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Aryl(TMP)iodonium Tosylate Reagents as a Strategic Entry Point to Diverse Aryl Intermediates: Selective Access to Arynes

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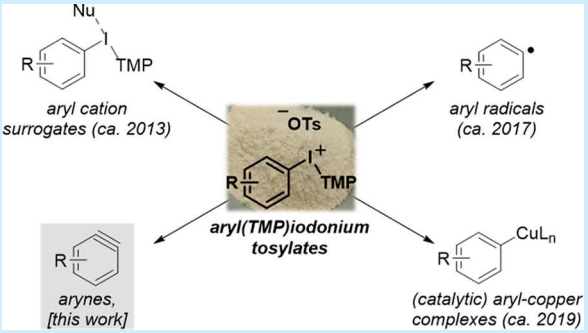
ABSTRACT: Arenes are broadly found motifs in societally important molecules. Access to diverse arene chemical space is critically important, and the ability to do so from common reagents is highly desirable. Aryl(TMP)iodonium tosylates provide one such access point to arene chemical space via diverse aryl intermediates. Here we demonstrate that controlling reaction pathways selectively leads to arynes with a broad scope of arenes and arynophiles (24 examples, 70% average yield) and efficient access to biologically active compounds.



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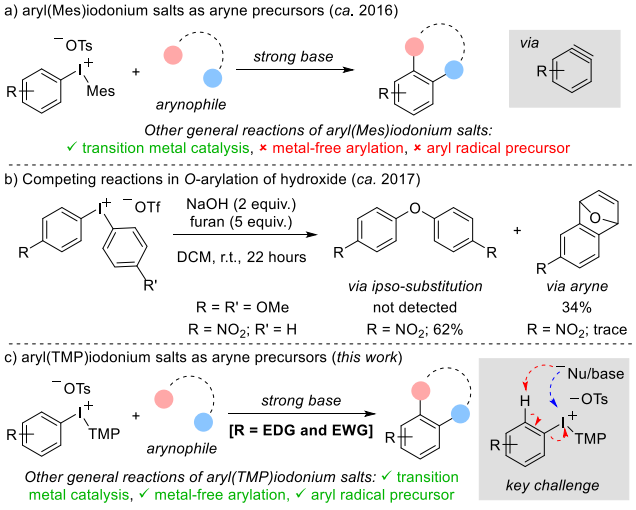
Access to diverse chemical space is central to medicinal chemistry and drug discovery. Arenes are a key motif in such efforts,[1] and aryl halides provide a primary entry point into the arene chemical space. Notwithstanding the wide range of metal-catalyzed reactions that involve oxidative addition,[2] other reaction pathways that involve a direct reaction with nucleophiles (S_NAr) or the generation of aryl radicals and arynes often either are limited in scope or require forcing conditions. Diaryliodonium salts are highly activated aryl pseudo halides that typically react under more mild conditions than traditional aryl halides.[3] They are also known to participate in metal-catalyzed reactions as well as metal-free reactions with nucleophiles, in single-electron transfer (SET) reduction to access aryl radicals, and as aryne precursors, all with a relatively broad scope.[3] However, two key challenges remain to fully realize the potential of diaryliodonium salts as strategic reagents to access a range of reactive intermediates. (1) Precise control over competing reaction pathways is not currently possible in all cases, especially between the direct reaction with nucleophiles and aryne formation.[4] (2) Unsymmetrical diaryliodonium salts reduce waste, yet a suitable auxiliary has not emerged to facilitate chemoselective aryl transfer in all of the previously mentioned reactions.[5]

Although the first observation of arynes via the ortho deprotonation of symmetrical diaryliodonium salts occurred in the 1970s,[6,7] the development of methods with synthetically useful yields has only recently emerged with aryl(Mes)-iodonium salts (Mes = 2,4,6-trimethylphenyl; Scheme 1a).[8] These recent advances aside, some limitations exist. From a practical standpoint, the aryl scope is often rather narrow; that is, strongly electron-donating and strongly electron-withdrawing substituents are largely absent, especially in the para position[8,9] and with *tert*-butoxide as the base.[10] Moreover, in some cases, the mesityl group undergoes competitive aryl transfer via ipso substitution.[5,11] Evidence of the challenges surrounding chemoselectivity have been documented by Olofsson and coworkers during their mechanistic study of

Scheme 1. Current State-of-the-Art and Mechanistic Knowledge in Aryne Formation from Diaryliodonium Salts



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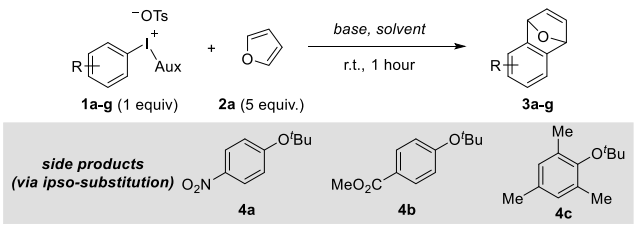
hydroxide arylation (Scheme 1b).[4] Trace or low (34%) yields of aryne adduct are observed when a *para*-nitro or *para*-methoxy substituent is present on the aryliodonium, respectively (Scheme 1b).

Herein we address the limitations of aryl(Mes)iodonium salts as aryne precursors by employing aryl(TMP)iodonium salts (TMP = 2,4,6-trimethoxyphenyl; Scheme 1c). Importantly, aryl(TMP)iodonium salts are also effective as aryl transfer reagents in direct reactions with nucleophiles, as aryl radical precursors, and in metal-catalyzed reactions.[12−14] Therefore, in addition to being easily synthesized,[15] stable,[16] free-flowing powders, aryl(TMP)iodonium salts are idealized reagents that provide a practicing chemist broad access to the chemical space via four distinct reactive intermediates;[17] here we demonstrate their first use as aryne precursors. Specifically, we show that pairing an appropriate base with aryl substituent effects and position is key to avoiding other reaction pathways, namely, direct ipso substitution of the transferring aryl group or auxiliary, and achieving the desired aryne formation. We demonstrate the broad scope of both aryl(TMP)iodonium salts and arynophiles and highlight that this approach increases both the yield and efficiency in synthesizing a bioactive compound. Finally, we demonstrate a relative reactivity scale for substituted aryl(TMP)iodonium salts and reveal the subtle reactivity difference related to the identity of base.

On the basis of ease-of-use and greenness, we prefer sodium *tert*-butoxide among the bases known to generate arynes from aryl(Mes)iodonium salts.[8,10] Therefore, we used sodium *tert*-butoxide in reactions with a series of salts having different electronic effects (**1a−g**) and auxiliaries (Mes and TMP). The arynes were trapped with furan **2a** as cycloadducts **3a−g** (Table 1). Additionally, we analyzed the crude reactions for side products from competitive pathways such as ipso substitution. The use of Mes as an auxiliary on salts **1a−d** confirms the narrow aryl scope often observed in these reactions and underscores a key limitation of the Mes auxiliary (Table 1, entries 1−4). Specifically, low yields (<40%) of **3** are observed for the electron-deficient and electron-rich salts (Table 1, entries 1, 2, and 4), and high yield (77%) is observed for the relatively electron-neutral **1c** (Table 1, entry 3). Moreover, in the low-yielding reactions, ipso substitution was a significant competing pathway. C−O coupling products **4a** and **4b** were observed in 25 and 16% yield, respectively (Table 1, entries 1 and 2). The case of **1d** demonstrates an even greater limitation of the Mes auxiliary as it undergoes competitive C−O coupling with *tert*-butoxide (Table 1, entry 4). Under identical conditions, switching to the TMP auxiliary reveals a partial solution to the limitations of the Mes auxiliary (Table 1, entries 5−8). The yield of cycloadducts **3a** and **3b** remains low (13 and 12%, respectively), but interestingly, the yield of ipso-substitution products is dramatically improved, which is consistent with the use of TMP as a general auxiliary for the direct reaction with nucleophiles.[12] The yields of **3c** and **3d** are both improved when TMP is used as the auxiliary (Table 1, cf. entries 3 and 7; cf. entries 4 and 8). The result with **1d** is particularly striking, as the TMP group remains inert during the reaction. The low yields of **3a** and **3b** are primarily a result of the competitive nucleophilicity of *tert*-butoxide, and so we assessed the reaction of **1a** and **1b** (with the TMP auxiliary) with LiHMDS as the base (Table 1, entries 9 and 10). With this change, we observed markedly increased yields of **3a** and **3b** (Table 1, entries 9 and 10). Additionally, when we tested the reaction of **1b**-Mes with LiHMDS as the base, a lower yield

Table 1. Effects of Substituents, Auxiliary, and Base on Reaction Outcome[a]



entry	R group	aux	base	yield **3a−g** (%)[b]
1	4-NO_2 (**1a**)	Mes	NaO^{t}Bu[c]	27; 25[d]
2	4-CO_2Me (**1b**)	Mes	NaO^{t}Bu[c]	17; 16[e]
3	4-Cl (**1c**)	Mes	NaO^{t}Bu[c]	77
4	4-OMe (**1d**)	Mes	NaO^{t}Bu[c]	37; 19[f]
5	4-NO_2 (**1a**)	TMP	NaO^{t}Bu[c]	13; 87[d]
6	4-CO_2Me (**1b**)	TMP	NaO^{t}Bu[c]	12; 45[e]
7	4-Cl (**1c**)	TMP	NaO^{t}Bu[c]	82
8	4-OMe (**1d**)	TMP	NaO^{t}Bu[c]	60
9	4-NO_2 (**1a**)	TMP	LiHMDS[g]	57
10	4-CO_2Me (**1b**)	TMP	LiHMDS[g]	76
11	4-CO_2Me (**1b**)	Mes	LiHMDS[g]	56
12	3-NO_2 (**1e**)	TMP	NaO^{t}Bu[c]	84
13	3-CO_2Me (**1f**)	TMP	NaO^{t}Bu[c]	24
14	3-CO_2Me (**1f**)	TMP	LiHMDS[g]	69
15	3-OMe (**1g**)	TMP	NaO^{t}Bu[c]	86

[a]Conditions: **1a−g** (1 equiv), **2a** (5 equiv), base (see below), solvent (see below), r.t., 1 h. [b]Yields are obtained from crude ^{1}H NMR spectra with 2,4-dichlorobenzaldehyde as the internal standard. [c]NaO^{t}Bu (1.5 equiv), TBME. [d]NMR yield of **4a**. [e]NMR yield of **4b**. [f]NMR yield of **4c**. [g]LiHMDS (1.1 equiv), toluene.

was observed, which is consistent with our previous observations[8a,9] and further highlights the advantage of the TMP auxiliary (Table 1, entry 11). Finally, we surveyed a series of meta-substituted iodonium salts **1e−g** with both NaO^{t}Bu and LiHMDS (Table 1, entries 12−15). Contrary to the situation with para substitution, salt **1e** generates aryne in high yield with NaO^{t}Bu (Table 1, cf. entries 5 and 12). Again, in the case of ester-substituted **1f**, the use of LiHMDS is the key to a high yield (Table 1, entries 13 and 14). Finally, *meta*-methoxy-substituted **1g** results in a high yield of aryne adduct when NaO^{t}Bu is used as the base (Table 1, entry 15). Taken together, these results support the wider generality of TMP as an auxiliary over Mes in aryne formation and other reactions.[12−14] Specifically, the greater electron richness of the TMP versus Mes auxiliary and the smaller size of the methoxy versus methyl groups[18] are the most likely contributing factors to the relative inertness of TMP to competing ipso-substitution pathways.

The scope with respect to aryl(TMP)iodonium tosylates is wide-ranging with respect to functional groups and substituent position. The bold bonds in **3** show the position of the previous C−I bond in **1** (Scheme 2). In alignment with our observations above, LiHMDS was used as the base for electron-withdrawing para substituents (**3a**,**b**,**h**), and moderate to high yields of aryne adducts were observed (Scheme 2). Additionally, LiHMDS was used for *meta*-ester **3f** and *meta*-nitro **3p**, resulting in high yields (Scheme 2). NaO*t*-Bu was used as the base for most meta substituents, and a high yield of aryne adduct was observed in all cases (**3e**,**j**,**k**, Scheme 2). Polysubstituted aryl(TMP)iodonium salts lead to several

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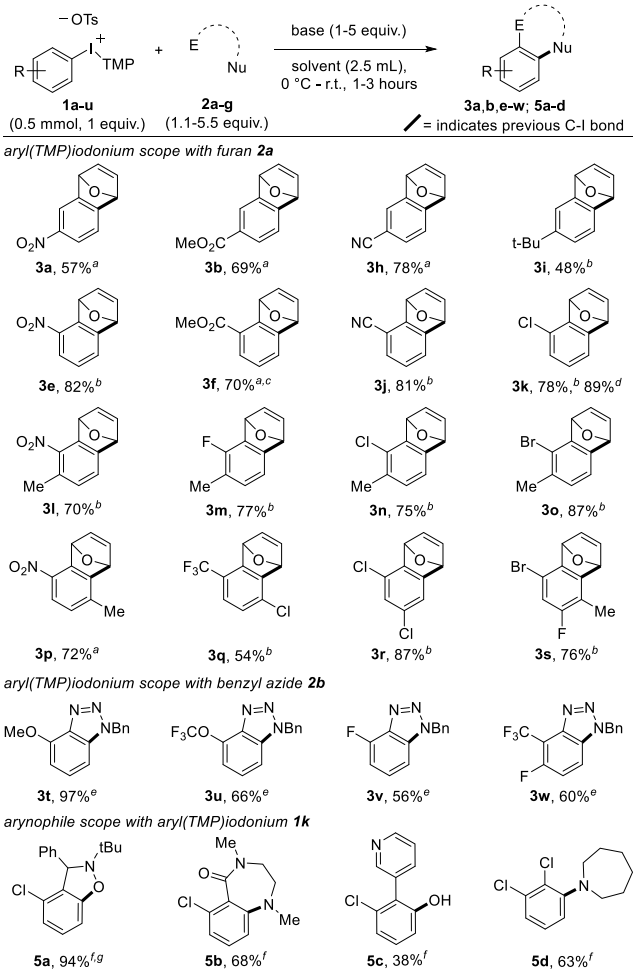
Scheme 2. Scope of Aryl(TMP)iodonium Salts and Arynophiles

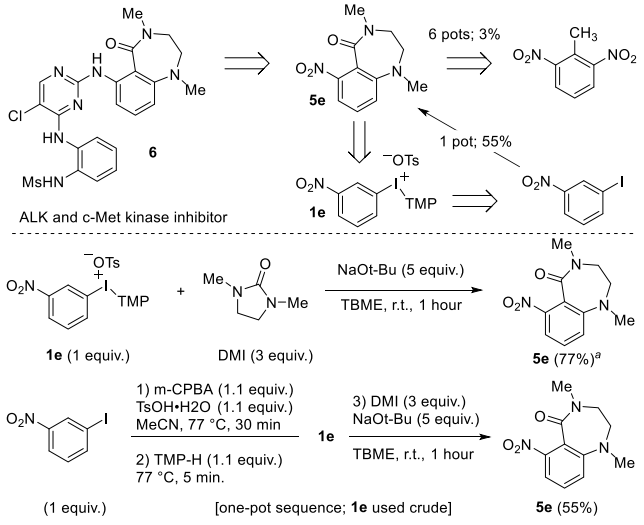


[a]Conditions: **2a** (2.75 mmol, 5.5 equiv), LiHMDS (0.5 mmol, 1 equiv), toluene (2 mL), r.t., 1 h. [b]Conditions: **2a** (2.75 mmol, 5.5 equiv), NaO*t*-Bu (1.5 to 3 equiv.; see the SI for variation), TBME (2.5 mL), r.t., 1 h. [c]8% yield of **3b** isolated as a side product. [d]1 mmol of **1k** used. [e]Conditions: **2b** (0.55 mmol, 1.1 equiv), NaO*t*-Bu (0.75 mmol, 1.5 equiv), TBME (2.5 mL), 0 °C, 1 h. [f]Conditions: **2c**–**f** (1–5.5 equiv; see the SI for variation), NaO*t*-Bu (1–5 equiv.; see the SI for variation), TBME (2.5 mL), r.t., 1–3 h. [g]Isolated as a mixture of regioisomers (11:1); major isomer shown.

medicinally relevant densely functionalized benzenoid substitution patterns (Scheme 2).[19] Substitution at the meta and para positions relative to the iodonium lead to 1,2,3,4-substituted oxabicyclic arenes in high yield (**3l**–**3o**, Scheme 2). Additionally, aryl(TMP)iodonium salts with substitution at the meta and ortho′ positions resulted in the distinct 1,2,3,4-substituted oxabicyclic arene products **3p** and **3q** (Scheme 2). Aryne adducts with 1,2,3,5- and 1,2,3,4,5-substitution were also obtained in high yield using this approach (**3r** and **3s**, Scheme 2). The yield was relatively insensitive to the scale, as a similar but slightly higher yield of **3k** was observed on the 1 mmol scale of **1k** (Scheme 2, cf. 78 vs 89%). Select salts were annulated with benzylazide to give the heterocyclic products **3t**–**3w** in moderate to high yield, which demonstrates the compatibility of methoxy, trifluoromethoxy, fluoro, and trifluoromethyl substituents (Scheme 2).[20] Additionally, several other arynophiles were compatible with this method using **1k** as the aryne precursor (Scheme 2). Nitrone is an efficient aryne trap resulting in a 94% yield of **5a** (Scheme 2).[21] Insertion into the C–N bond of cyclic urea (**5b**),[22] the N–O bond of pyridine *N*-oxide (**5c**),[23] and the N–Cl bond of *N*-chloroazepane (**5d**)[24] all proceeded in synthetically useful yield (38–68% yield, Scheme 2).[25]

We demonstrate the efficiency of our protocol through the short synthesis of **5e**, which is a key intermediate in the synthesis of ALK and c-Met inhibitor **6** (Scheme 3).[26] In the

Scheme 3. Application of Aryl(TMP)iodonium Tosylate to the Synthesis of a Biologically Active Compound



[a]Yield determined by ^{1}H NMR spectroscopy.

patent literature, **5e** is obtained in six pots (>80 h) from 2,6-dinitrotoluene in an overall yield of 3% (Scheme 3).[26] Recognizing that compound **5e** could be accessed from an *in-situ*-generated nitro-substituted aryne, we assessed the feasibility of synthesizing **5e** from aryl(TMP)iodonium salt **1e** (Scheme 3). We obtained an ^{1}H NMR yield of 77% for **5e** starting from **1e** and 2,5-dimethylimidazolidinone (DMI) and using NaO^{t}Bu as the base (Scheme 3). With the feasibility confirmed, we performed a one-pot sequence beginning with 3-nitroiodobenzene and telescoping the synthesis of **1e** and **5e** (Scheme 3). When performed in this way, **5e** was obtained in 55% yield from 3-nitroiodobenzene in <2 h, which represents a marked increase in the yield and reaction time efficiency.[27]

On the basis of the differences in reactivity observed for para- and meta-substituted aryl(TMP)iodonium salts with NaO^{t}Bu and LiHMDS as bases (Table 1), we sought to expand this study to include ortho-substituted analogues and determine a scale of relative reactivity via one-pot competition experiments (Scheme 4). Compounds **1k** (meta-) and **1x** (ortho-) lead to the same aryne and aryne adduct **3k**; therefore, each substrate competed against **1c**, and the ratio of products **3c**:**3k** (or **3x**) was used as a measure of the relative reactivity. The relative reactivity scale obtained from these experiments is meta (**1k**) > para (**1c**) > ortho (**1x**), and the magnitude of this relative scale is greater when NaO^{t}Bu is used as the base (Scheme 4). The greater reactivity of **1k** over **1c** aligns with the closer proximity of the inductively withdrawing chloro substituent. However, both **1c** and **1x** have an *ortho*-iodonium group and a *meta*-chloro group relative to the site of deprotonation; therefore, based on inductive electronic effects,

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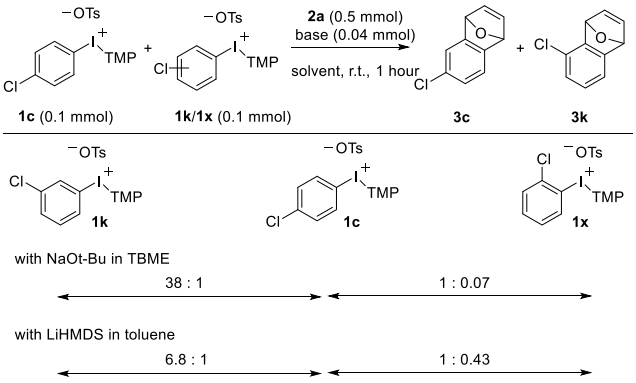
Scheme 4. Relative Reactivity of 1c,k,x[a]



[a]Relative ratios determined from ^{1}H NMR spectra; see the SI.

they should have similar reactivities. Yet **1c** is more reactive to deprotonation than **1x** with both bases (Scheme 4), which suggests the impact of steric effects, and perhaps iodonium conformation,[8a] on the relative reactivity of deprotonation and warrants further study.

To conclude, aryl(TMP)iodonium salts are compatible aryne precursors. This was found to be possible through insight into the relationship between the nucleophilicity of the base and the aryl substituent electronic effects. A range of aryl(TMP)iodonium salts and arynophiles are compatible in this method (24 examples, 70% average yield). We demonstrated the efficiency of this protocol though a one-pot synthesis of the medicinally relevant compound **6** and delineated a relative reactivity scale for monosubstituted aryl(TMP)iodonium salts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01534.

Experimental procedures, characterization data, and copies of ^{1}H, ^{13}C{^{1}H}, and ^{19}F{^{1}H} NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **1a−d**-Mes, **1f,h,m,o,p,s,u**, **3a,b,e,f,h−w**, and **5a−e** (ZIP)

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Author Contributions

Conceptualization of the project was done by A.N. and D.R.S. A.N. optimized the reaction and conducted initial studies on the base and substituent effects. A.N. and B.M. conducted the experimental investigation of the scope and data curation. Writing of the manuscript was performed by D.R.S. with input from A.N. and B.M.

Notes

The authors declare no competing financial interest.

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