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Unsymmetrical Aryl(2,4,6-trimethoxyphenyl)iodonium Salts: One-Pot Synthesis, Scope, Stability, and Synthetic Studies

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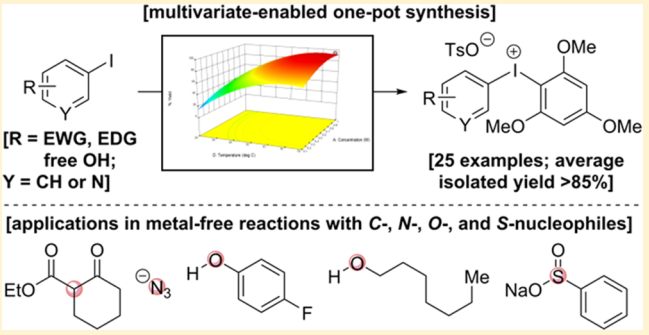
Supporting Information

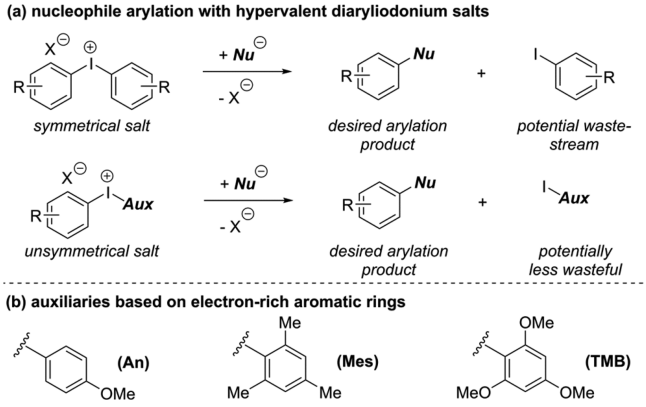
ABSTRACT: Diaryliodonium salts have recently attracted significant attention as metal-free-arylation reagents in organic synthesis, and efficient access to these salts is critical for advancement of their use in reaction discovery and development. The trimethoxybenzene-derived auxiliary is a promising component of unsymmetrical variants, yet access remains limited. Here, a one-pot synthesis of aryl(2,4,6-trimethoxyphenyl)iodonium salts from aryl iodides, *m*-CPBA, *p*-toluenesulfonic acid, and trimethoxybenzene is described. Optimization of the reaction conditions for this one-pot synthesis was enabled by the method of multivariate analysis. The reaction is fast (<1 h), provides a high yield of product (>85% average), and has broad substrate scope (>25 examples) including elaborate aryl iodides. The utility of these reagents is demonstrated in moderate to high yielding arylation reactions with *C*-, *N*-, *O*-, and *S*-nucleophiles including the synthesis of a liquid crystal molecule.



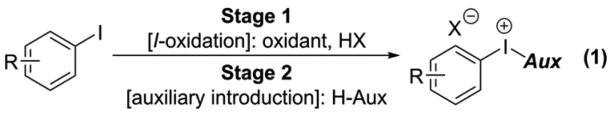
INTRODUCTION

Diaryliodonium salts are novel reagents for metal-free-arylation reactions in contemporary organic synthesis.[1−12] A renewal of interest in these salts is prompted by their good bench stability, low toxicity, and arylation reactivity that parallel transition metal catalysts.[13−17] Unsymmetrical aryl(auxiliary)iodonium salts are especially attractive in arylation chemistry because they are inherently less wasteful than their symmetrical counterparts. Specifically, a recoverable and potentially reusable auxiliary iodide is coproduced when an unsymmetrical salt reacts with a nucleophile, whereas half of the arylation reagent is potentially lost as aryl iodide with a symmetrical diaryliodonium salt (Scheme 1a). This is particularly relevant to the transfer of elaborate arenes in late-stage coupling reactions. While electron-rich auxiliaries derived from anisole (An),[3,5] mesitylene (Mes),[7,8] and trimethoxybenzene (TMB)[18,19] are promising (Scheme 1b), the general use of such auxiliaries is scarce in new metal-free methodology.[20]

Scheme 1. Diaryliodonium Salts As Arylation Reagents



Efficient one-pot protocols to access diaryliodonium salts from aryl iodides continue to be developed[21−27] in light of growing interest in metal-free arylation reactions of these reagents. In many cases a two-stage, one-pot approach has been adopted wherein the iodide moiety is oxidized under acidic conditions in the first stage and the auxiliary is introduced in a second stage (eq 1). The integration of two stages into a single



reaction vessel reduces waste and improves efficiency[28,29] but presents challenges in optimization as several variables must be integrated within the experimental space. In this approach to diaryliodonium salts, halogenatated solvents, such as dichloromethane (DCM) and trifluoroethanol (TFE), are common place in combination with *m*-CPBA as the oxidant and a sulfonic acid, such as triflic or tosic acid, in the first stage. While the former acid is more common, the latter is more attractive from a cost and safety perspective.[30] This general approach

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works well to introduce An- and Mes-auxiliaries in the second stage (Scheme 1b, left and center).

Despite a report of the trimethoxybenzene (TMB)-derived auxiliary (Scheme 1b, right) in a metal-free arylation of a malonate derivative with a diaryliodonium salt over a decade ago[31] there has been very little research activity into the potential of this spectator group.[32] Recently, in addition to malonate, this auxiliary has been investigated as a general spectator in chemoselective phenylation reactions of aniline and phenoxide nucleophiles with phenyl(2,4,6-trimethoxyphenyl)-iodonium triflate[18] and fluoride nucleophiles with aryl(2,4,6-trimethoxyphenyl)iodonium tosylates for applications in positron emission tomography (PET) imaging.[19] Indeed, in the former the TMB-auxiliary provided higher levels of phenyl transfer selectivity than both An- and Mes-auxiliaries.[18] In both of these reports,[18,19] and others,[33−35] the TMB auxiliary was introduced into diaryliodonium salts by reaction with hypervalent (diacetoxy)iodo arenes that were prepared in a separate step; the direct installation through a one-pot synthesis with aryl iodides is exceedingly rare.[26] We posit that the dearth of available methods to access aryl(2,4,6-trimethoxyphenyl)-iodonium salts has limited their broad adoption as reagents for metal-free arylation reactions. Moreover, improved synthetic methods with high functional group compatibility may lead to applications of elaborate aryl(2,4,6-trimethoxyphenyl)iodonium salts in late-stage metal-free coupling reactions.

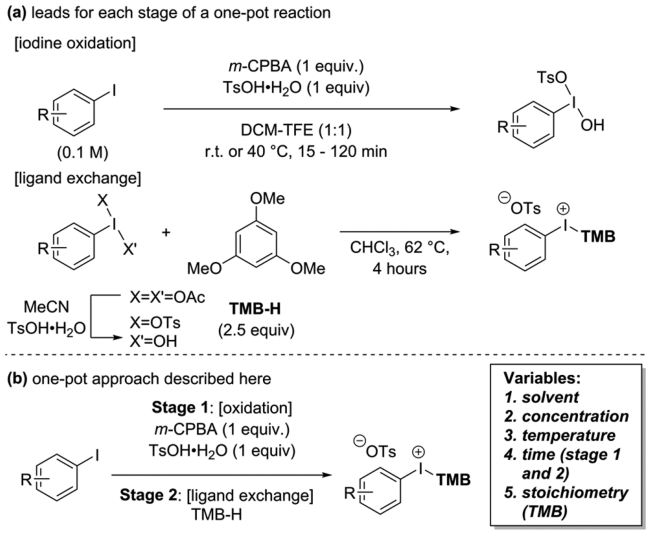
Herein, we describe our approach to a one-pot synthesis of aryl(2,4,6-trimethoxyphenyl)iodonium salts from aryl iodides. Reaction optimization was enabled by chemometric methods.[36] The one-pot reaction occurs in relatively short reaction time (<1 h total), provides a high yield of product (>85% average isolated yield), and has good functional group tolerance. Moreover, we highlight the utility of these reagents with *C*-, *N*-, *O*-, and *S*-nucleophiles, including the metal-free synthesis of a liquid crystal molecule. We also provide insight into the contribution of counteranion identity and aryl group electronic effects on the light and thermal stability of this nascent class of arylating reagent.

RESULTS AND DISCUSSION

Chemical reactions of organic compounds are complex systems comprised of many known and unknown variables. Moreover, the interaction of these variables presents a significant challenge to the development of new reactions. Multivariate analysis provides a systematic approach to reaction optimization wherein both the influence of individual variables and the interaction of variables may be determined.[37−39] We have leveraged this approach in the development of our one-pot synthesis of aryl(2,4,6-trimethoxyphenyl)iodonium salts.

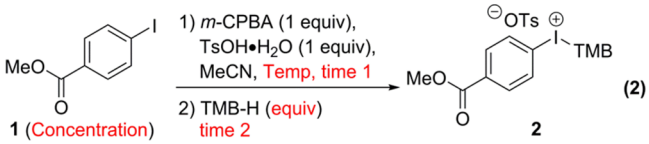
These studies were initiated by identifying promising leads for each "stage" of a one-pot reaction from aryl iodides (Scheme 2a). This was critical, as simply adding TMB-H to standard[22] one-pot reactions failed to provide appreciable quantities of aryl(2,4,6-trimethoxyphenyl)iodonium tosylate. Specifically, we surmised that electron-rich 1,3,5-trimethoxybenzene is incompatible with a strong acid (TfOH) under oxidizing conditions. The lead precedent for oxidation of aryl iodide produces a [hydroxy(tosyloxy)iodo]arene under more mild acidic conditions (TsOH);[40] the lead precedent for ligand exchange intercepts this intermediate to yield the aryl(2,4,6-trimethoxyphenyl)iodonium salt (Scheme 2a).[19,35] Several variables were identified that we anticipated would influence

Scheme 2. Synthetic Strategy for a One-Pot Approach to Aryl(2,4,6-trimethoxyphenyl)iodonium Salts



the reaction outcome: solvent, concentration, bath temperature, time of each stage, and stoichiometry of trimethoxybenzene (Scheme 2b). The identity of the solvent was first considered because a single solvent throughout the entire reaction will minimize unnecessary manipulation of the reaction system and waste associated with a solvent switch; acetonitrile emerged as a promising solvent. We turned our attention to a chemometric-based optimization of the other reaction variables.

A model reaction was used for optimization, and the response (yield) was determined by analysis of the crude ^{1}H NMR spectrum against DMF as an internal standard. Aryl iodide **1** was selected as the model substrate, as we anticipated that iodo-oxidation would be a challenging step (eq 2).[40] A



Placket−Burmann design[41] was used to assess the most influential continuous variables (concentration, temperature, time, and stoichiometry of TMB-H).[42] The same temperature was used for each stage as a practical consideration. This preliminary design revealed that the stoichiometry of trimethoxybenzene was optimal at 1 mol equiv; excess trimethoxybenzene was detrimental to the yield of **2** in this specific system.

Optimization was continued with a two-level factorial design focusing on the four remaining variables: concentration of **1**, time of Stage 1, time of Stage 2, and reaction bath temperature (Figure 1a). The actual and coded values for the variable ranges used in this design are shown in Figure 1a and represent the volume of the experimental space. Experiments for all combinations of the coded values (2^4 = 16 experiments) were performed, and an equation that correlates the response (yield) to the variables was obtained.[42] The β-coefficients of each variable of the model equation are listed in Figure 1a, and their relative magnitude indicates the relative influence of the corresponding variable on the yield of **2**. Notably, the magnitude of the coefficient for the time of Stage 2 was small (~ −0.7) and, therefore, had little influence on the yield of **2**.

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(a) Parameters for 2-level factorial design

variable (x_n)	range (coded) low	high	coefficient (β_n)
A: conc. of **1** (M)	0.1 (-1)	1 (+1)	+10.2
B: time stage 1 (min)	2 (-1)	30 (+1)	+10.7
C: time stage 2 (min)	2 (-1)	30 (+1)	—
D: temperature (°C)	25 (-1)	80 (+1)	+26.1
AB interaction	—		+1.6
AD interaction	—		+3.0
BD interaction	—		+0.03
ABD interaction	—		-5.1

(b) Curvature analysis

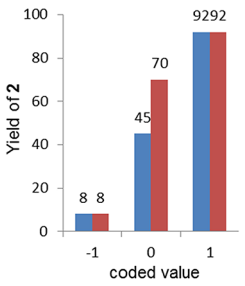

Figure 1. Results of a two level factorial design with **1**. Notes: (a) based on eq 2 with TMB-H set to 1 equiv; (b) predicted yield of **2** (blue) and experimental yield of **2** (red).

Moreover, it was found to be statistically insignificant in the model equation.[42] We further concluded from these data that the concentration of **1** (A) and time of Stage 1 (B) had similar moderate influence on the reaction outcome and that temperature (D) was the most influential variable on the yield of **2** (Figure 1a). Further, we were able to observe interaction effects between variables with this design and positive minor effects were noted between concentration and time of Stage 1 (AB) as well as concentration and temperature (AD; Figure 1a). Factorial designs on two levels are inherently linear and do not assess possible curvature in the response due to individual variables. Therefore, in addition to the extreme points (all coded variables "−1" or "+1") we probed the model by examining the center point (all coded variables "0") of the experimental space (Figure 1b). The experimental conditions for the "center point" are 0.55 M in **1**, 16 min for Stage 1, 16 min for Stage 2, and 53 °C. The experimentally observed (70%) and predicted (45%) yields for the center-point differ dramatically, thus suggesting curvature in the response.

The factorial design was augmented with 10 additional experiments, in a central composite design, in order to assess the expected curvature in the response.[42] Several surface plots were obtained from this design, and a sample is shown in Figure 2 that verifies curvature, in this case with respect to concentration and temperature. Excellent yields (>90%) are predicted by this model at both high temperature and concentration. Additionally, the contour lines on the temperature−concentration plane indicate that high yields (>70%) of **2** may be obtained with a broad range of combinations of concentration and temperature. This insight reveals both optimal conditions and synthetic flexibility in implementation of this method with other (perhaps more sensitive) substrates (*vide infra*).

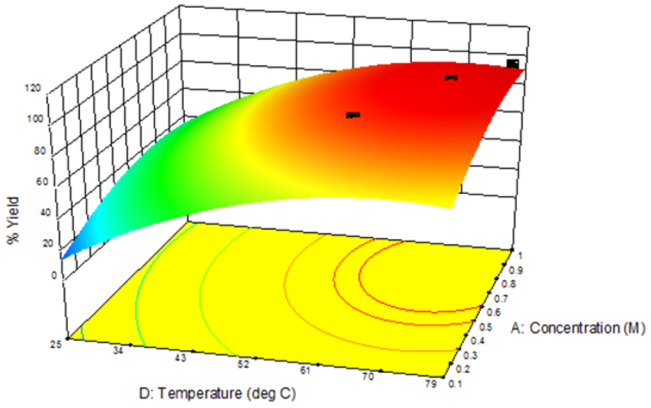

Figure 2. Surface plot obtained from central composite design with **1**. Notes: Conditions: [Stage 1] **1** (0.2 mmol), *m*-CPBA (0.2 mmol, 1 equiv), TsOH·H_2O (0.2 mmol, 1 equiv), MeCN (*y*-axis), temperature (*x*-axis), 30 min; [Stage 2] trimethoxybenzene (0.2 mmol, 1 equiv), 5 min. Black squares are confirmation points (Table 2; 0.2 mmol scale).

The central composite design that yielded the response surface plots and the corresponding model equation was obtained with 26 experiments. This is substantially more time and material efficient than the >600 experiments that would be required to assess all combinations of the same four variables on five different levels (5^4 = 625). Moreover, the depth of knowledge gained through these studies is deeper than typically obtained by one-variable-at-a-time (OVAT) optimization methods. Subsequently, the utility of the model was confirmed for its ability to predict the yield of **2** at experimental conditions not used to build the model (0.2 mmol scale) and for preparative reactions (5 mmol scale) at the optimal conditions. First, the experimentally obtained yield and the predicted yield for the center point are in much better agreement when curvature is taken into account with the central composite design (compare 70% and 74%, respectively) versus the 2-level factorial design (*vide supra*). Three additional points on the response surface in Figure 2 were selected to confirm the predictive ability of the model (Table 1). In each case good agreement was obtained between the predicted and experimental yields. Notably, on preparative scale, excellent yield (93%) was obtained at the conditions of the highest experimental yield (1.0 M and 77 °C, entry 1, Table 1).

Table 1. Model Confirmation for Composite Design[a]

entry	[1] (M)	temp (°C)	predicted yield (±10%)[b]	Experimental yield (%)[c]
1	1.0	77	92	95 ± 1 (93 ± 2)[d]
2	0.8	70	95	93 ± 4
3	0.5	60	88	89 ± 1

[a]Conditions (based on eq 2): [Stage 1] **1** (0.2 mmol), *m*-CPBA (0.2 mmol, 1 equiv), TsOH·H_2O (0.2 mmol, 1 equiv), MeCN (see table for concentration), temperature (see table), 30 min; [Stage 2] trimethoxybenzene (0.2 mmol, 1 equiv), 5 min. [b]Error of the model equation. [c]^{1}H NMR yield vs DMF as internal standard, average of 3 runs. [d]Isolated yield on 5 mmol scale of **1**, average of 3 runs.

The scope of the reaction is presented in Chart 1. While the reaction optimization was carried out on a single aryl iodide **1**, the resulting conditions were generally applied to aryl iodides having diverse electronic and steric effects. In total 25 different examples were examined and the yield of aryl(2,4,6-trimethoxyphenyl)iodonium tosylates range between 66% and 96% (>85% average) indicating that the optimal reaction conditions may be broadly applied with success. Electron-donating and -withdrawing substituents are tolerated on the aryl iodide in the *ortho*-, *meta*-, and *para*-positions. Even sensitive functional groups, such as benzyl bromide and an unprotected hydroxyl moiety, may be included on aryl iodides. It is interesting to note that when these specific examples were initially investigated under the optimal conditions, low yields and evidence of oxidative decomposition were observed. However, intimate knowledge of the influence of reaction variables, such as temperature and concentration (Figure 2), obtained from multivariate analysis prompted us to explore slightly modified conditions. When the reaction of these substrates was conducted at low temperature (rt) and high concentration (1

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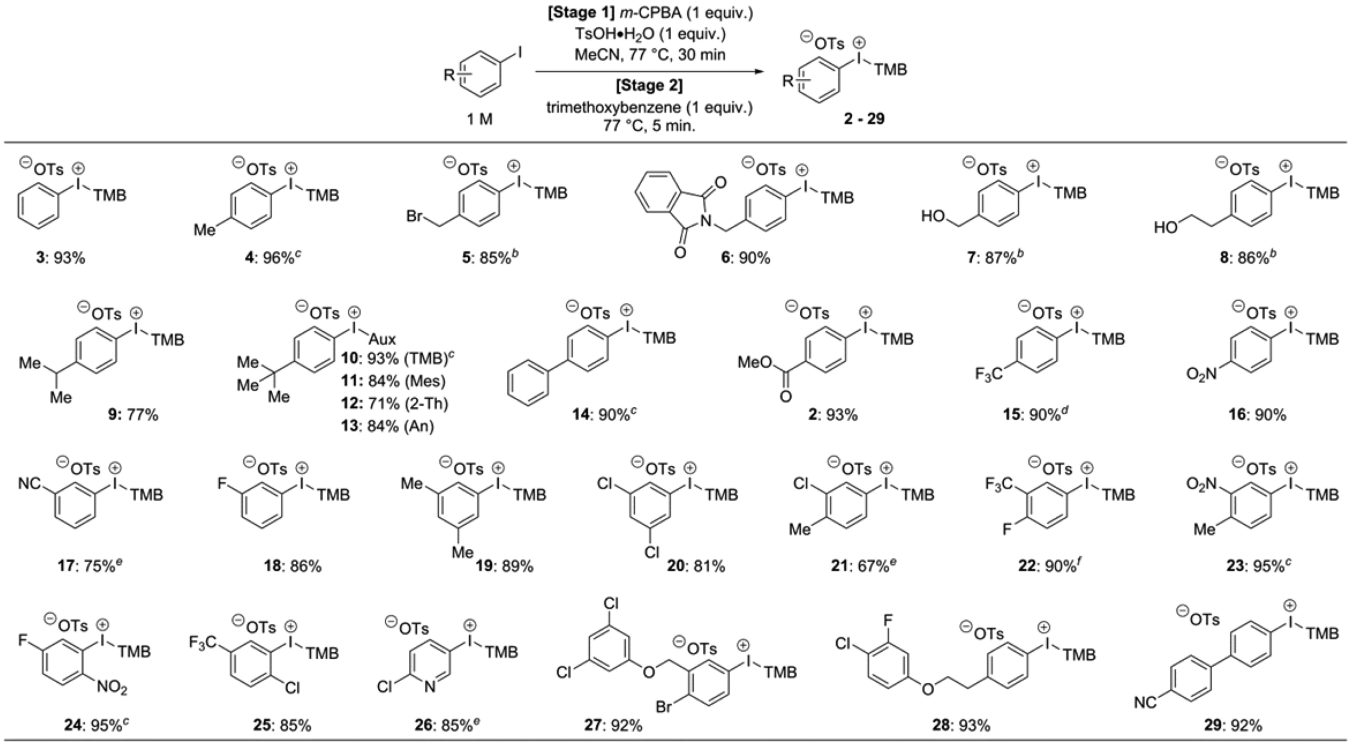
Chart 1. Scope of Aryl(auxiliary)iodonium Tosylate Salts Obtained in This Work

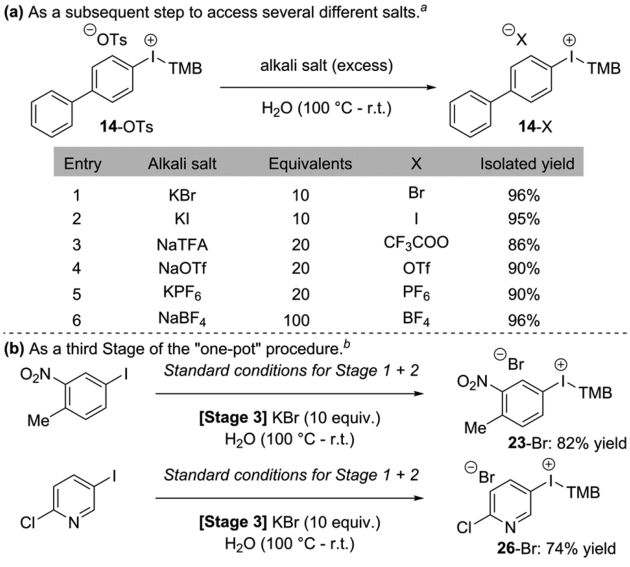


[a]Conditions: [Stage 1] aryl iodide (5 mmol), *m*-CPBA (5 mmol, 1 equiv), $TsOH·H_2O$ (5 mmol, 1 equiv), MeCN (5 mL), 77 °C, 30 min; [Stage 2] trimethoxybenzene (5 mmol, 1 equiv), 5 min. [b]Reaction conducted at room temperature. [c]10 mmol scale of aryl iodide. [d]30 mmol scale of aryl iodide. [e]1 mmol scale of aryl iodide. [f]20 mmol scale of aryl iodide.

M), a good yield of product is obtained (**5**, 85%; **7**, 87%; and **8**, 86%; Chart 1). The rapid identification of alternate reaction conditions was enabled by the multivariate approach taken in optimization of the reaction conditions. Iodonium salt products **19**–**29** bear polysubstituted or elaborate aryl groups and are obtained in moderate to high yield. These examples underscore the importance of unsymmetrical aryl(auxiliary)iodonium salts as the symmetric salts would be more expensive to prepare and more wasteful in subsequent arylation chemistry. Our method may also be used to introduce other auxiliaries including mesityl, 2-thienyl, and anisyl (**11**, **12**, and **13** respectively) in high yield. Moreover, similar to several other aryliodonium salts syntheses, this reaction does not require chromatographic purification of the products; analytically pure material was isolated by filtration after trituration with ether. All compounds were characterized by spectroscopic and spectrometric analysis.

Our scope studies have focused primarily on the synthesis of diaryliodonium tosylate salts (Chart 1). The counteranion is, however, an important structural feature of these reagents, and specifically, the ability to introduce or vary the counteranion is a critical screening element in reaction development with hypervalent iodonium salts. It is possible to incorporate counteranion exchange into this method, and this is described here in two ways (Scheme 3). In the first approach, which is appropriate when a variety of different counteranions for a single iodonium moiety are desired, the tosylate readily exchanges with several counteranions under aqueous conditions in high yield as demonstrated for **14**-OTs (Scheme 3b).[43,44] In the second approach, a third stage was appended to the standard one-pot protocol (Scheme 3a). Two examples highlight this strategy, and the isolated yields of the bromide salts are similar to those previously obtained for the tosylate salts in two stages (compare Chart 1, **23** and **26** and Scheme 3a). Collectively, these two strategies introduce diverse counteranions into aryl(2,4,6-trimethoxyphenyl)iodonium salts that influence reactivity and stability (*vide infra*).

Scheme 3. Counteranion Exchange



Entry	Alkali salt	Equivalents	X	Isolated yield
1	KBr	10	Br	96%
2	KI	10	I	95%
3	NaTFA	20	CF_3COO	86%
4	NaOTf	20	OTf	90%
5	KPF_6	20	PF_6	90%
6	$NaBF_4$	100	BF_4	96%

[a]Conditions: 14-OTs (2 mmol, 1 equiv), alkali salt (see table), H_2O (~50 mL), 100 °C to room temperature. [b]Conditions: [Stage 1] aryl iodide (5 mmol), *m*-CPBA (5 mmol, 1 equiv), $TsOH·H_2O$ (5 mmol, 1 equiv), MeCN (5 mL), 77 °C, 30 min; [Stage 2] trimethoxybenzene (5 mmol, 1 equiv), 5 min; [Stage 3] KBr (50 mmol, 10 equiv), H_2O (~100 mL), 100 °C to room temperature.

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In light of our interest in exploring and developing the synthetic utility of these reagents, we have investigated their bench stability over the course of this study. We have found that the relative light and thermal stability of these reagents depends on the electronic effects of the aryl group and the identity of the counteranion as shown in Figure 3. When

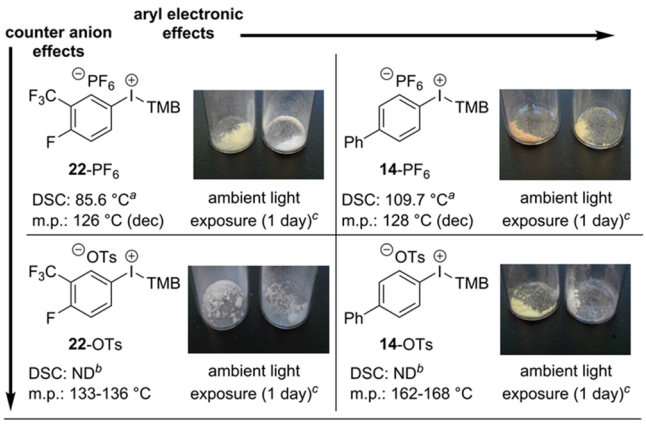


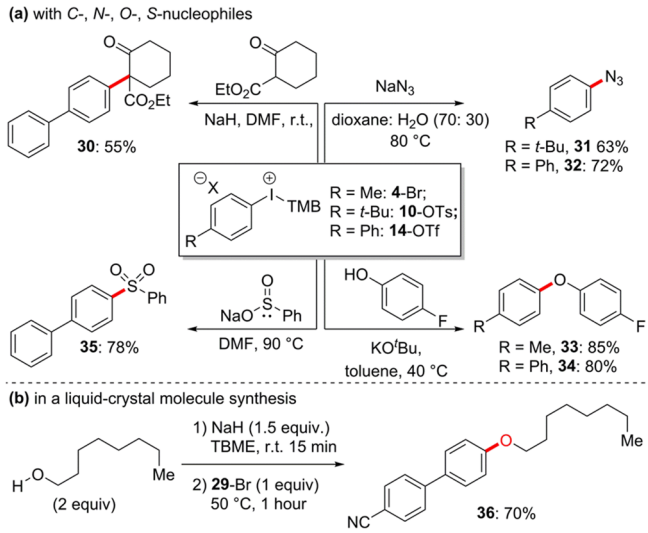
Figure 3. Light and thermal stability studies. [a] Notes: temperature of exothermic onset peak. [b] No exothermic onset peak noted below 200 °C. [c] Left-hand vial left open to ambient room and sun light; right-hand vial kept in the dark as a control.

exposed to ambient light, even for 1 day, diaryliodonium salts bearing more electron-rich aryl groups discolor more than their electron-deficient counterparts (compare **14**-PF_6 vs **22**-PF_6 or **14**-OTs vs **22**-OTs; Figure 3). Also, salts with more weakly coordinating counteranions discolor more than those with stronger coordinating counteranions (compare **14**-PF_6 vs **14**-OTs or **22**-PF_6 vs **22**-OTs; Figure 3).[45] After 30 days of ambient light exposure some salts appeared as brown oils.[42] All of the salts prepared in this study appear to be thermally stable at room temperature. However, we looked for evidence of exothermic events when heated in the solid state by differential scanning calorimetry (DSC) analysis.[42,46] This behavior was also dependent on aryl electronic effects and counteranion identity. Analogous to light stability, iodonium salts with PF_6 counteranions appeared less thermally stable than those with OTs counteranions as evidenced by exothermic onset peaks at lower temperature (compare **22**-PF_6 vs **22**-OTs or **14**-PF_6 vs **14**-OTs Figure 3). Aryl electronic effects appeared to have the opposite effect in which iodonium salts with more electron-rich aryl groups were more thermally stable, i.e., higher exothermic onset temperature (compare **22**-PF_6 vs **14**-PF_6; Figure 3). These data are in agreement with the decomposition or melting temperatures of these salts observed during melting point measurements (Figure 3). On the basis of these observations, we have found that storage of these reagents in a cool and dark place will retain the initial color and free-flowing appearance of these salts for all counteranions that we have investigated.

The exothermic onset peaks observed in the solid-state DSC analysis prompted us to assess the potential of such exothermic activity under the reaction conditions.[47] The internal reaction temperature was monitored for two select cases: (1) the synthesis of **2**, bearing an electron-withdrawing substituent, in a 77 °C oil bath, and (2) the synthesis of **4**, bearing an electron-donating substituent, at ambient room temperature. Both reactions were carried out on 20 mmol scale. Interestingly, under the reaction conditions, the internal reaction temperature in case 1 did not exceed the oil bath temperature of 77 °C, and the max temperature observed was 76 °C which occurred during Stage 1. The internal reaction temperature in case 2 decreased to a minimum of 8 °C at the beginning of Stage 1 during dissolution of the reactants in acetonitrile and increased to a maximum of 24 °C over the course of Stage 1. The maximum internal temperature observed in case 2, which was 31 °C, occurred after addition of TMB-H, and the internal temperature decreased to ~25 °C over 10 min. The temperature−time plots for these reactions are provided in the Supporting Information. The diverse examples presented in Chart 1 were obtained on a 1−30 mmol scale without incident, and in these two specific cases on the 20 mmol scale, no "run-away" exothermic event was observed. However, we urge extreme caution on scale-up of these reactions given the unknown energetics of reaction intermediates and products that depend on electronic effects of aryl groups and counteranion identity.

We have provided representative synthetic applications of aryl(2,4,6-trimethoxyphenyl)iodonium salts to complement the efficiency of the one-pot synthesis described here (Scheme 4).

Scheme 4. Synthetic Applications[a]



[a]Conditions: (with β-keto ester nucleophile) **14**-OTf (1.33 equiv), NaH (1.33 equiv), ethyl 2-oxocyclohexane-1-carboxylate (1 equiv), DMF (0.25 M), 0 °C; (with sodium azide) **10**-OTs or **14**-OTf (1 equiv), NaN_3 (1.4 equiv), dioxane/H_2O (70:30; 0.25 M), 80 °C, 2−65 h; (with phenol nucleophile) **14**-OTf or **4**-Br (1.2 equiv), 4-fluorophenol (1 equiv), KOtBu (1.1 equiv), toluene (0.3 M), 40 °C; (with sodium sulfinate nucleophile) **14**-OTf (1.1 equiv), sodium phenyl sulfinate (1 equiv), DMF (0.5 M), 90 °C; (with alkoxide nucleophile) 1-octanol (2 equiv), NaH (1.5 equiv), **29**-Br (1 equiv), TBME (0.2 M), 50 °C, 1 h.

Moreover, these examples contribute to a small, but important, body of literature that has begun to establish unsymmetrical aryl(2,4,6-trimethoxyphenyl)iodonium salts as synthetically useful metal-free arylation reagents.[31,48,18,19,49] Several highlights from these examples are worth noting. First, the compatibility of these electrophilic aryl reagents with four different nucleophiles including *C*-, *N*-, *O*-, and *S*-nucleophiles has been demonstrated in synthetically useful yields ranging from 55% to 85% (Scheme 4a). Specifically, enolate,[31] azide,[50] phenoxide,[51] and sulfinate[52] nuclophiles react with **4**-Br, **10**-

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OTs, and **14**-OTf chemoselectively at the aryl group. Second, the examples in Scheme 4a involve formal nucleophilic addition to electron-rich arenes (σ_p = −0.01, −0.17, −0.20 for Ph, Me, and *t*-Bu, respectively)[53] which remain a current challenge with unsymmetrical aryl(mesityl)iodonium salts.[8,18] Third, while each of the examples in Scheme 4a bears the TMB-derived auxiliary we have demonstrated that three different counteranions (Br, OTf, OTs) are compatible in these nucleophile arylation reactions. However, we also emphasize that these results were obtained from unoptimized combinations of a counteranion and the TMB-auxiliary and, therefore, demonstrate the breadth of possible counteranions used with this auxiliary. Fourth, we have demonstrated that **14**-OTf reacts with four diverse nucleophiles under mild and straightforward conditions to yield four diverse biphenyl derivatives in moderate (55%) to high (80%) yield. This result, together with the one-pot synthesis, points toward aryl(2,4,6-trimethoxyphenyl)iodonium salts as potential reagents for late-stage diversification reactions.[54−56] Finally, we have demonstrated the utility of these reagents in the synthesis of a liquid crystal nematic mesogen 8OCB **36** which is used in optical devices (Scheme 4b).[57] In this case octanol is arylated under basic conditions[8] with unsymmetrical **29**-Br to yield **36** in 70% yield. We are continuing to explore the synthetic utility of these reagents with carbon and heteroatom nucleophiles.

CONCLUSIONS

The optimization and scope of a one-pot synthesis to access a diverse range of aryl(2,4,6-trimethoxyphenyl)iodonium tosylate salts was described. The chemometric-based optimization yielded general conditions and insight into the experimental space. Under the optimal conditions, this reaction proceeds in a short reaction time (<1 h), at high concentration (1 M), in equal stoichiometry of all reactants, and in generally high yield (85% average). Anion metathesis with these salts may be accomplished in two different ways and leads to diaryliodonium bromide, iodide, trifluoroacetate, triflate, hexafluorophosphate, and tetrafluoroborate salts in high yield. The general stability of these reagents was assessed and point toward the utility of these compounds as thermally stable reagents at room temperature that should be stored away from light. Preliminary synthetic application of these reagents was highlighted with *C*-, *N*-, *O*-, and *S*-nucleophiles and in the synthesis of a liquid crystal molecule via metal-free C−O coupling; we are actively pursuing new synthetic directions with these reagents. Collectively, the method described here is inexpensive, operationally simple, scalable, and broad in scope; these points, in combination with the facile anion exchange chemistry, should increase the accessibility of unsymmetrical aryl(2,4,6-trimethoxyphenyl)-iodonium salts for discovery and development of metal-free arylation reactions. Moreover, the ability to vary both aryl electronic density and counteranion identity and insight into thermal and light stability thereof may provide new inspiration for previously inaccessible compounds that have applications beyond organic synthesis.

EXPERIMENTAL SECTION

General Considerations. Commercially available reagents and solvents were used without further purification unless otherwise stated. *m*-CPBA was obtained from a commercial source, dried, and assayed by iodometric titration before use according to literature procedures.[58] 4′-Iodo-[1,1′-biphenyl]-4-carbonitrile[59] and 2-(4-iodobenzyl)-isoindoline-1,3-dione[60] were prepared according to literature procedure. All other materials were prepared as described in detail below. Crude reaction mixtures were analyzed by ^{1}H NMR spectroscopy and thin-layer chromatography (TLC) on silica gel (60 Å F-254) TLC plates and visualized by UV irradiation. Crude material was purified by flash column chromatography on silica gel unless otherwise stated. ^{1}H, ^{13}C, ^{19}F 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 obtained from solutions in DCM or $CDCl_3$. High resolution mass spectrometry (HRMS) data were 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 the Synthesis of Aryl(2,4,6-trimethoxyphenyl)iodonium Tosylates (2−29) . Aryl iodide (5 mmol, 1 equiv) and acetonitrile (5 mL) were added to a 50 mL round-bottom flask, equipped with a magnetic stir bar. Toluenesulfonic acid (5.05 mmol, 1.01 equiv) was added in one portion, followed by one portion of *m*-CPBA (5.05 mmol, 1.01 equiv). After attaching a reflux condenser, the reaction was lowered into an oil bath set to 77 °C and stirred vigorously. After 30 min, the reflux condenser was removed in order to add 1,3,5-trimethoxybenzene (5.05 mmol, 1.01 equiv) in one portion and stirring was continued at 77 °C for 5 min. The reaction was removed from heat and concentrated under reduced pressure. The crude residue was triturated with diethyl ether. The precipitate was isolated by vacuum filtration and washed by slurry filtration with diethyl ether (3 × 20 mL). After drying under high vacuum the diaryliodonium salt was obtained in analytically pure form.

Compound ***2***. Prepared according to the general procedure above on 5 mmol scale and obtained in 93% yield (2.798 g) as a pale yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.5 Hz, 2H), 7.49 (d, J = 7.9 Hz, 2H), 7.11 (d, J = 7.8 Hz, 2H), 6.49 (s, 2H), 3.95 (s, 6H), 3.88 (s, 3H), 3.86 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.3, 165.1, 159.4, 145.5, 137.6, 134.5, 132.0, 131.7, 128.0, 125.4, 121.0, 92.1, 86.7, 57.3, 56.1, 52.6, 20.7. FT-IR: 3041, 2949, 2842, 1721, 1646, 1582, 1457, 1343, 1282, 1186, 1034, 816 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{17}H_{18}IO_5^+$ [M − OTs]$^+$, 429.0193; observed, 429.0167. Melting point: 169−175 °C.

Compound ***3***. Prepared according to the general procedure above on 5 mmol scale and obtained in 93% yield (2.520 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 7.5 Hz, 2H), 7.64−7.38 (m, 5H), 7.10 (d, J = 7.5 Hz, 2H), 6.47 (s, 2H), 3.94 (s, 6H), 3.86 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.1, 159.3, 145.5, 137.6, 134.2, 131.4(2), 131.3(6), 128.0, 125.4, 116.0, 92.0, 87.0, 57.2, 56.1, 20.7. FT-IR: 3041, 2949, 2842, 2842, 1721, 1646, 1582, 1457, 1343, 1282, 1186, 1034, 816 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{15}H_{16}IO_3^+$ [M − OTs]$^+$, 371.0139; observed, 371.0121. Melting point: decomposed 167 °C.

Compound ***4***. Prepared according to the general procedure above on 10 mmol scale and obtained in 96% yield (5.353 g) as an off-white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83−7.75 (m, 2H), 7.52−7.45 (m, 2H), 7.25 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 7.8 Hz, 2H), 6.45 (s, 2H), 3.94 (s, 6H), 3.86 (s, 3H), 2.30 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0, 159.3, 145.5, 141.8, 137.6, 134.3, 132.0, 128.0, 125.4, 112.4, 91.9, 87.2, 57.2, 56.1, 20.7 (one carbon signal unaccounted for due to overlapping methyl signals). FT-IR: 3023, 1642, 1585, 1458, 1414, 1207, 1185, 1035, 816 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{16}H_{18}IO_3^+$ [M − OTs]$^+$, 385.0295; observed, 385.0265. Melting point: decomposed 168 °C.

Compound ***5***. Prepared according to the general procedure above with the exception of running both stages at room temperature. The 5 mmol scale reaction yielded 85% (2.621 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92−7.87 (m, 2H), 7.54−7.44 (m, 4H), 7.10 (d, J = 7.8 Hz, 2H), 6.45 (s, 2H), 4.70 (s, 2H), 3.94 (s, 6H), 3.86 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0, 159.2, 145.4, 141.5, 137.6, 134.6, 132.0, 128.0, 125.4, 115.8, 91.9, 87.7, 57.2, 56.1, 32.7, 20.7. FT-IR: 3090, 3033, 2978, 2945, 2844, 1643, 1583, 1413, 1186, 815, 682, 565 cm^{-1}. HRMS (ESI$^+$): calculated for

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$C_{16}H_{17}BrIO_3^+$ [M − OTs]$^+$, 462.9400; observed, 462.9383. Melting point: decomposed 157 °C.

Compound **6**. Prepared according to the general procedure above on 5 mmol scale and obtained in 90% yield (3.164 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95−7.79 (m, 6H), 7.49 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 7.9 Hz, 2H), 6.44 (s, 2H), 4.81 (s, 2H), 3.94 (s, 6H), 3.85 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.6, 166.1, 159.3, 145.5, 140.3, 137.6, 134.5, 131.4, 130.2, 129.1, 128.0, 125.4, 123.2, 114.6, 91.9, 87.1, 57.2, 56.0, 40.2, 20.7. FT-IR: 3021, 2968, 2842, 1700, 1643, 1392, 1229, 1184, 788, 729 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{24}H_{21}INO_5^+$ [M − OTs]$^+$, 530.0459; observed, 530.0438. Melting point: decomposed 172 °C.

Compound **7**. Prepared according to the general procedure above on 5 mmol scale with the following deviations: (i) Stage 1 was run at ambient temperature; (ii) Stage 2 was run at ambient temperature; (iii) Stage 2 reaction progress was assessed by TLC, and Stage 2 reaction time was 1 h. The product was isolated in 87% yield (2.49 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87 (d, J = 8.4 Hz, 2H), 7.48 (d, J = 8.1 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 7.9 Hz, 2H), 6.45 (s, 2H), 5.50−5.25 (br. s, 1H), 4.52 (s, 2H), 3.94 (s, 6H), 3.85 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0, 159.2, 146.5, 145.4, 137.6, 134.1, 129.1, 128.0, 125.4, 113.6, 91.9, 87.2, 61.9, 57.2, 56.0, 20.7. FT-IR: 3410, 3080, 3033, 2995, 2918, 2852, 1644, 1572, 1443, 1412, 1340, 1040, 821 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{16}H_{18}IO_4^+$ [M − OTs]$^+$, 401.0244; observed, 401.0219. Melting point: 184−186 °C.

Compound **8**. Prepared according to the general procedure above on 5 mmol scale with the following deviations: (i) Stage 1 was run at ambient temperature; (ii) Stage 2 was run at ambient temperature; (iii) Stage 2 reaction progress was assessed by TLC, and Stage 2 reaction time was 35 min. The product was obtained in 86% yield (2.504 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.82 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 6.45 (s, 2H), 4.68 (s, 1H), 3.94 (s, 6H), 3.85 (s, 3H), 3.58 (t, J = 6.6 Hz, 2H), 2.72 (t, J = 6.6 Hz, 2H), 2.27 (s, 3H).[13]C NMR (101 MHz, DMSO-d_6) δ 166.0, 159.3, 145.4, 143.9, 137.7, 134.1, 132.0, 128.0, 125.4, 112.9, 91.9, 87.1, 61.4, 57.2, 56.1, 38.8, 20.7. FT-IR: 3424, 3083, 3030, 2948, 2906, 1640, 1577, 1339, 1218, 1177, 1033, 562 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{17}H_{20}IO_4^+$ [M − OTs]$^+$, 415.0401; observed, 415.0382. Melting point: 181−184 °C.

Compound **9**. Prepared according to the general procedure above on 5 mmol scale and obtained in 77% yield (2.251 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.83 (d, J = 8.4 Hz, 2H), 7.47 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 7.8 Hz, 2H), 6.46 (s, 2H), 3.95 (s, 6H), 3.86 (s, 3H), 2.90 (septet, J = 6.8 Hz, 1H), 2.28 (s, 3H), 1.16 (d, J = 6.9 Hz, 6H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 166.0, 159.3, 152.3, 145.7, 137.5, 134.4, 129.6, 127.9, 125.4, 112.6, 91.9, 87.0, 57.2, 56.1, 33.1, 23.4, 20.7. FT-IR: 3090, 3059, 3032, 2961, 2867, 2840, 1651, 1583, 1412, 1213, 1186, 815 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{18}H_{22}IO_3^+$ [M − OTs]$^+$, 413.0608; observed, 413.0587. Melting point: 149−152 °C.

Compound **10**. Prepared according to the general procedure above on 10 mmol scale and obtained in 93% yield (5.570 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.87−7.80 (m, 2H), 7.53−7.44 (m, 4H), 7.10 (d, J = 7.8 Hz, 2H), 6.47 (s, 2H), 3.96 (s, 6H), 3.87 (s, 3H), 2.28 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 166.0, 159.3, 154.5, 145.6, 137.5, 134.1, 128.5, 128.0, 125.4, 112.6, 91.9, 87.0, 57.3, 56.1, 34.7, 30.6, 20.7. FT-IR: 3071, 2953, 2867, 2840, 1036, 1634, 1583, 1467, 1412, 1208, 1125, 815 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{19}H_{24}IO_3^+$ [M − OTs]$^+$, 427.0765; observed, 427.0746. Melting point: 190−192 °C.

Compound **11**. Prepared according to the general procedure above on 5 mmol scale with the following deviations: (i) in Stage 2, mesitylene was added in place of TMB; (ii) Stage 2 reaction time was 6 h and reaction progress was monitored by TLC. The product was obtained in 84% yield (2.303 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.7 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.19 (s, 2H), 7.09 (d, J = 7.9 Hz, 2H), 2.60 (s, 6H), 2.28 (s, 6H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.6, 145.4, 142.8, 141.4, 137.5, 134.1, 129.6, 128.8, 127.9, 125.4, 122.6, 111.0, 34.7, 30.6, 26.2, 20.7, 20.4. FT-IR: 3090, 3062, 3039, 2965, 2871, 2843, 1640, 1393, 1214, 1187, 816 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{19}H_{24}I^+$ [M − OTs]$^+$, 379.0917; observed, 379.0895. Melting point: decomposed 175 °C.

Compound **12**. Prepared according to the general procedure above on 5 mmol scale with the following deviation: (i) in Stage 2, thiophene was used in place of TMB. The product was obtained in 71% yield (1.186 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.20−8.13 (m, 2H), 8.11−8.05 (m, 1H), 7.99−7.92 (m, 1H), 7.57−7.44 (m, 4H), 7.17−7.07 (m, 3H), 2.28 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 154.9, 145.1, 140.2, 137.8, 137.0, 134.3, 129.4, 128.6, 128.0, 125.4, 115.8, 100.7, 34.7, 30.6, 20.7. FT-IR: 3094, 3059, 2962, 2927, 2867, 1652, 1392, 1214, 1188, 1032, 816 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{14}H_{16}IS^+$ [M − OTs]$^+$, 343.0012; observed, 342.9998. Melting point: 125−136 °C.

Compound **13**. Prepared according to the general procedure above on 5 mmol scale with the following deviations: (i) in Stage 2, anisole was used in place of TMB; (ii) Stage 2 reaction time was 1 h and reaction progress was assessed by TLC; (iii) the solvent was not removed from the crude reaction and instead was immediately triturated with ethyl ether. The product was filtered and washed according to the general procedure and obtained in 84% yield (2.250 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24−8.17 (m, 2H), 8.16−8.10 (m, 2H), 7.56−7.51 (m, 2H), 7.50−7.45 (m, 2H), 7.12 (d, J = 7.9 Hz, 2H), 7.06−7.01 (m, 2H), 3.77 (s, 3H), 2.28 (s, 3H), 1.23 (s, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 161.7, 154.7, 145.5, 137.6, 137.2, 134.6, 128.5, 128.0, 125.5, 117.2, 113.5, 105.4, 55.6, 34.7, 30.6, 20.7. FT-IR: 3091, 3061, 3050, 2963, 2902, 2869, 2840, 1395, 1254, 1184, 817 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{17}H_{20}IO^+$ [M − OTs]$^+$, 367.0553; observed, 367.0528. Melting point: 177−180 °C.

Compound **14**. Prepared according to the general procedure above on 10 mmol scale and obtained in 90% yield (5.533 g) as an off-white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, J = 8.6 Hz, 2H), 7.74 (d, J = 8.6 Hz, 2H), 7.70−7.62 (m, 2H), 7.56−7.32 (m, 5H), 7.10 (d, J = 7.9 Hz, 2H), 6.49 (s, 2H), 3.97 (s, 6H), 3.88 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.1, 159.3, 145.6, 143.1, 138.1, 137.5, 134.8, 129.5, 129.0, 128.5, 128.0, 126.9, 125.4, 114.5, 92.0, 87.0, 57.3, 56.1, 20.7. FT-IR: 3089, 3068,2967, 2943, 2878, 2839, 1646, 1586, 1468, 1339, 1209, 1033, 816, 765, 684 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{21}H_{20}IO_3^+$ [M − OTs]$^+$, 447.0452; observed, 447.0431. Melting point: 162−164 °C.

Compound **15**. Prepared according to the general procedure above on 30 mmol scale and obtained in 90% yield (16.527 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.13 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H), 7.52−7.43 (m, 2H), 7.11 (d, J = 7.8 Hz, 2H), 6.50 (s, 2H), 3.96 (s, 6H), 3.89 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.4, 159.4, 145.5, 137.6, 135.0, 131.3 (q, J_{C-F} = 32.4 Hz), 128.1 (q, J_{C-F} = 3.5 Hz), 128.0, 125.4, 123.4 (q, J_{C-F} = 272.8 Hz), 120.3 (br. s), 92.1, 87.0, 57.3, 56.2, 20.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ −61.6. FT-IR: 3090, 2979, 2847, 1467, 1644, 1584, 2949, 1414, 1210, 1182, 1034, 816 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{16}H_{15}F_3IO_3^+$ [M − OTs]$^+$, 439.0013; observed, 438.9989. Melting point: 167−170 °C.

Compound **16**. Prepared according to the general procedure above on 5 mmol scale and obtained in 90% yield (2.656 g) as a pale yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.27−8.11 (m, 4H), 7.50−7.43 (m, 2H), 7.14−7.05 (m, 2H), 6.50 (s, 2H), 3.95 (s, 6H), 3.88 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.4, 159.4, 149.0, 145.5, 137.6, 135.4, 128.0, 125.9, 125.4, 122.3, 92.1, 87.1, 57.3, 56.2, 20.7. FT-IR: 3094, 3058, 3017, 2981, 2946, 2846, 1643, 1583, 1527, 1468, 1346, 1346, 1210, 1034, 848, 816 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{15}H_{15}INO_5^+$ [M − OTs]$^+$, 415.9989; observed, 415.9963. Melting point: 158−165 °C.

Compound **17**. Prepared according to the general procedure above on 1 mmol scale and obtained in 75% yield (0.428 g) as a pink powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (dd (appears as triplet), J = 1.5 Hz, 1H), 8.22−8.17 (m, 1H), 8.10−8.03 (m, 1H), 7.65

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(dd (appears as triplet), J = 8.0 Hz, 1H), 7.47 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 6.48 (s, 2H), 3.95 (s, 6H), 3.88 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.3, 159.3, 145.4, 138.8, 137.6, 137.3, 135.2, 132.2, 128.0, 125.4, 116.9, 116.1, 113.6, 92.0, 87.1, 57.3, 56.1, 20.7. FT-IR: 3088, 2946, 2846, 2232, 1647, 1583, 1468, 1413, 1229, 1187, 1035, 785 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{16}H_{15}INO_3^+$ [M − OTs]$^+$, 396.0091; observed, 396.0076. Melting point: 175−178 °C.

Compound ***18***. Prepared according to the general procedure above on 5 mmol scale and obtained in 86% yield (2.395 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88−7.82 (m, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.55−7.40 (m, 4H), 7.11 (d, J = 7.9 Hz, 2H), 6.48 (s, 2H), 3.95 (s, 6H), 3.88 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.3, 161.7 (d, J_{C-F} = 251.9 Hz), 159.4, 145.5, 137.7, 133.2 (d, J_{C-F} = 7.8 Hz), 130.3 (d, J_{C-F} = 3.2 Hz), 128.0, 125.4 121.2 (d, J_{C-F} = 24.6 Hz), 118.7 (d, J_{C-F} = 20.8 Hz), 115.6 (d, J_{C-F} = 7.4 Hz), 92.0, 87.2, 57.3, 56.1, 20.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ −108.1. FT-IR: 3086, 2945, 2845, 1650, 1581, 1468, 1414, 1344, 1209, 1035 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{15}H_{15}FIO_3^+$ [M − OTs]$^+$, 389.0044; observed, 389.0021. Melting point: 181−182 °C.

Compound ***19***. Prepared according to the general procedure above on 5 mmol scale and obtained in 89% yield (2.532 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (s, 2H), 7.47 (d, J = 8.0 Hz, 2H), 7.21 (s, 1H), 7.10 (d, J = 7.9 Hz, 2H), 6.46 (s, 2H), 3.95 (s, 6H), 3.86 (s, 3H), 2.32−2.22 (m, 9H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0, 159.3, 145.6, 141.0, 137.5, 132.9, 131.6, 128.0, 125.4, 115.6, 92.0, 86.7, 57.2, 56.1, 20.7, 20.5. FT-IR: 3086, 3054, 3010, 2976, 2945, 2916, 2840, 1582, 1413, 1207, 1189, 1034, 815 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{17}H_{20}IO_3^+$ [M − OTs]$^+$, 399.0452; observed, 399.0434. Melting point: 166−168 °C.

Compound ***20***. Prepared according to the general procedure above on 5 mmol scale with the following deviations: (i) the reaction was removed from the heat bath for 10 min before starting Stage 2; (ii) Stage 2 was run for 10 min at room temperature. The product was obtained in 81% yield (2.478 g) as a light pink powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (d, J = 1.8 Hz, 2H), 7.83 (s, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 6.50 (s, 2H), 3.97 (s, 6H), 3.89 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.5, 159.4, 145.3, 137.7, 135.5, 132.1, 131.4, 128.0, 125.4, 116.6, 92.1, 87.3, 57.3, 56.2, 20.7. FT-IR: 3067, 3037, 2980, 2959, 2939, 2839, 1646, 1587, 1409, 1211, 1188, 816, 795, 657, 563 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{15}H_{14}Cl_2IO_3^+$ [M − OTs]$^+$, 438.9359; observed, 438.9342. Melting point: 193−196 °C.

Compound ***21***. Prepared according to the general procedure above on 1 mmol scale and obtained in 67% yield (0.397 g) as a white powder. ^{1}H NMR (400 MHz, DMSO) δ 7.98−7.96 (m, 1H), 7.76−7.72 (m, 1H), 7.50−7.39 (m, 3H), 7.10 (d, J = 7.8 Hz, 2H), 6.47 (s, 2H), 3.95 (s, 6H), 3.87 (s, 3H), 2.33 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.2, 159.3, 145.5, 139.7, 137.6, 134.8, 133.7, 133.6, 132.8, 128.0, 125.4, 112.8, 92.0, 87.2, 57.3, 56.1, 20.7, 19.4. FT-IR: 3093, 2945, 2845, 1649, 1582, 1467, 1414, 1186, 1211, 1033 cm^1. HRMS (ESI$^+$): calculated for $C_{16}H_{17}ClIO_3^+$ [M − OTs]$^+$, 418.9905; observed, 418.9877. Melting point: 176−178 °C.

Compound ***22***. Prepared according to the general procedure above on 20 mmol scale and obtained in 90% yield (11.258 g) as a white powder. ^{1}H NMR (400 MHz, DMSO) δ 8.36 (dd, J = 6.6, 1.8 Hz, 1H), 8.27−8.18 (m, 1H), 7.66−7.56 (m, 1H), 7.47 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 6.50 (s, 2H), 3.96 (s, 6H), 3.89 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.4, 160.3 (d, J_{C-F} = 259.6 Hz), 159.3, 145.4, 141.5 (d, J_{C-F} = 9.9 Hz), 137.7, 133.3 (d, J_{C-F} = 4.6 Hz), 128.0, 125.4, 121.4 (q, J_{C-F} = 267.6 Hz), 120.7 (d, J_{C-F} = 21.8 Hz), 118.8 (dq, J_{C-F} = 33.3, 13.3 Hz), 110.5 (d, J_{C-F} = 3.7 Hz), 92.1, 87.5, 57.3, 56.2, 20.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ −60.4 (d, J = 12.5 Hz), −110.5 (q, J = 12.5 Hz). FT-IR: 3091, 3063, 3034, 2947, 2886, 2886, 2846, 1469, 1345, 1229, 1210, 1033, 816, 682, 665, 566 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{16}H_{14}F_4IO_3^+$ [M − OTs]$^+$, 456.9918; observed, 456.9895. Melting point: 133−136 °C.

Compound ***23***. Prepared according to the general procedure above on 10 mmol scale and obtained in 95% yield (5.715 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.50 (d, J = 1.8 Hz, 1H), 8.06 (dd, J = 8.2, 1.9 Hz, 1H), 7.60−7.53 (m, 1H), 7.49−7.41 (m, 2H), 7.10 (d, J = 7.8 Hz, 2H), 6.48 (s, 2H), 3.96 (s, 6H), 3.88 (s, 3H), 2.51 (s, 3), 2.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.3, 159.3, 149.3, 145.5, 138.1, 137.6, 136.5, 135.4, 129.7, 128.0, 125.4, 112.5, 92.1, 87.3, 57.3, 56.1, 20.7, 19.3. FT-IR: 3079, 2975, 2942, 2841, 1581, 1455, 1411, 1272, 1161, 1024 cm^1. HRMS (ESI$^+$): calculated for $C_{16}H_{17}INO_5^+$ [M − OTs]$^+$, 430.0146; observed, 430.0116. Melting point: decomposed 113 °C.

Compound ***24***. Prepared according to the general procedure above on 10 mmol scale and obtained in 95% yield (5.715 g) as a pale yellow powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (dd, J = 9.1, 4.7 Hz, 1H), 7.83−7.71 (m, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.15−7.06 (m, 3H), 6.62 (s, 2H), 3.97 (s, 3H), 3.93 (s, 6H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.8, 165.7 (d, J_{C-F} = 262.8 Hz), 160.3, 145.4, 143.0 (d, J_{C-F} = 2.9 Hz), 137.7, 130.2 (d, J_{C-F} = 10.2 Hz), 128.0, 125.4, 119.5 (d, J_{C-F} = 23.6 Hz), 118.9 (d, J_{C-F} = 27.7 Hz), 110.8 (d, J_{C-F} = 7.8 Hz), 92.5, 84.6, 57.5, 56.4, 20.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ −98.1. FT-IR: 3090, 2949, 2847, 2847, 1643, 1582, 1525, 1460, 1347, 1347, 1212, 1187, 1034, 869 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{15}H_{14}FINO_5^+$ [M − OTs]$^+$, 433.9895; observed, 433.9876. Melting point: 173−174 °C.

Compound ***25***. Prepared according to the general procedure above on 5 mmol scale and obtained in 85% yield (2.750 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 7.95 (s, 2H), 7.49 (d, J = 7.6 Hz, 2H), 7.10 (d, J = 7.6 Hz, 2H), 6.47 (s, 2H), 3.95 (s, 6H), 3.86 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.4, 159.5, 145.2, 140.4, 138.0, 135.9−135.5 (m), 131.1, 130.6−130.3 (m), 129.1 (q, J_{C-F} = 33.1 Hz), 128.2, 125.5, 122.7 (q, J_{C-F} = 273.1 Hz), 120.1, 92.2, 87.6, 57.1, 56.2, 20.8. ^{19}F NMR (376 MHz, DMSO-d_6) δ −61.4. FT-IR: 3032, 2942, 2847, 1643, 1590, 1457, 1407, 1212, 1072, 1037 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{16}H_{14}ClF_3IO_3^+$ [M − OTs]$^+$, 472.9623; observed, 472.9594. Melting point: 168−170 °C.

Compound ***26***. Prepared according to the general procedure above on 1 mmol scale and obtained in 85% yield (0.4933 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (d, J = 2.2 Hz, 1H), 8.38 (dd, J = 8.5, 2.3 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 6.47 (s, 2H), 3.96 (s, 6H), 3.88 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.3, 159.2, 153.5, 152.6, 145.3, 145.1, 137.7, 128.0, 127.4, 125.4, 113.8, 92.0, 87.2, 57.3, 56.1, 20.7. FT-IR: 3035, 2943, 2847, 1581, 1455, 1413, 1301, 1210, 1186, 1031, 815 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{14}H_{14}ClINO_3^+$ [M − OTs]$^+$, 405.9701; observed, 405.9684. Melting point: decomposed 165 °C.

Compound ***27***. The precursor aryl iodide (**S1**) was prepared according to a literature procedure[8] on 10 mmol scale and obtained in 51% yield (2.349 g) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 2.2 Hz, 1H), 7.52 (dd, J = 17.0, 2.3 Hz, 1H), 7.31 (d, J = 8.4 Hz, 1H), 7.02 (d (appears as a triplet), J = 1.8 Hz, 1H), 6.90 (d, J = 1.8 Hz, 2H), 5.01 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 138.5, 137.5, 137.3, 135.5, 134.2, 121.9, 121.9, 113.9, 92.7, 69.0. FTIR: 3053, 1573, 1265 cm^{-1}. HRMS (AP$^+$): calculated for $[C_{13}H_8BrCl_2IO]^+$, 455.8180; observed, 455.8203. Melting point: 123−125 °C. R_f: 0.20 in 100% hexanes. **27**: Prepared according to the general procedure above on 5 mmol scale and obtained in 92% yield (2.871 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, J = 2.1 Hz, 1H), 7.86−7.74 (m, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.20 (t, J = 1.7 Hz, 1H), 7.14−7.06 (m, 4H), 6.45 (s, 2H), 5.19 (s, 2H), 3.92 (s, 6H), 3.88 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.2, 159.2, 159.1, 145.5, 138.4, 137.6, 135.5, 135.4, 134.6, 134.4, 128.0, 126.1, 125.4, 121.0, 114.7, 114.0, 91.9, 87.1, 69.0, 57.2, 56.1, 20.7. FT-IR: 3033, 2945, 2845, 1640, 1580, 1413, 1212, 1186, 815, 680 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{22}H_{19}BrCl_2IO_4^+$ [M − OTs]$^+$, 622.8883; observed, 622.8856. Melting point: decomposed 180 °C.

Compound ***28***. The precursor aryl iodide (**S2**) was prepared according to the literature procedure[8] on 10 mmol scale and obtained in 77% yield (2.915 g) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.56 (m, 2H), 7.04−7.02 (m, 3H), 6.91−6.89 (m, 1H), 6.74−6.70 (m, 1H), 4.09 (t, J = 6.7 Hz, 2H), 3.02 (t, J = 6.7 Hz,

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2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9 (d, J_{C-F} = 2.4 Hz), 152.7 (d, J_{C-F} = 241.3 Hz), 137.6, 137.5, 131.0, 121.0 (d, J_{C-F} = 19.1 Hz), 116.7 (d, J_{C-F} = 22.5 Hz), 116.2, 114.0 (d, J_{C-F} = 6.7 Hz), 91.9, 69.0, 35.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ −126.1. FTIR: 3024, 2253, 1499, 1202, 909 cm^{-1}. HRMS (EI): calculated for $C_{14}H_{11}ClFIO$, 375.9527; observed, 375.9516. R_f: 0.26 in 100% hexanes. **28**: Prepared according to the general procedure above on 5 mmol scale and obtained in 93% yield (2.586 g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.86 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.28 (t, J = 9.1 Hz, 1H), 7.15−7.06 (m, 3H), 6.93−6.85 (m, 1H), 6.46 (s, 2H), 4.18 (t, J = 6.5 Hz, 2H), 3.95 (s, 6H), 3.86 (s, 3H), 3.04 (t, J = 6.4 Hz, 2H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.0, 159.3, 154.8 (d, J_{C-F} = 2.1 Hz), 151.7 (d, J_{C-F} = 238.8 Hz), 145.6, 142.4, 137.5, 134.3, 132.1, 128.0, 125.4, 119.6 (d, J_{C-F} = 19.0 Hz), 117.1 (d, J_{C-F} = 22.3 Hz), 115.8, 114.9 (d, J_{C-F} = 6.9 Hz), 113.5, 92.0, 87.0, 68.3, 57.2, 56.1, 34.19, 20.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ −127.1. FT-IR: 3092, 3059, 2960, 2927, 2867, 1657, 1394, 1214, 1187, 816 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{23}H_{22}ClFIO_4^+$ [M − OTs]$^+$, 543.0230; observed, 543.0206. Melting point: 128−130 °C.

Compound ***29***. Prepared according to the general procedure above on 5 mmol scale and obtained in 92% yield (2.931g) as a white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06−7.78 (m, 8H), 7.47 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 7.8 Hz, 2H), 6.49 (s, 2H), 3.97 (s, 6H), 3.88 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.6, 166.1, 159.2, 145.6, 140.3, 137.5, 134.5(3), 134.5(0), 134.2, 131.4, 130.1, 127.9, 125.4, 123.2, 114.4, 91.9, 87.0, 57.2, 56.0, 20.7. FT-IR: 3089, 3056, 2980, 2946, 2839, 2227, 1645, 1582, 1413, 1164, 815. HRMS (ESI$^+$): calculated for $C_{22}H_{19}INO_3^+$ [M − OTs]$^+$, 472.0404; observed, 472.0375. Melting point: 174−179 °C.

General Procedure for Anion Exchange of 14-OTs to 14-X (Scheme 3a), 4-OTs to 4-Br, 22-OTs to 22-PF$_6$, and 29-OTs to 29-Br. Reactions were carried out on 1−2.5 mmol scale of **14-OTs**, **22-OTs**, or **29-OTs** as indicated below. **14-OTs**, **22-OTs**, or **29-OTs** (1 equiv) was added to 50 mL of boiling water. If the iodonium salt did not dissolve after boiling for 1−2 min, then methanol was added portionwise until the solution had a homogeneous appearance. While the mixture was still hot, a salt containing the target anion was added in excess (10−100 equiv). The resulting solution was left to cool to ambient temperature, before chilling further in an ice-bath. The mixture was suction filtered, and the filter cake was washed by slurry filtration with water (3 × 30 mL). The cake was dried under suction for 10−20 min and then washed by slurry filtration with diethyl ether (3 × 30 mL). The sample was finally dried under high vacuum to remove residual solvent. If a low yield is obtained and the iodonium salt is suspected to remain in the aqueous filtrate, then it may be extracted with a suitable solvent such as dichloromethane or ethyl acetate.

Compound ***14-Br***. Prepared according to the general anion exchange procedure above on 2.5 mmol scale, using potassium bromide (6.00 g, 50 mmol, 20 equiv) and obtained in 96% yield (1.28 g) as an off-white to light brown powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00−7.95 (m, 2H), 7.71 (d, J = 8.6 Hz, 2H), 7.68−7.63 (m, 2H), 7.53−7.37 (m, 3H), 6.45 (s, 2H), 3.95 (s, 6H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.6, 159.2, 142.6, 138.3, 134.6, 129.3, 129.0, 128.3, 126.8, 116.5, 91.9, 89.9, 57.2, 56.0. FT-IR: 3072, 2944, 2836, 1636, 1587, 1467, 1338, 1232, 1158, 1033, 824 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{21}H_{20}IO_3^+$ [M − Br]$^+$, 447.0452; observed, 447.0423. Melting point: 193−195 °C.

Compound ***14-I***. Prepared according to the general anion exchange procedure above on 1 mmol scale, using potassium iodide (1.765 g, 11 mmol, 11 equiv) and obtained in 95% yield (0.544 g) as an off-white to light brown powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.03−7.95 (m, 2H), 7.77−7.70 (m, 2H), 7.70−7.62 (m, 2H), 7.54−7.39 (m, 3H), 6.47 (s, 2H), 3.97 (s, 6H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.8, 159.2, 142.8, 138.2, 134.8, 129.4, 129.0, 128.4, 126.8, 115.6, 92.0, 88.6, 57.3, 56.1. FT-IR: 3055, 3036, 2970, 2833, 1645, 1585, 1468, 1229, 1162, 1030, 808 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{21}H_{20}IO_3^+$ [M − I]$^+$, 447.0452; observed, 447.0422. Melting point: 164−165 °C.

Compound ***14-O$_2$CCF$_3$***. Prepared according to the general anion exchange procedure above on 1 mmol scale, using sodium trifluoroacetate (2.758 g, 20 mmol, 20 equiv) and obtained in 86% yield (0.481 g) as an off-white to light brown powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, J = 8.1 Hz, 2H), 7.73 (d, J = 8.1 Hz, 2H), 7.67 (d, J = 7.4 Hz, 2H), 7.53−7.35 (m, 3H), 6.47 (s, 2H), 3.97 (s, 6H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.1, 159.5, 158.1 (q, J_{C-F} = 30.9 Hz), 143.1, 138.2, 134.8, 129.5, 129.1, 128.5, 126.9, 117.2 (q, J_{C-F} = 300.4 Hz), 114.9, 92.0, 87.4, 57.2, 56.0. ^{19}F NMR (376 MHz, DMSO-d_6) δ −73.4. FT-IR: 3061, 2946, 2843, 1681, 1583, 1414, 1230, 1160, 1026, 803 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{21}H_{20}IO_3^+$ [M − CF_3COO]$^+$, 447.0452; observed, 447.0431. Melting point: 175−177 °C.

Compound ***14-OTf***. Prepared according to the general anion exchange procedure above on 2 mmol scale with sodium triflate (6.99 g, 40.6 mmol, 20 equiv) and obtained in 90% yield (1.094 g) as an off-white to light brown powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.01 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 7.4 Hz, 2H), 7.59−7.38 (m, 3H), 6.50 (s, 2H), 3.99 (s, 6H), 3.89 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.2, 159.4, 143.2, 138.1, 134.9, 129.6, 129.1, 128.5, 126.9, 120.7 (q, J_{C-F} = 322.3 Hz), 114.5, 92.0, 87.0, 57.3, 56.1. ^{19}F NMR (376 MHz, DMSO) δ −77.7. FT-IR: 3090, 3063, 2944, 2883, 2846, 1578, 1457, 1415, 1259, 1162, 1027, 815 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{21}H_{20}IO_3^+$ [M − OTf]$^+$, 447.0452; observed, 447.0471. Melting point: decomposed 93 °C.

Compound ***14-PF$_6$***. Prepared according to the general anion exchange procedure above on 1 mmol scale with potassium hexafluorophosphate (3.821 g, 20.8 mmol, 20.8 equiv) and obtained in 90% yield (0.556 g) as an off-white to light brown powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.04 (d, J = 7.9 Hz, 2H), 7.76 (d, J = 7.9 Hz, 2H), 7.67 (d, J = 7.1 Hz, 2H), 7.59−7.36 (m, 3H), 6.51 (s, 2H), 4.00 (s, 6H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.2, 159.4, 143.2, 138.2, 134.9, 129.6, 129.1, 128.5, 126.9, 114.5, 92.0, 87.0, 57.3, 56.1. ^{19}F NMR (376 MHz, DMSO-d_6) δ −70.1 (d, J_{F-P} = 711.5 Hz). FT-IR: 3109, 1636, 2949, 1583, 2848, 3065, 1473, 1415, 1231, 1163, 1065, 843 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{21}H_{20}IO_3^+$ [M − PF_6]$^+$, 447.0452; observed, 447.0425. Melting point: decomposed 127 °C.

Compound ***14-BF$_4$***. Prepared according to the general anion exchange procedure above on 1 mmol scale, using sodium tetrafluoroborate (11.438 g, 104 mmol, 104 equiv) and obtained in 96% yield (0.532 g) as an off-white to light brown powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H), 7.67 (d, J = 7.5 Hz, 2H), 7.53−7.38 (m, 3H), 6.49 (s, 2H), 3.97 (s, 6H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.2, 159.4, 143.2, 138.1, 134.9, 129.6, 129.1, 128.6, 126.9, 114.5, 92.0, 87.0, 57.3, 56.1. ^{19}F NMR (376 MHz, DMSO-d_6) δ −148.3. FT-IR: 3088, 3061, 2945, 2845, 1625, 1582, 1472, 1413, 1230, 1034, 817 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{21}H_{20}IO_3^+$ [M − BF_4]$^+$, 447.0452; observed, 447.0427. Melting point: 160−162 °C.

Compound ***4-Br***. Prepared according to the general anion exchange procedure above on 1 mmol scale using potassium bromide (12.5 g, 10.5 mmol, 10.5 equiv) and obtained in 85% yield (0.395 g) as a white powder. ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.77 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 6.42 (s, 2H), 3.92 (s, 6H), 3.85 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 165.5, 159.1, 141.1, 134.0, 131.7, 114.4, 91.8, 90.0, 57.1, 56.0, 20.7. FT-IR: 3014, 2966, 2933, 1580, 1464, 1227, 1032, 808 cm^{-1}. HRMS (ESI$^+$): calculated for $C_{16}H_{18}IO_3^+$ [M − Br]$^+$, 385.0295; observed, 385.0324. Mp 192−193 °C.

Compound ***22-PF$_6$***. Prepared according to the general anion exchange procedure above on 1 mmol scale and obtained in 61% yield (0.365 g) as a white powder. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.39−8.35 (m, 1H), 8.26−8.18 (m, 1H), 7.68−7.54 (m, 1H), 6.49 (s, 2H), 3.96 (s, 6H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.7, 160.6 (dd, J = 260.1, 1.8 Hz), 159.6, 141.7 (d, J_{C-F} = 9.6 Hz), 133.6, (d, J_{C-F} = 3.9 Hz), 121.54 (q, J = 273.1 Hz), 120.9 (d, J = 21.8 Hz), 119.2 (dq, J = 33.2, 13.2 Hz), 110.5 (d, J = 3.7 Hz), 92.2, 87.5, 57.4, 56.2. ^{19}F NMR (376 MHz, DMSO-d_6) δ −60.6 (d, J = 12.5 Hz), −70.2 (d, J_{P-F} = 711.3 Hz), −110.3 (q, J = 12.5 Hz). FT-IR: 3116, 3064,

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2952, 2952, 2848, 1414, 1311, 1163, 845 cm^{1}. HRMS (ESI^+): calculated for $C_{16}H_{14}F_4IO_3^+$ $[M - PF_6]^+$, 456.9889; observed, 456.9895. Melting point: decomposed 126 °C.

Compound ***29-Br***. Prepared according to the general anion exchange procedure above on 1.9 mmol scale, using potassium bromide (4.5 g, 36 mmol, 19 equiv) and obtained in 91% yield (1.733 g) as a white powder. ^1H NMR (400 MHz, DMSO-d_6) δ 8.11−7.69 (m, 8H), 6.45 (s, 2H), 3.96 (s, 6H), 3.87 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.6, 159.2, 142.8, 140.4, 134.6, 132.9, 129.6, 127.8, 118.7, 118.6, 110.9, 91.9, 90.9, 57.2, 56.0. FT-IR: 3089, 3056, 2980, 2946, 2839, 2227, 1645, 1582, 1413, 1164, 815 cm^{-1}. HRMS (ESI^+): calculated for $C_{22}H_{19}INO_3^+$ $[M - Br]^+$, 472.0404; observed, 472.0375. Melting point: 175−176 °C.

Representative Procedure for One-Pot Synthesis of Aryl-(2,4,6-trimethoxyphenyl)iodonium Bromides (Scheme 3b). *Compound* ***23-Br***. 4-Methyl-3-nitro iodobenzene (1.33 g, 5.1 mmol, 1 equiv) and acetonitrile (5 mL) were added to a 250 mL round-bottom flask, equipped with a stir bar. Toluenesulfonic acid monohydrate (0.965 g, 5.1 mmol, 1.0 equiv) was added in one portion, followed by one portion of *m*-CPBA (1.09 g, 5.1 mmol, 1.0 equiv). After a reflux condenser was attached, the reaction was lowered into a heat bath set to 77 °C and stirred vigorously. After 30 min, the reflux condenser was removed in order to add 1,3,5-trimethoxybenzene (0.858 g, 5.1 mmol, 1.0 equiv) in one portion and stirring was continued at 77 °C for 5 min. The reaction was removed from heat, and 100 mL of water were added. The mixture was brought to near boiling until dissolved, and KBr (6.0 g, 50 mmol, 10 equiv) was added. After stirring for 2 min the solution was removed from heat and allowed to cool to ambient temperature, before chilling further in an ice−water bath. The mixture was suction filtered, and the filter cake was washed by slurry filtration with water (3 × 30 mL). The cake was dried under suction for 10−20 min and then washed by slurry filtration with ethyl ether (3 × 30 mL). The sample was finally dried under high vacuum to remove trace solvent. If iodonium salt is suspected to remain in the aqueous filtrate, then it may be extracted with a suitable solvent such as dichloromethane or ethyl acetate. After drying under high vacuum, **23-Br** was obtained in 82% yield (2.112 g, 4.2 mmol) as a white powder. ^1H NMR (400 MHz, DMSO-d_6) δ 8.51 (d, J = 1.7 Hz, 1H), 8.06 (dd, J = 8.2, 1.8 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 6.44 (s, 2H), 3.95 (s, 6H), 3.87 (s, 3H), 2.51 (d, J = 6.7 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.7, 159.1, 149.1, 138.0, 135.8, 135.0, 129.4, 116.2, 91.9, 91.8, 57.2, 56.0, 19.3. FT-IR: 3079, 2975, 2942, 2841, 1581, 1524, 1455, 1411, 1342, 1272, 1161, 1024, 815 cm^{-1}. HRMS (ESI^+): calculated for $C_{16}H_{17}INO_5^+$ $[M - Br]^+$, 430.0146; observed, 430.0125. Melting point: 166−167 °C.

Compound ***26-Br***. Prepared analogously to the representative one-pot procedure above on 5 mmol scale and isolated in 74% yield (2.298 g), as an off-white powder. ^1H NMR (400 MHz, DMSO-d_6) δ 8.83 (d, J = 2.2 Hz, 1H), 8.36 (dd, J = 8.5, 2.4 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 6.44 (s, 2H), 3.96 (s, 6H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 165.6, 159.0, 153.2, 151.8, 144.7, 127.0, 117.7, 92.1, 91.9, 57.2, 56.1. FT-IR: 3075, 3039, 2971, 2942, 2842, 1582, 1454, 1412, 1342, 1161, 817, 731 cm^{-1}. HRMS (ESI^+): calculated for $C_{14}H_{14}ClINO_3^+$ $[M - Br]^+$, 405.9701; observed, 405.9684. Melting point: 161−163 °C.

Procedures for Synthetic Applications (Scheme 4). Literature procedures were applied to **4-Br**, **10-OTs**, **14-OTf**, and **29-Br** on 0.34−1 mmol scale.

Compound ***30***. Prepared according to literature procedure[31] on 0.4 mmol scale of **14-OTf** and obtained in 55% yield (0.070 g) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (dt, J = 8.9, 2.0 Hz, 4H), 7.46−7.39 (m, 2H), 7.37−7.28 (m, 3H), 4.31−4.19 (m, 2H), 2.88−2.76 (m, 1H), 2.66−2.54 (m, 2H), 2.37 (ddd, J = 10.5, 6.9, 3.1 Hz, 1H), 2.09−1.94 (m, 1H), 1.93−1.72 (m, 3H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.6, 171.2, 140.6, 140.4, 135.8, 128.8, 128.2, 127.4, 127.1, 127.1, 66.2, 61.8, 40.9, 35.4, 27.7, 22.3, 14.0. FT-IR: 3054, 2985, 1713, 1265, 1133 cm^{-1}. HRMS (ESI^+): calculated for $C_{21}H_{23}O_3^+$ $[M + H]^+$, 323.1647; observed, 323.1619. Melting point: 131−132 °C. R_f: 0.22 in 15% diethyl ether/hexane.

Compound ***31***. Prepared according to literature procedure[50] on 0.5 mmol scale of **10**-OTs and obtained in 63% yield (0.0613 g) as a pale yellow oil. ^1H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 1.30 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.0, 137.1, 126.7, 118.6, 34.4, 31.3. The spectral data were consistent with those previously reported.[61]

Compound ***32***. Prepared according to literature procedure[50] on 0.5 mmol scale of **14**-OTf and obtained in 72% yield (0.0706 g) as a pale yellow solid. ^1H NMR (600 MHz, $CDCl_3$) δ 7.59−7.49 (m, 4H), 7.41 (t, J = 7.7 Hz, 2H), 7.32 (t, J = 7.4 Hz, 1H), 7.05 (t, J = 8.2 Hz, 2H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 140.2, 139.2, 138.0, 129.0, 128.5, 127.4, 126.9, 119.4. The spectral data were consistent with those previously reported.[62]

Compound ***33***. Prepared according to literature procedure[51] on 0.34 mmol scale of **4**-Br and obtained in 85% yield (0.0586 g) as a colorless liquid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.14−7.11 (m, 2H), 7.02−6.92 (m, 4H), 6.88−6.86 (m, 2H), 2.32 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.56 (d, J_{C-F} = 241.0 Hz), 155.2, 153.4 (d, J_{C-F} = 2.4 Hz), 132.8, 130.2, 119.9 (d, J_{C-F} = 8.2 Hz), 118.5, 116.15 (d, J_{C-F} = 23.2 Hz), 20.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ 120.79. The spectral data were consistent with those previously reported.[63]

Compound ***34***. Prepared according to literature procedure[51] on 1.0 mmol scale of **14-OTf** and obtained in 80% (0.213 g) as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58−7.52 (m, 4H), 7.45−7.39 (m, 2H), 7.35−7.30 (m, J = 5.9, 4.7, 2.3 Hz, 1H), 7.09−6.99 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.1, 157.7, 157.3, 152.8, 140.5, 136.2, 128.6 (d, J_{C-F} = 33.3 Hz), 127.0, 126.8, 120.6 (d, J_{C-F} = 8.2 Hz), 118.4, 116.3 (d, J_{C-F} = 23.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −119.9. FT-IR: 1500, 1265, 1214 cm^{-1}. HRMS (EI): calculated for $C_{18}H_{13}FO$, 264.0950; observed, 264.0942. Melting point: 76−78 °C. R_f: 0.6 in 100% hexane.

Compound ***35***. Prepared according to literature procedure[52] on 1.0 mmol scale of **14-OTf** and obtained in 78% yield (0.235 g) as a white powder. ^1H NMR (400 MHz, $CDCl_3$) δ 8.03−7.95 (m, 4H), 7.73−7.67 (m, 2H), 7.60−7.36 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.2, 141.8, 140.1, 139.2, 133.2, 129.3, 129.1, 128.6, 128.2, 127.9, 127.6, 127.3. FT-IR: 1637, 1265, 1158 cm^{-1}. HRMS (ESI^+): calculated for $C_{18}H_{15}O_2S^+$ $[M + H]^+$, 295.0793; observed, 295.0763. Melting point: 142.8−147 °C. R_f: 0.20 in 20% diethyl ether/hexane.

Compound ***36***. Prepared according to literature procedure[8] on 1 mmol scale of **29-Br** and obtained in 70% yield after purification (0.215 g) as a white powder. The crude product was purified by column chromatography with silica gel and gradient elution (hexane, 1% ethyl ether, 2% ethyl ether). Mixed fractions were again chromatographed according to the same procedure for a combined 70% yield of **33**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68−7.55 (m, 4H), 7.53−7.43 (m, 2H), 7.02−6.91 (m, 2H), 3.98 (t, J = 6.6 Hz, 2H), 1.88−1.70 (m, 2H), 1.52−1.21 (m, 10H), 0.89 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 145.2, 132.6, 131.2, 128.3, 127.0, 119.1, 115.1, 110.0, 68.2, 31.9, 29.4, 29.2(9), 29.2(8), 26.1, 22.7, 14.2. The spectral data were consistent with those previously reported.[64]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02833.

Additional details of multivariate experimental designs, qualitative light stability studies, DSC, *in situ* temperature monitoring of reactions, and ^1H, ^{13}C, ^{19}F NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Shi, W.-M.; Ma, X.-P.; Pan, C.-X.; Su, G.-F.; Mo, D.-L. *J. Org. Chem.* **2015**, *80*, 11175−11183.
(2) Gonda, Z.; Novák, Z. *Chem. - Eur. J.* **2015**, *21*, 16801−16806.
(3) Ma, X.-P.; Shi, W.-M.; Mo, X.-L.; Li, X.-H.; Li, L.-G.; Pan, C.-X.; Chen, B.; Su, G.-F.; Mo, D.-L. *J. Org. Chem.* **2015**, *80*, 10098−10107.
(4) Dey, C.; Lindstedt, E.; Olofsson, B. *Org. Lett.* **2015**, *17*, 4554−4557.
(5) Xiong, W.; Qi, C.; Peng, Y.; Guo, T.; Zhang, M.; Jiang, H. *Chem. - Eur. J.* **2015**, *21*, 14314−14318.
(6) Miralles, N.; Romero, R. M.; Fernández, E.; Muñiz, K. *Chem. Commun.* **2015**, *51*, 14068−14071.
(7) Matsuzaki, K.; Okuyama, K.; Tokunaga, E.; Saito, N.; Shiro, M.; Shibata, N. *Org. Lett.* **2015**, *17*, 3038−3041.
(8) Sundalam, S. K.; Stuart, D. R. *J. Org. Chem.* **2015**, *80*, 6456−6466.
(9) Tinnis, F.; Stridfeldt, E.; Lundberg, H.; Adolfsson, H.; Olofsson, B. *Org. Lett.* **2015**, *17*, 2688−2691.
(10) Hu, B.; Miller, W. H.; Neumann, K. D.; Linstad, E. J.; DiMagno, S. G. *Chem. - Eur. J.* **2015**, *21*, 6394−6398.
(11) Margraf, N.; Manolikakes, G. *J. Org. Chem.* **2015**, *80*, 2582−2600.
(12) Monastyrskyi, A.; Namelikonda, N. K.; Manetsch, R. *J. Org. Chem.* **2015**, *80*, 2513−2520.
(13) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299−5358.
(14) Merritt, E. A.; Olofsson, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9052−9070.
(15) Yusubov, M. S.; Maskaev, A. V.; Zhdankin, V. V. *ARKIVOK* **2011**, 370−409.
(16) Ochiai, M. Reactivities, Properties, and Structure. In *Hypervalent Iodine Chemistry*; Wirth, T., Ed.; Springer-Verlag: Berlin, 2003; Vol. *224*, pp 5−68.
(17) Zhdankin, V. V. *Hypervalent Iodine Chemistry: Preparation, Structure and Synthetic Applications of Polyvalent Iodine Compounds*; John Wiley & Sons: West Sussex, 2014; pp 145−336.
(18) Malmgren, J.; Santoro, S.; Jalalian, N.; Himo, F.; Olofsson, B. *Chem. - Eur. J.* **2013**, *19*, 10334−10342.
(19) Chun, J.-H.; Pike, V. W. *Org. Biomol. Chem.* **2013**, *11*, 6300−6306.
(20) A PubMed (http://www.ncbi.nlm.nih.gov/pubmed; accessed 10/15/2015) search for "diaryliodonium" limited to "the last 5 years" yielded only four examples that used unsymmetrical aryl(auxiliary) iodonium salts in the evaluation of the scope of a metal-free arylation reaction.
(21) Kryska, A.; Skulski, L. *Molecules* **2001**, *6*, 875−880.
(22) Bielawski, M.; Olofsson, B. *Chem. Commun.* **2007**, 2521−2523.
(23) Bielawski, M.; Zhu, M.; Olofsson, B. *Adv. Synth. Catal.* **2007**, *349*, 2610−2618.
(24) Zhu, M.; Jalalian, N.; Olofsson, B. *Synlett* **2008**, *2008*, 592−596.
(25) Bielawski, M.; Aili, D.; Olofsson, B. *J. Org. Chem.* **2008**, *73*, 4602−4607.
(26) Dohi, T.; Yamaoka, N.; Itani, I.; Kita, Y. *Aust. J. Chem.* **2013**, *64*, 529−535.
(27) 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**, *2015*, 5919−5924.
(28) Clarke, P. A.; Santos, S.; Martin, W. H. C. *Green Chem.* **2007**, *9*, 438−440.
(29) Vaxelaire, C.; Winter, P.; Christmann, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3605−3607.
(30) Henderson, R. K.; Hill, A. P.; Redman, A. M.; Sneddon, H. F. *Green Chem.* **2015**, *17*, 945−949.
(31) Oh, C. H.; Kim, J. S.; Jung, H. H. *J. Org. Chem.* **1999**, *64*, 1338−1340.
(32) For an example where the TMB group is the transferring aryl group, see: Yamaoka, N.; Sumida, K.; Itani, I.; Kubo, H.; Ohnishi, Y.; Sekiguchi, S.; Dohi, T.; Kita, Y. *Chem. - Eur. J.* **2013**, *19*, 15004−15011.
(33) Tohma, H.; Morioka, H.; Harayama, Y.; Hashizume, M.; Kita, Y. *Tetrahedron Lett.* **2001**, *42*, 6899−6902.
(34) Dohi, T.; Yamaoka, N.; Kita, Y. *Tetrahedron* **2010**, *66*, 5775−5785.
(35) Chun, J.-Y.; Pike, V. W. *J. Org. Chem.* **2012**, *77*, 1931−1938.
(36) Carlson, R.; Carlson, J. E. *Design and Optimization in Organic Synthesis*, Revised and Enlarged 2nd ed.; Elsevier: Amsterdam, 2005.
(37) García-Muñoz, S.; Luciani, C. V.; Vaidyaraman, S.; Seibert, K. D. *Org. Process Res. Dev.* **2015**, *19*, 1012−1023.
(38) Chen, X.; Laughlin, K.; Sparks, J. R.; Linder, L.; Farozic, V.; Masser, H.; Petr, M. *Org. Process Res. Dev.* **2015**, *19*, 995−1003.
(39) Colleville, A. P.; Horan, R. A. J.; Tomkinson, N. C. O. *Org. Process Res. Dev.* **2014**, *18*, 1128−1136.
(40) Merritt, E. A.; Carneiro, V. M. T.; Silva, L. F., Jr.; Olofsson, B. *J. Org. Chem.* **2010**, *75*, 7416−7419.
(41) Plackett, R. L.; Burman, J. P. *Biometrika* **1946**, *33*, 305−325.
(42) See the SI for details.
(43) Kraszkiewicz, L.; Skulski, L. *Synthesis* **2008**, *2008*, 2373−2380.
(44) Chan, L.; McNally, A.; Toh, Q. Y.; Mendoza, A.; Gaunt, M. J. *Chem. Sci.* **2015**, *6*, 1277−1281.
(45) Crivello, J. V.; Lam, J. H. W. *Macromolecules* **1977**, *10*, 1307−1315.
(46) Woods, B. P.; Hoye, T. R. *Org. Lett.* **2014**, *16*, 6370−6373.
(47) For information on the decomposition of *m*-CPBA, see: Rao, A. S.; Mohan, H. R.; Charette, A. 2005. *m*-Chloroperbenzoic Acid. e-EROS Encyclopedia of Reagents for Organic Synthesis.
(48) Jalalian, N.; Olofsson, B. *Tetrahedron* **2010**, *66*, 5793−5800.
(49) Ghosh, R.; Olofsson, B. *Org. Lett.* **2014**, *16*, 1830−1832.
(50) Lubinkowski, J. J.; Gomez, M.; Calderon, J. L.; McEwen, W. E. *J. Org. Chem.* **1978**, *43*, 2432−2435.
(51) Jalalian, N.; Ishikawa, E. E.; Silva, L. F., Jr.; Olofsson, B. *Org. Lett.* **2011**, *13*, 1552−1555.
(52) Umierski, N.; Manolikakes, G. *Org. Lett.* **2013**, *15*, 188−191.
(53) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165−195.
(54) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 10139−10147.
(55) DiRocco, D. A.; Dykstra, K.; Krska, S.; Vachal, P.; Conway, D. V.; Tudge, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 4802−4806.
(56) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, *45*, 546.
(57) Clapp, T. V.; Crossland, W. A.; Davey, A. B.; Grasmann, M.; Hannington, J. P.; King, R. K.; Pivnenko, M.; Robson, S.; Xu, H. *Liquid Crystal Formulations and Structures for Smectic A Optical Devices*. U.S. Patent 13,635,334, Mar. 15, 2011.
(58) Jalalian, N.; Olofsson, B. *Org. Synth.* **2014**, *90*, 1−9.
(59) Uldry, A.-C.; Griffin, J. M.; Yates, J. R.; Pérez-Torralba, M.; Santa Maria, M. D.; Webber, A. L.; Beaumont, M. L. L.; Samoson, A.; Claramunt, R. M.; Pickard, C. J.; Brown, S. P. *J. Am. Chem. Soc.* **2008**, *130*, 945−954.
(60) Park, K. D.; Morieux, P.; Solomé, C.; Cotton, S. W.; Reamtong, O.; Eyers, C.; Gaskell, S. J.; Stables, J. P.; Liu, R.; Kohn, H. *J. Med. Chem.* **2009**, *52*, 6897−6911.

DOI: 10.1021/acs.joc.5b02833
J. Org. Chem. 2016, 81, 1998−2009

(61) Kumar, A. S.; Reddy, M. A.; Knorn, M.; Reiser, O.; Sreedhar, B. *Eur. J. Org. Chem.* **2013**, *2013*, 4674−4680.
(62) Li, Y.; Gao, L.-X.; Han, F.-S. *Chem. - Eur. J.* **2010**, *16*, 7969−7972.
(63) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623−1626.
(64) Mert, H.; Dinçer, H.; Çalişkan, E.; Şen, B. N.; Gürsel, Y. H. *J. Appl. Polym. Sci.* **2015**, *132*, DOI: 10.1002/app.41574.

DOI: 10.1021/acs.joc.5b02833
J. Org. Chem. 2016, 81, 1998−2009