Org. Chem.* **2006**, *71*, 9903. (d) Bielawski, M.; Olofsson B.; *Chem. Commun.* **2007**, 2521. (e) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610. (f) Bielawski, M.; Malmgren, J.; Pardo, L. M.; Wikmark, Y.; Olofsson B.; *ChemistryOpen* **2014**, *3*, 19.

(g) Qin, L.; Hu, B.; Neumann, K. D.; Linstad, E. J.; McCauley, K.; Veness, J.; Kempinger, J. J.; DiMagno, S. G. *Eur. J. Org. Chem.* **2015**, 5919.

7. For one-pot reactions to synthesize diaryliodonium tetrafluoroborates, see: (a) Ochiai, M.; Toyonari, M.; Sueda, T.; Kitagawa, Y. *Tetrahedron Lett.* **1996**, *37*, 8421. (b) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (c) Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, *73*, 4602.
8. For one-pot methods to synthesize diaryliodonium tosylates, see: (a) Margida, A. J.; Koser G. F.; *J. Org. Chem.* **1984**, *49*, 2643. (b) Dohi, T.; Ito, M.; Morimoto, K.; Minamitsuji, Y.; Takenaga, N.; Kita, Y. *Chem. Commun.* **2007**, 4152. (c) Zhu, M.; Jalalian, N.; Olofsson, B. *Synlett* **2008**, 592. (d) Chun, J.-H.; Pike, V. W. *J. Org. Chem.* **2012**, *77*, 1931. (e) Seidl, T. L.; Sundalam, S. K.; McCullough, B.; Stuart, D. R. *J. Org. Chem.* **2016**, *81*, 1998.
9. For an example in which addition of sodium triflate improved reactions of diphenyliodonium tetrafluoroborate or tosylate, see: Reitti, M.; Villo, P.; Olofsson, B. *Angew. Chem. Int. Ed.* **2016**, *55*, 8928.
10. For other recent methods to aryl azides, see: (a) Prieto, L. G.; Fiego, M. J. L.; Chopa, A. B.; Lockhart, M. T. *J. Organomet. Chem.* **2017**, *830*, 26. (b) Zhao, F.; Chen, Z.; Lei, P.; Kong, L.; Jiang, Y. *Tetrahedron Lett.* **2015**, *56*, 2197. (c) Li, Y.; Gao, L.-X.; Han, F.-S. *Chem. Eur. J.* **2010**, *16*, 7969.
11. For metal-free synthesis of aryl-azides from diaryliodonium salts, see: (a) Lubinkowski, J. J.; Gomez, M.; Calderon, J. L.; McEwen, W. E. *J. Org. Chem.* **1978**, *43*, 2432. (b) Wang, B.; Graskemper, J. W.; Qin, L.; DiMagno, S. G. *Angew. Chem. Int. Ed.* **2010**, *49*, 4079 – 4083. (c) Graskemper, J. W.; Wang, B.; Qin, L.; Neumann, K. D.; DiMagno, S. G. *Org. Lett.*, **2011**, *13*, 3158 – 3161.
12. A similar trend, though lower yields, was observed in acetonitrile as solvent. See the ESI for details.

13. Synthesis of diaryliodonium acetate salts typically requires the use of AgOAc, see: (a) Beringer, F. M.; Galton, S. A.; Huang, S. J. *J. Am. Chem. Soc.* **1962**, *84*, 2819. (b) Miralles, N.; Romero, R. M.; Fernandez, E.; Muñiz, K. *Chem. Commun.* **2015**, *51*, 14068. Similarly, the synthesis of diaryliodonium fluorides requires the use of AgF, see: (c) Iwama, T.; Birman, V. B.; Kozmin, S. A.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 673. (d) Chan, L.; McNally, A.; Toh, Q. Y.; Mendoza, A.; Gaunt, M. J. *Chem. Sci*., **2015**, *6*, 1277.
14. We have obtained preliminary evidence from ^{13}C NMR spectra titration that supports anion exchange in the presence of 4 equivalents of added anion. See the ESI for details.
15. Aryl bromide was observed as a competitive by-product in the crude GCMS trace of these reactions.
16. For a recent observation and discussion of the common ion effect, see: Byrne, P. A.; Kobayashi, S.; Würthwein, E.-U.; Ammer, J.; Mayr, H. *J. Am. Chem. Soc.* **2017**, *139*, 1499.
17. See the Supporting Information for further details.
18. Sletten, E. M.; Bertozzi, C. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 6974.
19. (a) Gartner, C. A. *Curr. Med. Chem.* **2003**, *10*, 671. (b) Rizk, M. S.; Shi, X.; Platz, M. S. *Biochemistry* **2006**, *45*, 543.
20. (a) Watson, I. D. G.; Yu, L.; Yudin, A. K. *Acc. Chem. Res.* **2006**, *39*, 194, (b) Singh, G. S.; D'Hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080.
21. Ackermann, L.; Dell'Acqua, M.; Fenner, S.; Vicente, R.; Sandmann, R. *Org. Lett.* **2011**, *13*, 2358.
22. (a) Petersen, T. B.; Khan, R.; Olofsson, B. *Org. Lett.* **2011**, *13*, 3462. (b) Jalalian, N.; Petersen, T. B.; Olofsson, B. *Chem. Eur. J.* **2012**, *18*, 14140.
23. Carreras, V.; Sandtorv, A. H.; Stuart, D. R. *J. Org. Chem.* **2017**, *82*, 1279.
24. Barr, L.; Lincoln, S.; Easton, C. *Supramolec. Chem.* **2005**, *17*, 547.

25. Yang, H.; Li, Y.; Jiang, M.; Wang, J.; Fu, H. *Chem. Eur. J.* **2011**, 5652.

26. Brems, D.; Riling, H. *Biochemistry* **1979**, *18*, 860.