Arynes

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A Selective C–H Deprotonation Strategy to Access Functionalized Arynes by Using Hypervalent Iodine

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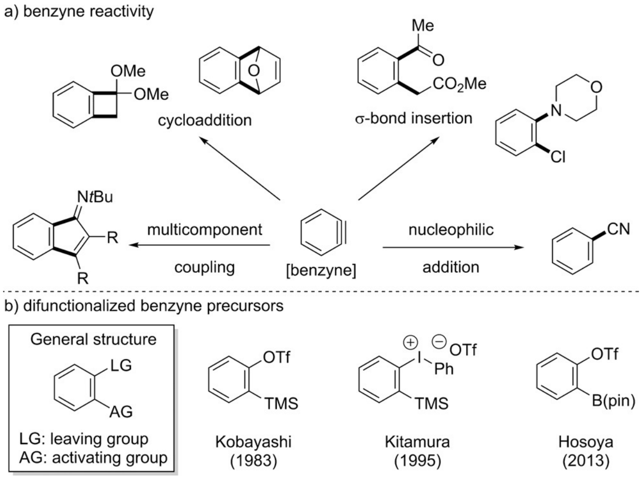
Abstract: *Described here is an efficient method to access highly functionalized arynes from unsymmetrical aryl(mesityl)iodonium tosylate salts. The iodonium salts are prepared in a single pot from either commercially available aryl iodides or arylboronic acids. The aryne intermediates are generated by ortho-C–H deprotonation of aryl(mesityl)iodonium salt with a commercially available amide base and trapped in a cycloaddition reaction with furan in moderate to good yields. Coupling partners for the aryne intermediates beyond furan are also described, including benzyl azide and alicyclic amine nucleophiles. The regio- and chemoselectivity of this reaction is discussed and evidence for the spectator aryl ligand of the iodonium salt as a critical control element in selectivity is presented.*

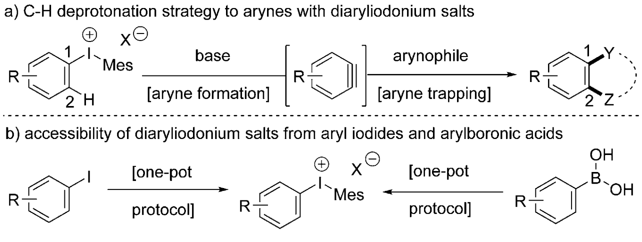
Arynes are a unique class of reactive intermediate in organic synthesis. Their high reactivity enables rapid elaboration of aryl moieties through the formation of multiple carbon–carbon or carbon–heteroatom bonds and therefore provides access to diverse product structures (Scheme 1 a).[1] Consequently, arynes have been used strategically in the early stages of synthetic sequences toward natural products.[2] Contemporary methods to access arynes have primarily focused on *ortho*-difunctionalized arenes (Scheme 1 b). The pioneering work of Kobayashi and co-workers[3] remains the archetypal approach though modifications have been made to both the triflate[4] leaving group and the silyl[5] activating group (Scheme 1 b). Collectively, these methods provide a mild approach to benzyne. However, access to elaborate and highly functionalized arynes remains a limitation of contemporary methodology because of the length of the synthesis (3–5 steps) needed to install the requisite *ortho*-situated groups.[6]



Scheme 1. Representative benzyne reactivity and contemporary benzyne precursors. Tf = trifluoromethynesulfonyl, TMS = trimethylsilyl.

Conversely, the seminal discovery and ensuing mechanistic investigation of aryne reactivity was found to occur by *ortho*-C–H deprotonation of an aryl halide at low temperature (−33 °C) followed by halide elimination.[7] Despite the inherent efficiency of this strategy over contemporary methods, application to highly functionalized substrates has also been limited in practice because of challenges in both regioselective deprotonation at C–H bonds and chemoselective elimination of a single leaving group when multiple potential groups are present.[8] A recent example of this strategy at ambient temperature further exemplifies the challenge of substrates having multiple leaving groups wherein polysubstitution and competing S_NAr reactivity were observed.[9]

Herein, we describe the discovery and development of an approach that offers recourse to difunctionalized aryne precursors and provides high and predictable selectivity in the formation of aryne intermediates by C–H deprotonation. In this work, unsymmetrical aryl(mesityl)iodonium salts engage an amide base at mild temperature and the transient aryne intermediate is trapped in cycloaddition and nucleophilic addition reactions (Scheme 2 a). The hypervalent iodine moiety serves as an element of regiocontrol over C–H deprotonation and as a broadly chemoselective leaving group in this process. Unsymmetrical iodonium salts are novel relative to contemporary aryne precursors because of their facile one-pot syntheses from either aryl iodide[10] or arylboronic acid[11] building blocks (Scheme 2 b). Ultimately they provide access to elaborate arynes in an efficient manner.



Scheme 2. C–H deprotonation strategy to access arynes. Mes = mesityl.

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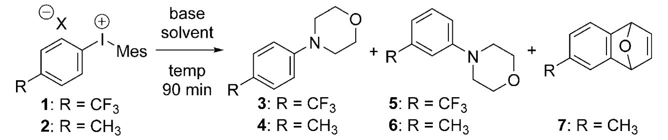
On the basis of our recent success in the arylation of alkoxide nucleophiles with unsymmetrical aryl(mesityl)iodonium salt electrophiles[12] we turned our attention to N nucleophiles. Morpholine is a privileged motif in biologically active compounds and was selected as a representative alicyclic amine nucleophile. The compound **1**, bearing an electron-deficient aryl ring, was used as the iodonium electrophile to survey reaction conditions. We found that the combination of morpholine and sodium *tert*-butoxide produced the desired and expected *ipso*-substitution product **3** along with a second and unexpected product **5** in equimolar quantity (Table 1, entry 1). Moreover, the combined yield of *ipso*- and *cine*-substitution products was excellent (89 %). The yield of **3** and **5** was only slightly reduced at 25 °C (entry 2). However, when the iodonium salt contained an electron-rich aryl group (**2**) the combined yield of **4** and **6** was significantly lower (entry 3). The product distribution observed for the reaction of morpholine with either **1** or **2** is in stark contrast to our previous alkoxide arylation chemistry,[12] and to the best of our knowledge other recent O-arylation methods.[13] The approximate 1:1 ratio of *ipso*- and *cine*-substitution isomers formed in this reaction is, however, consistent with classic reactivity of a 4-substituted aryne intermediate.[7] While the hypernucleofugality of iodine(III)[14] has been exploited to access high-energy arynes[4] (Scheme 1), there are virtually no reports of high-yielding formation of arynes from diaryliodonium salts which are initiated by *ortho*-C−H deprotonation. Specifically, such reactivity has only been observed at high temperature (80–140 °C) and in low yield (ca. 10 %).[15] Therefore, given the facile synthesis of elaborate aryl(mesityl)iodonium salts[10,11] and the promising reactivity observed here, we viewed this development as an opportunity to address the limitations of accessibility of difunctionalized aryne precursors.[3–5]

Table 1: Reaction discovery and optimization.[a]



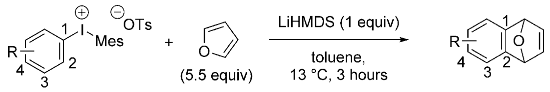
Entry	Ar_2I^+	Arynophile (equiv)	Base (equiv)	Solvent	*T* [°C]	Yield [%] (ratio)[b]
1[c]	**1**-OTf	morpholine (2)	NaO*t*Bu (1.1)	TBME	50	**3**+**5**: 89 (1:1)
2[c]	**1**-OTf	morpholine (2)	NaO*t*Bu (1.1)	TBME	25	**3**+**5**: 82 (1:1)
3[c]	**2**-OTf	morpholine (2)	NaO*t*Bu (1.1)	TBME	50	**4**+**6**: 24 (1:1)
4	**2**-OTf	furan (4)	NaO*t*Bu (2)	TBME	25	**7**: 22
5	**2**-OTf	furan (4)	$NaNH_2$	TBME	25	**7**: 20
6	**2**-OTf	furan (4)	NaHMDS (2)	TBME	25	**7**: 39
7	**2**-OTs	furan (4)	NaHMDS (2)	TBME	25	**7**: 36
8	**2**-OTs	furan (4)	LiHMDS (2)	TBME	25	**7**: 39
9	**2**-OTs	furan (4)	LiHMDS (2)	toluene	25	**7**: 48
10	**2**-OTs	furan (4)	LiHMDS (2)	toluene	13	**7**: 52
11	**2**-OTs	furan (4)	LiHMDS (3)	toluene	13	**7**: 47
12	**2**-OTs	furan (1)	LiHMDS (3)	toluene	13	**7**: 14
13	**2**-OTs	furan (4)	LiHMDS (1)	toluene	13	**7**: 62
14[d]	**2**-OTs	furan (5.5)	LiHMDS (1)	toluene	13	**7**: 78, 70[e]

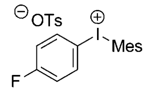
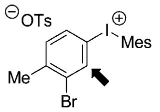
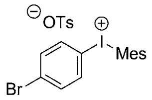
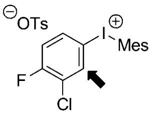
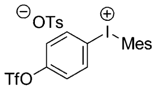
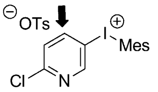
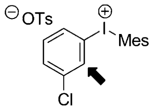
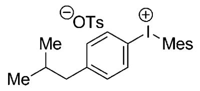
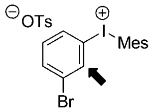
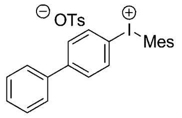
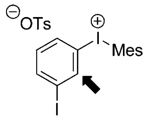
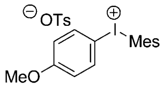
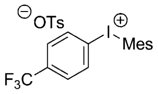
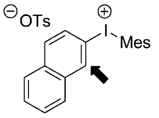
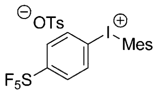
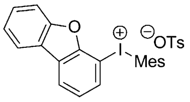
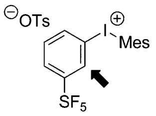
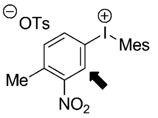
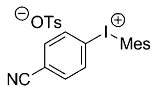
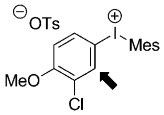
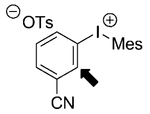
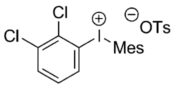
[a] Reaction conditions: **1** or **2** (0.2 mmol, 1 equiv), morpholine or furan (see table), base (see table), solvent (3 ml total), temperature (see table), 90 minutes. [b] Yield and ratio determined from ^{1}H NMR spectrum of the crude reaction mixture versus 1,3,5-trimethoxybenzene as an internal standard. [c] Solvent volume 0.66 mL total. [d] Reaction time of 3 hours. [e] Yield of isolated product is based on 0.5 mmol scale of **2**. HMDS = hexamethyldisilazide, TBME = *tert*-butyl methyl ether.

The electron-rich substrate **2** was selected to further study the influence of reaction conditions on this transformation and the putative aryne was trapped with furan as further evidence of this intermediate. The identity of the base was first explored at 25 °C and NaHMDS provided the highest yield of **7** (Table 1, entry 4–6). Moreover, we found that the identity of the counter ion of **2** or the base had little influence on the yield (entry 6–8). The accessibility[10c] of the tosylate derivative and the yield of **7** obtained with LiHMDS as base prompted us to continue the study with this combination. A solvent screen revealed that the use of toluene improved the yield of **7** from 39 to 48 % (entries 8 and 9) and an additional small increase in yield was observed when the reaction was conducted at 13 °C (entry 10). The reaction stoichiometry of furan and LiHMDS had a significant influence on the yield of **7** (entries 10–13). Specifically, excess furan (4 equiv) and stoichiometric LiHMDS provided **7** in 62 % yield (entry 13). The yield of **7** was increased to 78 % (70 % upon isolation) when the stoichiometry of furan was increased to 5.5 equivalents and the reaction was carried out for 3 hours (entry 14).

The scope with respect to the aryl(mesityl)iodonium tosylate substrates which are compatible in this C−H deprotonative aryne-forming reaction are presented in Table 2. The oxabicyclic products are obtained in moderate to excellent yield (69 % average) and illustrate several important aspects of the preparation of aryne precursors and selectivity of the formation of arynes. First, each substrate presented in Table 2 was prepared in a one-pot reaction from commercially available aryl iodide (entries 1–3 and 7–14) or arylboronic acid (entries 4–6 and 15–22). The synthesis of these aryne precursors is practical as they are prepared in good yield (71 % average yield), on synthetically useful scale (> 1 g), and are isolated by filtration after trituration with ether. Second, the hypervalent iodine moiety imparts high selectivity for the formation of the aryne intermediate. In all cases, the C−H deprotonation event is regioselective for the *ortho*-position to the iodonium (2- or 6-position; Table 2). Moreover, in the presence of halide and pseudohalide leaving groups, the reaction is highly chemoselective for departure of the iodonium leaving group (entries 1–6 and 12, 13, 21, and 22).[16] Substituents at the *ortho*-, *meta*-, and *para*-positions on the aryl moiety which becomes the aryne are tolerated. Importantly, when *meta*-substitution is present C−H deprotonation is selective for the 2-position (entries 4–6, 9, 11–13, 18–21). As a limitation of the method we have noted that several substrates resulted in low yield (ca. 30 %). Specifically, these substrates were one with an ester in the *para*-position and a substrate with multiple electron-withdrawing groups. We are continuing to investigate the source of poor reactivity with these aryne precursors.

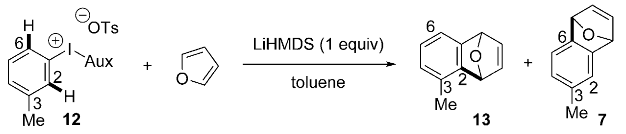
Table 2: Scope of substrates compatible in the formation of arynes.[a]



Entry	Substrate	Yield (%)	Entry	Substrate	Yield (%)
1		58, 69[b]	12		72
2		79, 80[b]	13		82
3		67, 70[b]	14		51
4		69, 73[b]	15		72
5		84, 85[b]	16		67
6		89, 81[b]	17		67
7		65	18		53
8		67	19		75
9		50	20		79
10		65	21		86
11		40	22		75

[a] Reaction conditions: aryl(mesityl)iodonium tosylate (0.5 mmol, 1 equiv), furan (200 µL, 2.75 mmol, 5.5 equiv), LiHMDS (1 M in toluene; 0.5 mL, 0.5 mmol, 1 equiv), toluene (7.0 mL), 13 °C, 3 hours. [b] Yield determined by ^{1}H NMR analysis of 0.2 mmol of the iodonium salt with 1,3,5-trimethoxybenzene as an internal standard; average of 2 runs.

Table 3: Auxiliary and temperature controlled selectivity of C–H deprotonation.



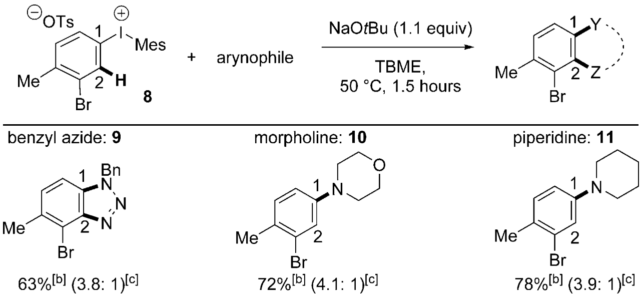
Entry	Aux	T [°C]	**13**/**7**[b]
1	2′,4′,6′-trimethylphenyl (Mes)	13	4.2:1
2	2′,4′,6′-triisopropylphenyl	13	5.3:1
3	2′,4′,6′-triisopropylphenyl	−10	6.7:1

[a] Reaction conditions: **12** (0.2 mmol, 1 equiv), furan (80 µL, 1.1 mmol, 5.5 equiv), LiHMDS (1 M in toluene; 0.2 mL, 0.2 mmol, 1 equiv), toluene (2.8 mL), temperature (see table), 3 h. [b] Ratio determined by ^{1}H NMR analysis of the crude reaction mixture.

The C–H deprotonation selectivity we observed (> 20:1) when an inductively electron-withdrawing group is present in the 3-position is consistent with proximity-induced acidity of the proton at the 2-position relative to that at the 6-position.[17] We were therefore surprised to find that an electron-donating and sterically bulky methyl substituent in the 3-position still led to a preference, albeit lower, for deprotonation at the 2-position, thus producing **13** and **7** in a 4.2:1 ratio (Table 3, entry 1). A survey of other auxiliaries revealed that increasing the steric effect of the auxiliary from 2′,6′-dimethyl substitution to 2′,6′-di-isopropyl substitution increased the selectivity for deprotonation at the less sterically accessible 2-position (entry 2). When the reaction was conducted at −10 °C the selectivity for **13** further improved to 6.7:1 (entry 3). Taken together, these results are consistent with the auxiliary steric effect and the temperature exerting a modest influence on the population of reactive conformers which lead to arynes. We are further exploring the identity of the conformers and the nature of the selectivity determining step in this process.

The oxabicyclic products from the reaction of arynes with furan are useful synthetic intermediates toward natural products[18] and active pharmaceutical ingredients.[19] However, given that arynes participate in diverse reaction classes, preliminary examples of reactions which incorporate nitrogen coupling partners under slightly modified reaction conditions are presented in Table 4. Specifically, cycloaddition of **8** with

Table 4: Representative examples of cycloaddition and nucleophilic addition reactions.[a]



[a] Reaction conditions: aryl(mesityl)iodonium tosylate (0.5 mmol, 1 equiv), benzyl azide, morpholine, piperidine (1 mmol, 2 equiv), NaO*t*Bu (0.55 mmol, 1.1 equiv), TBME (1.65 mL), 50 °C, 1.5 hours. [b] Combined yield of regioisomers. [c] Ratio of regioisomers; major regioisomer shown.

benzyl azide produced a mixture (3.8:1) of benzotriazole products in 63% combined yield. Trapping of the electrophilic aryne intermediate with morpholine or piperidine as nucleophilic amines was also demonstrated. The aryl amines **10** and **11** are the major regioisomeric products of this reaction and were isolated in 58 and 62% yield, respectively. The formation of regioisomers is consistent with an aryne intermediate and the regioselectivity observed for the cycloaddition and nucleophilic addition in these cases is consistent with previous experimental and theoretical analysis of reactions of 3-substituted aryne intermediates bearing an inductively electron-withdrawing group.[20] We are continuing to explore the compatibility of generating aryne intermediates in this way with other reaction classes.

In conclusion, we have described a novel and efficient method to access aryne intermediates and it avoids the need for difunctionalized aryne precursors. The hypervalent iodine moiety serves as a general and chemoselective leaving group in the presence of other potential leaving groups such as fluoride, chloride, bromide, iodide, and triflate and the aryne intermediates are trapped with furan, benzyl azide, or alicyclic amines. Insight into the C−H deprotonation event revealed an unprecedented role of the leaving group in modulating regioselectivity and sets the hypervalent iodonium moiety apart from traditional halide leaving groups in this regard. Moreover, the realization of a general C−H deprotonation strategy toward arynes from aryl(mesityl)iodonium salts expands the breadth of reaction manifolds accessible with this emergent class of transition-metal-free arylation reagent. Mechanistic studies and expanded scope of this reaction are underway in our laboratories.

Experimental Section

The iodonium salt (0.5 mmol, 1 equiv) is weighed out in air and placed in an oven-dried vial containing a magnetic stir bar and is sealed with a Teflon-lined septum cap. The vial is purged with nitrogen gas for approximately 10 minutes. Toluene (7 mL) and furan (200 μL, 2.75 mmol, 5.5 equiv) are added sequentially by syringe through the septum. The vial is placed in an ice-cooled water bath maintained at 13 °C. LiHMDS (0.5 mL (1 M in toluene), 0.5 mmol, 1 equiv) is added by syringe through the septum and the reaction is stirred for 3 hours. The vial is removed from the ice-bath and the reaction is quenched with an aqueous solution of ammonium chloride (5 mL). The biphasic mixture is placed in a separatory funnel and washed with DCM (3 × 5 mL). The combined organic phases are dried with $MgSO_4$, the drying agent removed by suction filtration, and the solvent removed on the rotary evaporator. The crude residue is purified by flash column chromatography on silica gel with an ether/hexane mixture as the eluent.

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Keywords: arynes · cycloaddition · hypervalent compounds · regioselectivity · synthetic methods

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