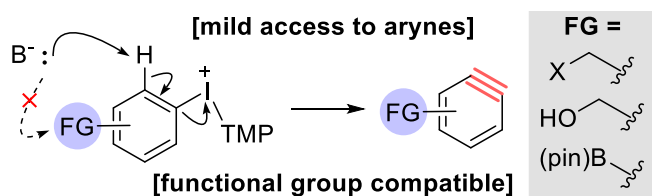


Deprotonation of arenes with weak base: assessing and expanding the functional group compatibility of aryne chemistry

Bryan E. Metze, Riley A. Roberts, Aleksandra Nilova, and David R. Stuart*

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

Abstract: Arynes hold immense potential as reactive intermediates in organic synthesis as they engage in a diverse range of mechanistically distinct chemical reactions. However, the poor functional group compatibility of generating arynes or aryne precursors has stymied their widespread use. Here, we show that generating arynes can be both efficient and mild by deprotonating aryl(TMP)iodonium salts with potassium phosphate (TMP = 2,4,6-trimethoxyphenyl) and these conditions are uniquely compatible with acyclic diaryliodonium salts. We have also performed the first comparison of functional group compatibility by the method of additives across a range of reaction conditions, including the current state-of-the-art, to generate arynes. The scope of the reaction conditions includes sensitive functional groups such as benzylic halides, ketones, alcohols, and boronate esters that are not compatible with prior methods and charts a new course forward for aryne chemistry.



Introduction

Functional group compatibility is an aspirational goal in the development of chemical reactions for organic synthesis. Indeed, chemoselectivity¹ underpins the efficient synthesis of complex molecules,² and the application of bio-orthogonal reactions.³ Arynes are highly reactive intermediates that continue to attract attention from synthetic chemists because of their diverse reactivity profile.⁴ Although arynes are well-established electrophiles and dipolarophiles, and the electrophilicity parameter of arynes has been determined,⁵ the functional group compatibility of these intermediates, and methods to generate them, remains anecdotal. Here, we describe the formal analysis of functional group compatibility of three methods to generate arynes, including novel conditions for β -elimination by arene deprotonation with a weak base and extrusion of a super leaving group.

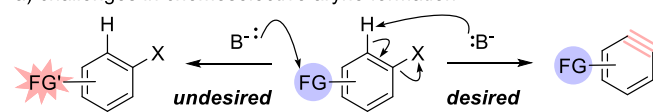
The use of [*o*-trimethylsilyl]phenyl triflate reagents is generally regarded as the current state of the art and the most mild, and therefore functional group compatible, approach to arynes due to the highly chemoselective reaction between the fluoride activator and electrofugal trimethylsilyl leaving group.^{5h,6} However, the relatively limited commercial availability and multi-step synthesis of these reagents is a drawback to their use and ultimately limits the range of functional groups that are included on these reagents. On the other hand, accessing arynes by deprotonating an arene and ejection of an ortho-leaving group, which is typically a

(pseudo)halide, is highly efficient because of the extensive commercial availability of such reagents (Scheme 1a).⁷ However, this approach requires strong bases, such as lithium amides, butyllithium, and metal alkoxides.⁷ Consequently, the potential for undesired reactions of the base with functional groups (FG) on the aryl halide is high, which also limits the functional groups that are included on arynes formed in this way. (Scheme 1a).

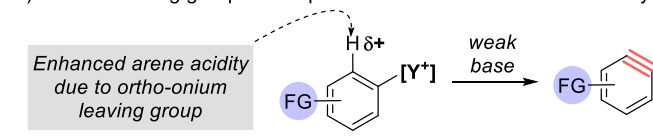
The use of onium leaving groups to generate arynes has been known for some time,⁸ and recent advances include more robust synthetic protocols and expanded scope.⁹ Most of these advances have involved aryliodonium leaving groups, which are synthetically accessible, but still require relatively strong bases (eg. NaO*t*-Bu or LiHMDS).⁹ However, the super leaving group ability and very strong inductive withdrawing effects of “onium” groups offers the potential to generate arynes under more mild conditions than with neutral (pseudo)halide leaving groups (Scheme 1b).¹⁰ The enhanced acidity of the proton at the ortho-position to the “onium” leaving group is a potential solution to chemoselectivity of generating arynes via deprotonation because relatively weak bases will leave electrophilic and Lewis and Bronsted acidic functional groups intact (Scheme 1b).

Scheme 1. Recent efforts toward generating arynes with weak base.

a) challenges in chemoselective aryne formation

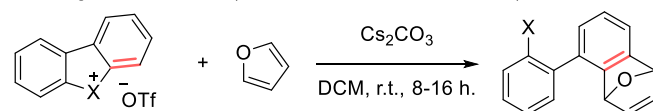


b) “onium” leaving groups are a potential solution for chemoselectivity

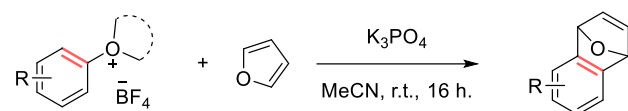


c) recent examples of deprotonation/onium ejection with weak base

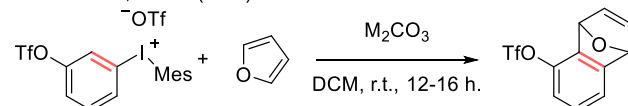
- Wencel-Delord: 2021, X=Br (92%)
- McCormick/Stuart: 2022, X=Cl (86%, OMs salt used)
- Zhang/Wu: 2023, X=I (30%, *t*-BuOH, 120 °C, 4 hours)



- Paton/Burton/Smith: 2023 (31-97%)



- Li: 2023, M = Cs (91%)
- Han: 2023, M = K (82%)



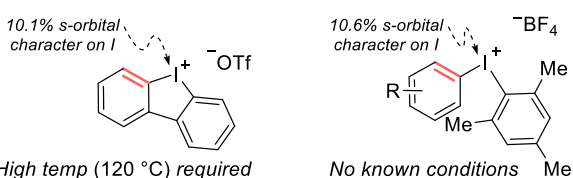
The first examples of success in this approach have been reported with cyclic diarylhalonium salts, but have since included aryloxonium salts and acyclic diaryliodonium salts (Scheme 1c).¹¹ Wencel-Delord and then Li have shown that arynes can be generated from

cyclic diaryliodonium salts with Cs_2CO_3 at room temperature in dichloromethane (Scheme 1c).^{11a-c} Subsequently, we found that the corresponding diarylchloroniums are kinetically more reactive aryne precursors than the diaryliodoniums (Scheme 1c).^{11d} In fact, we observed a periodic trend in aryne generation from cyclic diarylhalonium salts and correlated kinetic reactivity to the contribution of s- and p-orbitals on the onium leaving group to the C-X bond being broken.^{11d} Wencel-Delord has also more fully developed diarylchloronium salts as aryne precursors.^{11e} Zhang and Wu recently showed that the cyclic diaryliodonium salts could function as aryne precursors with Cs_2CO_3 as base if heated to 120 °C in *t*-BuOH as solvent, though trapping with furan resulted in low yield (Scheme 1c).^{11f} Non-cyclic aryne precursors have also recently featured “onium” leaving groups to generate arynes with mild base. Paton, Burton, and Smith have posted a pre-print demonstrating that triaryloxonium groups generate arynes when treated with K_3PO_4 in MeCN at room temperature (Scheme 1c).^{11g} The isolated yields are generally high, though the efficiency of the generating arynes by this approach is compromised by the multi-step synthesis of the triaryloxonium salts similar to [*o*-trimethylsilyl]phenyl triflate reagents.^{11g} Finally, Li has shown that aryl(Mes)iodonium salts bearing a 3-sulfonyl activating group lead to arynes when treated with Cs_2CO_3 in dichloromethane and used this approach in sequential aryne trapping reactions which eliminate both iodonium and sulfonyl leaving groups.^{11h} Han and co-workers have developed similar conditions with K_2CO_3 as base in dichloromethane for the same aryl(Mes)iodonium substrate bearing a 3-triflyloxy group (Scheme 1c).¹¹ⁱ Notwithstanding the significant advance of generating arynes with either Cs_2CO_3 or K_3PO_4 as weak bases, there are relatively few examples where this approach is actually needed.^{11g} That is, almost no base-sensitive, electrophilic or Lewis/Bronsted acidic functional groups present in the aforementioned methods have been reported.

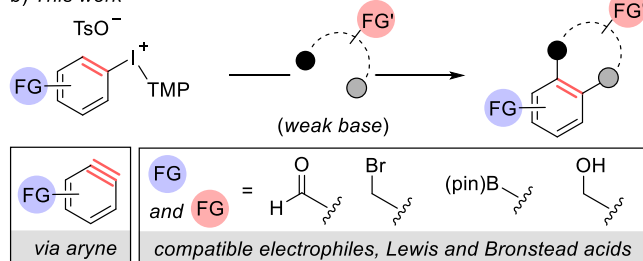
Scheme 2. Challenges and approach to generating arynes from diaryliodonium salts.

a) Challenge of accessing arynes from diaryliodonium salts:

poor kinetic reactivity (leaving group ability) based on analysis of bonding orbitals.



b) This work

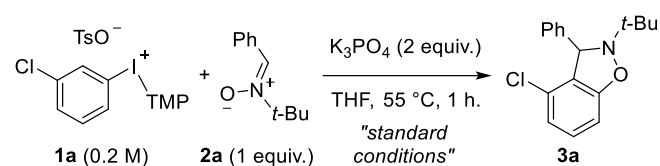


Our prior work provided a rationale for the lack of reactivity of cyclic diaryliodonium salts as aryne precursors with Cs_2CO_3 at room temperature (Scheme 2a).^{11d} Consequently, Zhang and Wu showed that high temperatures were needed to overcome the kinetic barrier of these reactions. Additionally, we and others previously described the use of aryl(Mes)iodonium salts to access arynes with LiHMDS or NaOt-Bu as bases.^{9a,h} As a continuation of our efforts to efficiently generate arynes under mild conditions, we now report a method using K_3PO_4 as a

mild base to generate arynes from aryl(TMP)iodonium salts that do not require an activating 3-triflyloxy group (Scheme 2b). This method generates arynes in 1 hour and is compatible with a range of sensitive functional groups on both aryne and arynophile, including electrophilic aldehyde and benzyl halides, Lewis acidic boronate esters, and Bronsted acidic O-H groups (Scheme 2b).

Results and Discussion

Method development. Concurrent with our own investigation of a method to use weak base to generate arynes from diaryliodonium salts, several other groups reported conditions to generate arynes from cyclic diarylhalonium salts, aryloxonium salts, and 3-sulfonyloxyaryl(Mes)iodonium salts (Scheme 1c).¹¹ Our own investigation employed 3-chlorophenyl(TMP)iodonium salt **1a**, and related analogs, and as other methods were reported we tested them on **1a** using furan as a trap.¹¹ In each case, low yield (11-34%) was observed,¹² and consequently we continued our investigation. Here, we focused on acyclic diaryliodonium salts because they are readily synthesized from simple building blocks and therefore provide access to a wide range of unique arynes.¹³ However, the inherent inertness of acyclic diaryliodonium salts to deprotonation with weak base is a significant hurdle,^{11a,d,g} and we anticipated that even in successful cases the concentration of aryne in the reaction mixture may be very low. Therefore, we selected nitrene **2a** as the arynophile, given its high trapping efficiency,¹⁴ so that even small amounts of aryne generated could be trapped and detected. A large number of screening experiments revealed that high yield of cycloadduct **3a** was obtained from the stoichiometric coupling of **1a** and **2a** using K_3PO_4 as base and THF as solvent at 55 °C for 1 hour (Table 1, entry 1). Table 1 delineates the control experiments that demonstrates the importance of each component of the reaction, including several components used in other recent reports.¹¹ The corresponding aryl(Mes)iodonium tosylate derivative of **1a** resulted in only a slightly diminished yield (79%), whereas using the DMIX auxiliary resulted in a much lower yield (17%; cf. Table 1, entries 2 and 3).¹⁵ Changing the leaving group to thianthrenium resulted in low yield (9%) of **3a** when mild base was used suggesting that iodonium is a superior leaving group than thianthrenium (Table 1, entry 4).⁹ⁱ Several other weak bases were also tested. The use of Cs_2CO_3 as base resulted in only slightly diminished yield of **3a** (75%), but the use of K_2CO_3 produced much lower yield (17%; Table 1, entry 5 and 6). The use of MeCN and DCM as solvent resulted in moderate yield of **3a** (53% and 62%, respectively), but toluene resulted in low yield of **3a** (12%; Table 1 entries 7-9). We found that when the reaction was conducted at room temperature only trace product **3a** was observed in the crude 1H NMR spectrum, though when the reaction time was increased to 24 hours a high yield of **3a** was observed (Table 1, entries 10 and 11). We have previously shown, via DFT calculations, that *ortho*-deprotonation and ejection of iodonium is concerted,^{9g,11g} and lack of deuterium incorporation under our standard conditions suggests a similar scenario here.¹² Although generating the aryne is likely rate-determining and the arynophile is not involved, we do observe an impact on yield when we use a different arynophile. When furan **2b**, a less efficient aryne trap,¹⁴ was used as the arynophile a 64% yield of cycloadduct was observed (Table 1, entry 12). Incidentally, under our conditions arynes were generated and trapped in moderate to high yield from cyclic diphenylchloronium and diphenylbromonium salts, though cyclic diaryliodonium salts remained unreactive under our conditions (Table 1, entry 1).¹²

Table 1. Analysis of reaction conditions^a

Entry	Deviation from "standard conditions"	Yield 3a ^[b]
1	None	88%
2	Mes instead of TMP	79%
3	DMIX instead of TMP	17%
4	TT ⁺ TfO ⁻ instead of (TMP)I ⁺ TsO ⁻	9%
5	Cs ₂ CO ₃ instead of K ₃ PO ₄	75%
6	K ₂ CO ₃ instead of K ₃ PO ₄	17%
7	MeCN instead of THF	53%
8	DCM instead of THF	62%
9	Toluene instead of THF	12%
10	r.t. instead of 55 °C	Trace
11	r.t. instead of 55 °C for 24 hours	88%
12	furan (5 equiv.) instead of 2a , r.t., 24 hours	64%

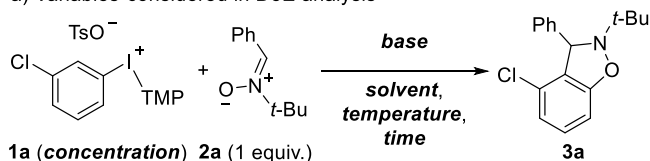
^aConditions: **1a** (0.1 mmol, 1 equiv.), **2a** (0.1 mmol, 1 equiv.), K₃PO₄ (0.2 mmol, 2 equiv.), THF (0.5 mL), 55 °C, 1 hour. ^bYield determined by ¹H NMR spectroscopy with 2,3,5,6-tetrachloronitrobenzene as internal standard.

The similarity in substrate structure between our study (**1a**) and the previous studies independently conducted by Li and Han (3-sulfonyloxyphenyl(Mes)iodonium),^{11h,i} and what could be perceived as similar conditions prompted us to perform an analysis of the reaction variables by Design of Experiment (DoE).¹⁶ The reaction between **1a** and **2a** to generate cycloadduct **3a** was used in the DoE analysis (Scheme 3a). The key variables that distinguish our work by that of Han include the solvent identity (A), the concentration of **1a** (B), the reaction temperature (C), the reaction time (D), and the identity of the base (E) (Scheme 3a). The conditions developed by Han (coded -1 for the DoE analysis) resulted in 8% yield of **3a**,¹¹ⁱ and the conditions developed described here resulted in 89% yield of **3a** (Scheme 3a). The 2⁵ full factorial design revealed that temperature, time and base were the variable with the largest impact on yield and solvent and concentration had the smallest, though non-negligible, impact on yield.¹² Additionally, a substantial positive interaction effect, almost as large in magnitude as the primary effects, existed between time, temperature, and base, which can be easily missed when variables are screened one at a time.^{12,16} In the context of sustainability, we constrained the concentration of **1a** to 0.2 M and the reaction time to 1 hour and extracted the primary and interaction effects of solvent (A), temperature (C), and base (E) (Scheme 3b). In this case, temperature and base were again the most influential variables on yield, and also had a large interaction effect (Scheme 3b, equation). However, some interesting observations were noted with respect to the reaction variables. Dichloromethane (DCM) is used in seven of the nine prior reports on generating arynes with mild base, which are also conducted at room temperature.^{11a-}

^{e,h,i} Indeed, in our analysis higher yield is observed in DCM than THF at room temperature, irrespective of the base used (*cf.* 2% vs 1% and 15% vs 7%, Scheme 3b). Even at 55 °C the yield of **3a** is similar in DCM and THF when K₂CO₃ is used as base (*cf.* 23% and 24%, Scheme 3b). However, there is a larger difference in yield of **3a** between DCM and THF when the reaction is conducted at 55 °C and K₃PO₄ is used as the base (*cf.* 62% and 89%, Scheme 3b). Additionally, the impact of base is most notable at higher temperature (55 °C) and the impact of temperature is notable irrespective of the level of the other variables. These observations, taken together, support the notion that the combination of variables that we have discovered are uniquely able to generate arynes from aryl(TMP)iodonium salts, and we were impelled by the use of mild base to fully assess the functional group compatibility of these conditions.

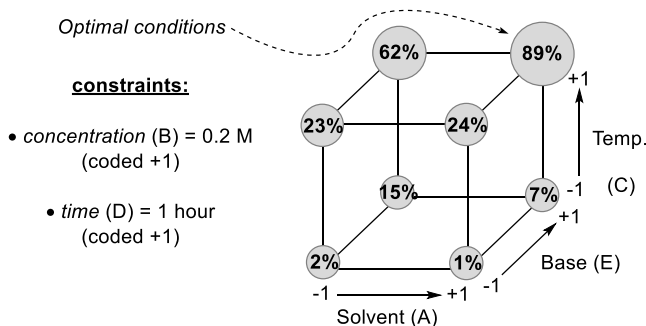
Scheme 3. Analysis of reaction variables by Design of Experiment (DoE).

a) Variables considered in DoE analysis



Variables	From ref. 11i (coded -1)	This work (coded +1)
Solvent (A)	Dichloromethane (DCM)	Tetrahydrofuran (THF)
Concentration (B)	0.13 M	0.2 M
Temperature (C)	r.t.	55 °C
Time (D)	12 hours	1 hour
Base (E)	K ₂ CO ₃ (1.2 equiv.)	K ₃ PO ₄ (2 equiv.)
	Yield of 3a = 8%	Yield of 3a = 89%

b) 2³ full factorial design to analyze solvent (A), temp (C), and base (E)



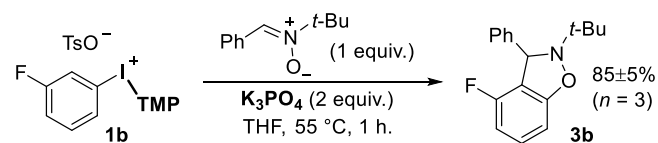
$$\% \text{ yield of } \mathbf{3a} = 28 + 2\mathbf{A} + 22\mathbf{C} + 15\mathbf{E} + 5\mathbf{AC} + 2\mathbf{AE} + 11\mathbf{EC} + 4\mathbf{ACE}$$

Functional group compatibility. Generating arynes from [*o*-(trimethylsilyl)]aryl triflates is generally perceived to be the most mild and functional group compatible method.^{4h,17} Conversely, using strong base to deprotonate an aryl (pseudo)halide is generally perceived to be harsh and not functional group tolerant. Yet, there are no comprehensive analyses of these and other aryne generating strategies. Here, we compared our conditions using mild base with the more common methods of generating arynes. In this analysis, we used aryl(TMP)iodonium

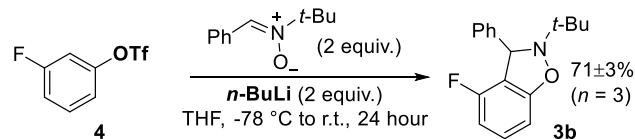
salt **1b** bearing a fluoride group and the conditions presented in Table 1, entry 1 are considered “conditions A” (Scheme 4a). In order to assess the functional group compatibility of generating arynes via deprotonation of aryl (pseudo)halide with strong base, we used aryl triflate **4** and *n*-BuLi as base and these are considered “conditions B” (Scheme 4b).¹⁸ We did test other strong bases that are known to generate arynes from aryl triflates, such as LDA and LiTMP, but these were competitive nucleophiles for the aryne with the nitron arynophile.^{13,19} Finally, we assessed the functional group compatibility of [*o*-(trimethylsilyl)]aryl triflate **5** with CsF as the activator and these are considered “conditions C” (Scheme 4c).²⁰ In each case, using **1b**, **4**, or **5** results in the same aryne intermediate and product **3b** (Scheme 4). The yield of **3b** using conditions A-C range from 68-85% and are reproducible over three trials (Scheme 4).

Scheme 4. Aryne generating systems used to test functional group compatibility.

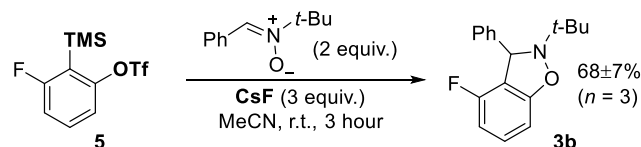
a) iodonium leaving group with weak base (conditions A)



b) triflate leaving group with strong base (conditions B)



c) *o*-trimethylsilylaryl triflate with fluoride activation (conditions C)



The functional group compatibility was tested for each set of conditions by the method of additives.²¹ Electrophilic, Lewis and Bronsted acidic, as well as a protecting group were tested as additives under each set of conditions (**6-15**, Scheme 5). The yield of the remaining additive (**6-15**) as well as the product **3b** was quantified for each reaction, and the reproducibility was checked with additive **8** by triplicate runs for each set of conditions. The yields of both additive (**6-15**) and product **3b** were color coded as low (red; 0-33%), moderate (beige; 34-66%), and high (blue; 67-100%) in Scheme 5. Inspection of Scheme 5 reveals several key trends. First, under conditions A, the percent remaining additive **6-13**, **15** is high (78-92%), indicating high functional group compatibility (Scheme 5). Moreover, the observed yield of **3b** is high (66-79%) in all but one case in which it is moderate (**13**, 61%; Scheme 4). Second, the use of aryl triflate **4** with strong base (BuLi, conditions B) almost universally results in low to moderate (0-59%) recovery of the additives (Scheme 5).²² The recovery of additives is especially low for electrophilic and acidic functional groups. Under these conditions a value of <5% refers to the observation of only trace quantities of the additive remaining in the crude ¹H NMR spectrum. Using conditions B, low to moderate yield of **3b** was observed (0-64%, Scheme 5). Third, under conditions C, which are the state-of-the-art method for generating arynes, the percent recovery of additive was generally high (69-98%) except for the additive **15** bearing a silyl ether

protecting group, which was quantitatively consumed (Scheme 5). The yield of **3b** under conditions D ranged from moderate to high (35-76%, Scheme 5). Notably, the addition of H₂O (**14**) as an additive had only a modest impact on the yield of **3b** for conditions A and C, but completely inhibited the formation of **3b** when BuLi was used as the base (Scheme 5). Although this result is not overly surprising with respect to the result in the presence of BuLi, it does point to the robustness of the conditions developed here using K₃PO₄ and that rigorously dried solvents, Schlenk techniques, and glove boxes are not needed.

Scheme 5. Analysis of functional group compatibility in aryne reactions.^a

additives	conditions									
	6	7	8	9	10	11	12	13	14	15
A	6: 83%	7: 89%	8: 90±5%	9: 92%	10: 93%	11: 87%	12: 85%	13: 85%	Δ: -19% ^[b]	15: 78%
	3b: 78%	3b: 73%	3b: 75±4%	3b: 75%	3b: 74%	3b: 69%	3b: 73%	3b: 61%	3b: 66%	3b: 79%
B	6: <5%	7: <5%	8: 29±2%	9: 16%	10: 21%	11: <5%	12: 59%	13: 83%	Δ: -71% ^[b]	15: 81%
	3b: 20%	3b: 56%	3b: 64±3%	3b: 62%	3b: 44%	3b: 53%	3b: 58%	3b: 52%	3b: <5%	3b: 51%
C	6: 74%	7: 77%	8: 88±2%	9: 95%	10: 69%	11: 79%	12: 98%	13: 74%	Δ: -14% ^[b]	15: <5%
	3b: 47%	3b: 52%	3b: 72±4%	3b: 75%	3b: 50%	3b: 59%	3b: 51%	3b: 76%	3b: 54%	3b: 35%

^aConditions: **1b**, **4**, or **5** (0.1 mmol, 1 equiv.), **2a** (0.1 mmol, 1 equiv.), **6-15** (0.1 mmol, 1 equiv.), see Scheme 3 for base, solvent, temperature, and time. ^bΔ is calculated as the different in yield of **3b** in the presence of H₂O and absence of H₂O (yield from Scheme 3).

The functional group compatibility of each set of conditions is summarized in Table 2. Based on percent remaining additive the order of functional group compatibility is conditions A > C >> B (Table 2). The combination of a super leaving group and a weak base allows for inclusion of a wide variety of base sensitive functional groups. The average percent yield of **3b** for each set of conditions (A-C) over all the additives (**6-15**) is not a fair comparison because each of the model reactions has a different yield as a starting point (Scheme 4). Therefore, the difference in yield (D % yield) of **3b** between the model reactions (Scheme 4) and the reactions with additives (as an average, Scheme 5) is a more accurate assessment of functional group compatibility. Incidentally, “D % yield” generally aligns with functional group compatibility (Table 2). The most chemoselective conditions (A and C) had the smallest difference in yield (13% and 11%, respectively), and the least chemoselective conditions (B) involving strong base had a substantially larger difference in yield (25%, Table 2).

Table 2. Summary of functional group compatibility.

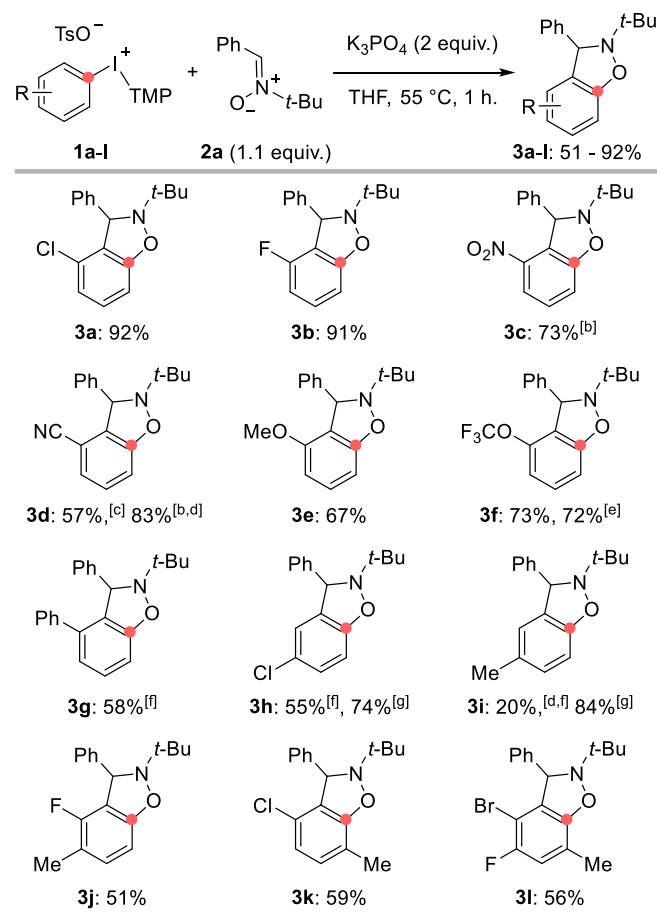
Entry	Conditions	Avg. % additive	Avg. % yield 3b	Δ % yield ^[a]
1	A	87 \pm 5%	72 \pm 6%	-13%
2	B	32 \pm 32%	46 \pm 20%	-25%
3	C	73 \pm 29%	57 \pm 13%	-11%

^aCalculated as the difference in average yield of **3b** in the absence and presence of additives (cf. average yields from Scheme 3 and column 3 above).

Reaction scope. We assessed the reaction scope of generating aryne from aryl(TMP)iodonium salts with potassium phosphate in two different ways. First, we assessed the electronic and steric effects of ring substituents on the aryne precursor (Scheme 6). The conditions presented in Table 1, entry 1 include a stoichiometric quantity of aryne trap **2a**, 2 equivalents of K₃PO₄, in THF as solvent and the reaction is heated to 55 °C for 1 hour. Here, we assessed the scope on 0.5 mmol scale of **1a-l** and isolated products **3a-l** in moderate to high yield (51-92%) and one substrate isolated in low yield (20%; Scheme 6). In the products **3a-l**, the position formerly occupied by the iodonium leaving group is indicated by a red dot, and both the relative reactivity and regioselectivity of deprotonation and addition to the aryne are influenced by the ring substituents (Scheme 6). We have previously shown that halogens *meta* to the iodonium leaving group activate aryne formation^{9h} and here we observed high yield in both cases in which a chloro and fluoro-substituent are placed at this position (**3a** and **3b**, Scheme 6). We also observed that nitro (**3c**), cyano (**3d**), methoxy (**3e**) and trifluoromethoxy (**3f**) were compatible inductively withdrawing substituents in the *meta*-position (Scheme 6). In the case of the nitro (**3c**) and cyano (**3d**) substituents higher yields were observed when the reactions were conducted at room temperature for 24 hours. Consistent with our previous observations,^{9a,g,h} in each of these cases (**1a-f**) deprotonation occurs selectively between the substituent and the iodonium leaving group and the aryne forms next to the substituent (Scheme 6). In each of these cases (**3a-f**) trapping of the aryne occurs selectively consistent with the aryne distortion model and the negatively polarized end of the nitrene dipole attacks the carbon distal to the s-withdrawing substituent (Scheme 6).^{23,24} The phenyl substituent in **3g** is substantially less inductively withdrawing than the substituents in **3a-f**,²⁵ yet we still observed selective deprotonation at the more sterically hindered position albeit in moderate yield; this substrate also required extended reaction time of 24 hours (**3g**, Scheme 6). Substrates with substituents located *para* to the iodonium leaving group were less reactive. Substrate **1h**, with a chloro-substituent, produced aryne adduct **3h** in 55% yield after 24 hours of reaction time; compare this to substrate **1a** that yields 92% of **3a** after only 1 hour (Scheme 6). Additionally, substrate **1i**, bearing an electron donating methyl substituent in the *para*-position, results in low yield of **3i** (20%; Scheme 6). It is important to note that neither **1h** nor **1i** have “sensitive” functional groups and therefore using a stronger base, such as NaOt-Bu,^{9g,h} results in substantially higher yields of the aryne adducts (74 and 84%, respectively; Scheme 6). We attempted to remedy the low yield of **3i** by using the acyclic *p*-tolyl(Mes)bromonium and chloronium salts. However, in both cases complete consumption of the halonium substrates occurred with only trace product of **3i** formed suggesting that these acyclic diarylhalonium salts lack the stability to be efficient aryne precursors. Finally, aryne intermediates may facilitate the synthesis of highly substituted benzenoid rings, which are challenging to synthesize by other

methods. Substrates **1j-l** with various substitution patterns on the aryne precursor result in tetra and penta-substituted benzenoid products (Scheme 6).

Scheme 6. Scope of electronic and steric effects on aryne precursors.^a

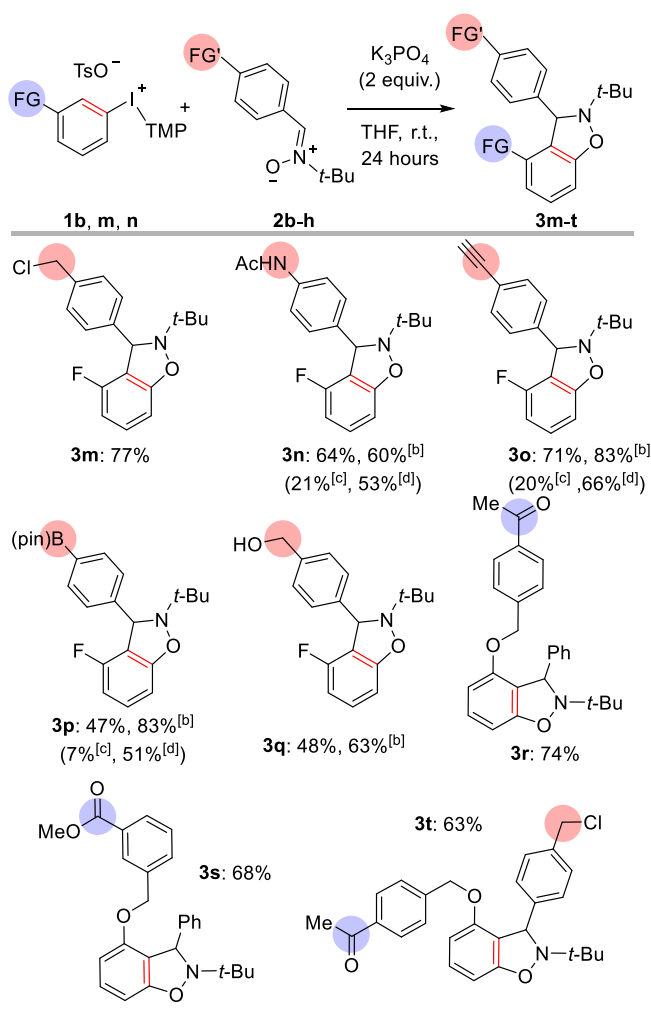


^aConditions: **1** (0.5 mmol, 1 equiv.), **2a** (0.5 mmol, 1 equiv.), K₃PO₄ (1 mmol, 2 equiv.), THF (2.5 mL), 55 °C, 1 hour; major regioisomer shown, see ESI for details. ^bReaction conducted at r.t. for 24 hours. ^cMes salt used. ^dYield obtained from the crude ¹H NMR spectrum vs 2,3,5,6-tetrachloronitrobenzene as internal standard. ^eReaction conducted on 1.5 mmol scale of **1f** for 1.5 hours. ^f24-hour reaction time. ^gConditions: **1** (0.5 mmol, 1 equiv.), **2a** (0.5 mmol, 1 equiv.), NaOt-Bu (0.75 mmol, 1.5 equiv.), TBME (2.5 mL), r.t., 1 hour.

The second way in which we assessed the scope of generating arynes using mild base was to test the functional group compatibility of the reaction with aryne precursors and traps bearing sensitive functional groups (Scheme 7). Arynes were successfully generated from **1b** and trapped with functional nitrones under our mild base conditions (**3m-q**, Scheme 7). Specifically, aryne-nitron cycloadducts bearing benzyl chloride (**3m**), acetanilide (**3n**), terminal alkyne (**3o**), pinacol boronate ester (**3p**), and benzylic alcohol (**3q**), were obtained in moderate to high yield consistent with our functional group compatibility study (Scheme 5 and 7). In the cases of boronate ester (**3p**) and benzylic alcohol (**3q**) the isolated yield was reduced by challenging purification, however the ¹H NMR yields were 83% and 63% for **3p** and **3q**,

respectively (Scheme 7). Additionally, we tested the coupling of **4** and **5** with nitrones functionalized with an acetanilide (**2c**) or boronate ester (**2e**) under conditions B and C using strong base (BuLi) and fluoride activation, respectively (Scheme 4 and 7). Substantially, lower yields of **3n**, **3p**, and **3o** were observed when BuLi was used to generate an aryne from **4** in the presence of these functional nitrones (Scheme 7). Moderate yields of **3n**, **3p**, and **3o** were observed when the aryne was generated from **5** and CsF (Scheme 7). Taken together these results highlight the mildness and functional group compatibility of these reaction conditions. Functionalized aryne precursors (**1m** and **1n**) are also compatible under the mild base conditions (Scheme 7). Nitron adducts **3r** and **3s** bearing ketone and ester groups were obtained in 74% and 68% yield, respectively, when **1m** and **1n** are used as aryne precursors (Scheme 7). Finally, we tested the coupling of acetophenone functionalized aryne precursor **1m** and benzyl chloride functionalized aryne trap **2b** under our mild base conditions (Scheme 7). The alkylation of acetophenone with benzyl halides under basic conditions has been previously described.^[26] Here we show that our conditions result in chemoselective aryne formation and trapping in the formation of **3t** (63% yield) and both acetophenone and benzyl chloride functional groups remain intact (Scheme 7).

Scheme 7. Scope of functional groups.^a



^aConditions: **1** (0.5 mmol, 1 equiv.), **2** (1.5 mmol, 3 equiv.), K₃PO₄ (1.0 mmol, 2 equiv.), THF (2.5 mL), r.t., 24 hours. ^bYield obtained from the crude ¹H NMR spectrum vs 2,3,5,6-tetrachloronitrobenzene as internal standard. ^cYield obtained from conditions B using **4** (Scheme 4). ^dYield obtained from conditions C using **5** (Scheme 4).

Conclusions

We have discovered reaction conditions that generate arynes from aryl(TMP)iodonium salts by deprotonation/elimination with K₃PO₄ as a weak base. DoE revealed that the combination of solvent identity (THF vs DCM), temperature (55 °C vs r.t.), and base identity (K₃PO₄ vs K₂CO₃) are uniquely responsible for high yield of aryne adducts. This method, is a more functional group compatible way to generate arynes than fluoride activation of *o*-trimethylsilylaryl triflates, the current state-of-the-art, based on analysis by the method of additives. The scope of aryl(TMP)iodonium salts as aryne precursors includes groups *meta* to the iodonium leaving group, even marginally withdrawing phenyl groups. Substrates with substituents *para* to the iodonium leaving group are less reactive. The use of a weak and non-nucleophilic base renders sensitive functional groups compatible in this reaction, including benzyl halide, boronate esters and ketones. This work provides new opportunities to generate arynes under conditions that are highly functional group compatible.

Data Availability. The data supporting this study is available in the manuscript and the accompanying Supporting Information.

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