Synthesis B. E. Metze et al. Special Topic

Parameterization of Arynophiles: Experimental Investigations towards a Quantitative Understanding of Aryne Trapping Reactions

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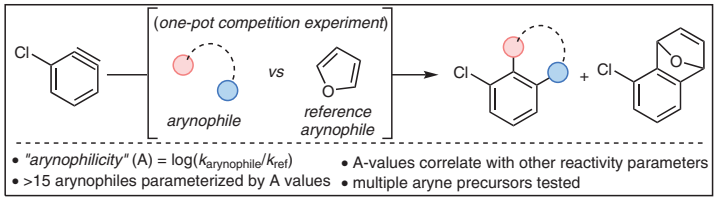

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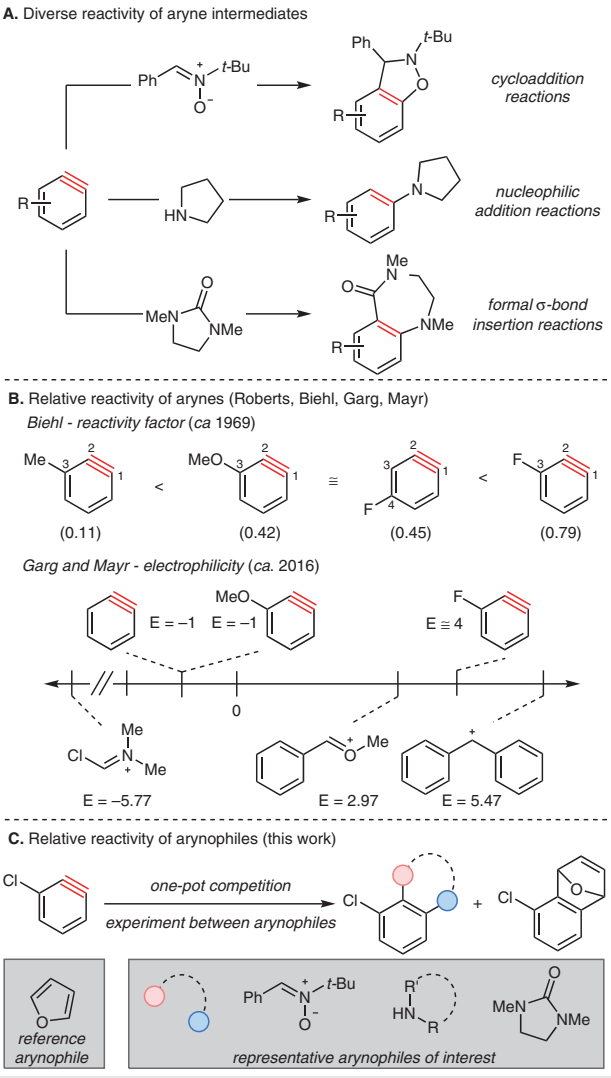
Abstract Arynes are highly reactive intermediates that may be used strategically in synthesis by trapping with arynophilic reagents. However, 'arynophilicity' of such reagents is almost completely anecdotal and predicting which ones will be efficient traps is often challenging. Here, we describe a systematic study to parameterize the arynophilicity of a wide range of reagents known to trap arynes. A relative reactivity scale, based on one-pot competition experiments, is presented by using furan as a reference arynophile and 3-chlorobenzyne as a the aryne. More than 15 arynophiles that react in pericyclic reactions, nucleophilic addition, and σ-bond insertion reactions are parameterized with arynophilicity (A) values, and multiple aryne precursors are applicable.

Key words LFER, aryne, arynophile, percyclic reaction, δ-bond insertion, nucleophilic addition

Arynes play a critical role as intermediates in modern organic synthesis and have been implemented in the synthesis of various natural products and diverse aromatic scaffolds.[1] The versatility of arynes is attributed to the multitude of reaction pathways in which they participate, i.e., cycloaddition reactions, nucleophilic addition reactions, formal σ-bond insertion, and transition-metal-catalyzed reactions (Scheme 1a).[1c] Moreover, these general pathways can also lead to rearrangements and be integrated into multi-component coupling reactions.[1c] The high electrophilic character of arynes has been well-established theoretically[2] and experimentally, and in some cases they even react with typically inert solvents.[3] Linear free energy relationships (LFER) have been used effectively to characterize the relative reactivity of aryne intermediates (Scheme 1b). For instance, Beihl and co-workers devised a 'reactivity factor' scale and correlated it to the polar substituent constant, σ (Scheme 1b).[4] They found that the proximity and identity of the aryne substituent impacts reactivity; 3-substituted arynes are more reactive than 4-substituted arynes with the same substituent, and reactivity correlates with inductive σ′ constants (Scheme 1b).[4] More recently, Garg, Mayr and co-workers quantified the electrophilicity of benzyne and other arynes via the diffusion-clock method (Scheme 1b).[5] Garg and Mayr found that aryne intermediates have electrophilicity (E) parameters that range from –1 to ~4. These values place benzyne electrophilicity between Vilsmeier iminium and oxocarbenium cations, and the highly electrophilic 3-fluorobenzyne is similar in electrophilicity to diarylcarbonium cation (Scheme 1b).[6] Additionally, consistent between Biehl's earlier work and Garg's recent work is that 3-fluorobenzyne is more reactive (electrophilic) than 3-methoxybenzyne. Although Garg and Mayr's work permits comparison of nucleophilic arynophiles, there is little recourse to predict the outcome of reactions with arynophiles that participate in other pathways, e.g., cycloaddition, and those whose nucleophilicity parameters have not been determined. Additionally, given the high reactivity of arynes, and propensity to even react with solvent, delineating the relative reactivity of arynophiles to engage in productive trapping would elevate the use of these versatile intermediates.

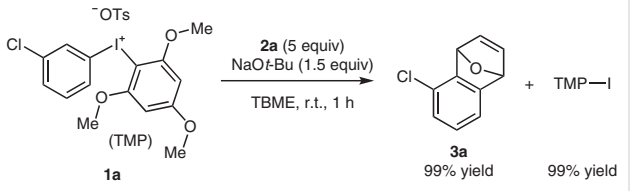
Herein, we describe the development of a relative reactivity scale for arynophiles that undergo cycloaddition ([3+2] and [4+2]), nucleophilic addition (aromatic and aliphatic amines), and formal σ-bond insertion (chloroamines, ureas) reactions with arynes. In total, 19 arynophiles are characterized by an arynophilicity (A) parameter, in which furan is used as a reference arynophile with an A-value defined as 0 (Scheme 1c). Where possible, the A-values obtained correlate with Mayr nucleophilicity (N) parameters, but also extend to a large number of non-nucleophilic arynophiles. The A-values obtained in this work are



Scheme 1 Reactivity of arynes

applied to multiple aryne precursors (diaryliodonium salts and *ortho*-(trimethyl)silylphenyl triflates) to demonstrate the generality of this scale.

A key consideration of our approach to developing a relative reactivity scale for arynophiles is a high-yielding method to generate arynes. We found that 3-chlorophenyl(2′,4′,6′-trimethoxyphenyl)iodonium tosylate **1a** extrudes aryne in high yield when treated with NaO*t*-Bu (1.5 equiv) as base in TBME at room temperature, as evidenced by quantitative formation of by-product trimethoxyphenyl iodide (TMP-I; Scheme 2).[7] Moreover, in the presence of 5 equivalents of furan **2a**, we observed quantitative ^{1}H-NMR yield of cycloadduct **3a** (Scheme 2). Aryne formation is the rate-determining step and aryne trapping is the product-determining step. Therefore, this is an ideal system for one-pot competition experiments between arynophiles and furan as a reference arynophile to assess relative aryophilicity.



Scheme 2 Archetypal system for aryne generation and trapping

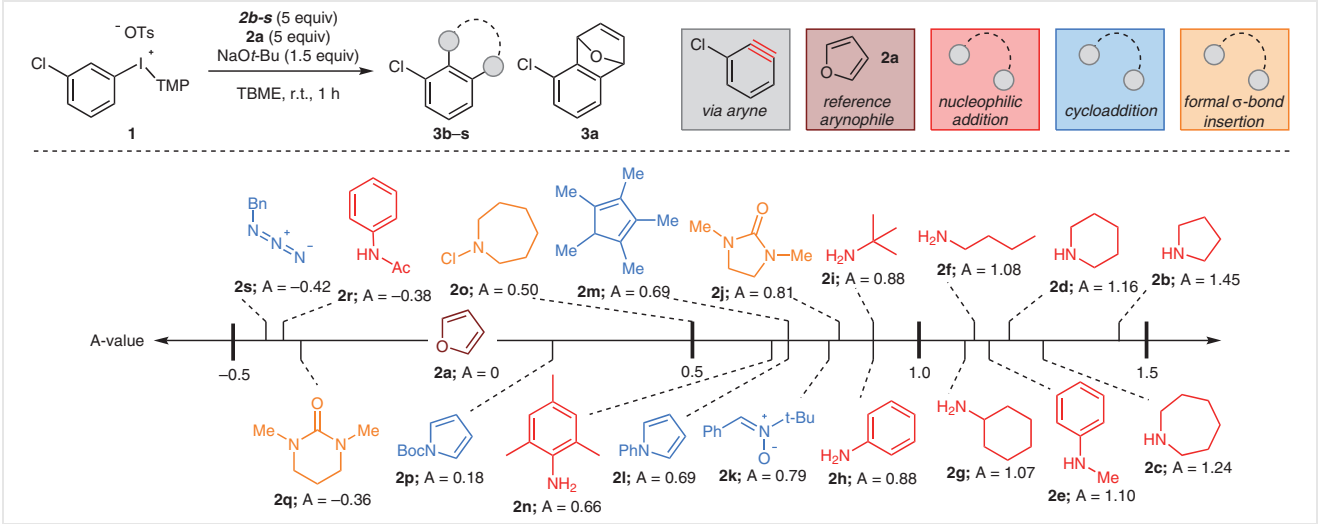
In the one-pot competition experiments, a large and equal excess of furan and an arynophile of interest are added to the archetypal system (Scheme 3). Product ratios of **3b–s**/**3a** are proportional to the ratio of rate constants ($k_{arynophile}/k_{furan}$) and are determined by integration of product peaks in the crude ^{1}H NMR spectrum.[8] The A-parameters are calculated from Equation 1 and presented in Scheme 3.

$$log\frac{k_{arynophile}}{k_{furan}} = A;\ \frac{k_{arynophile}}{k_{furan}} \propto \frac{Int_{3b-s}}{Int_{3a}} \times \frac{\#\ protons_{3a}}{\#\ protons_{3b-s}}$$

Equation 1 Method used to determine A-values

In addition to the reference arynophile, furan **2a**, 18 additional arynophiles **2b–s** were parameterized in this work (Scheme 3). We focused on three different reaction pathways: nucleophilic addition (red), cycloaddition (blue), and formal σ-bond insertion (orange) reactions, and each is color coded in Scheme 3. The relative reactivity scale that we have constructed reflects differences in reactivity for the three reaction pathways studied and accounts for both electronic and steric effects of the individual arynophiles. Our analysis reveals that *N*-nucleophiles **2b–i** were the most reactive of the arynophiles we studied. Within, this subset, cyclic secondary amines **2b–d** were the most reactive, and for acyclic amines reactivity decreased with increasing steric effects of the alkyl substituent in the order 1° > 2° > 3° for **2f**, **2g**, and **2i**, respectively (Scheme 3). Aniline **2h** has identical A-parameter (A = 0.88) as *tert*-butyl amine **2i**, whereas *N*-methylaniline **2e** is more reactive (A = 1.10) and acetanilide **2r** is much less reactive (A = –0.38), which reflects the different electronic effects of these aromatic amine substrates (Scheme 3). Additionally, 2,4,6-trimethyl aniline **2n** is less reactive (A = 0.66) than unsubstituted aniline **2h** (A = 0.88) as a result of greater steric effects in **2n** (Scheme 3).

Arynophiles that participate in cycloaddition reactions include nitrone **2k**, pyrroles **2l** and **2p**, pentamethyl cyclopentadiene **2m**, and *N*-benzyl azide **2s** (Scheme 3). Generally, these substrates are more reactive than **2a**, but broadly have moderate to low A-values (Scheme 3). The most arynophilic of this subset is nitrone **2k** (A = 0.79), which



Scheme 3 Relative reactivity scale of arynophiles (A-value)

participates in a [3+2] cycloaddition with 3-chlorobenzyne. However, at the other end of the spectrum is benzyl azide **2s**, which has the lowest A-value measured in this study (A = –0.42; Scheme 3). Consistent with electronic effects, *N*-phenylpyrrole **2l** was more arynophilic (A = 0.69) than *N*-Boc pyrrole **2p** (A = 0.18; Scheme 3). Pentamethylcyclopentadiene **2m** has the same arynophilicity as *N*-phenylpyrrole **2l** (A = 0.69; Scheme 3).

Formal σ-bond insertion into the C–N bond of ureas **2j** and **2q** as well as the Cl–N bond of chloroazepane **2o** was also studied (Scheme 3). The arynophilicity of urea **2j** (A = 0.81) is comparable to aniline **2h** (A = 0.88) and nitrone **2k** (A = 0.79; Scheme 3). However, urea **2q** has one of the lowest arynophilicities observed in this study (A = –0.36; Scheme 3). *N*-Chloroazepane **2o** adds a Cl–N bond across 3-chlorobenzyne derived from **1a**. The arynophilicity of **2o** (A = 0.50) is intermediate between urea **2j** and **2q**, but is substantially lower than the corresponding *N*-H azepane **2c** (A = 1.24), likely due to the reduced nucleophilicity of **2o**, which stems from the withdrawing chloro substituent (Scheme 3).

The A-values obtained here align with other reactivity parameters and concepts used to describe several of the compounds studied in this work (Figure 1). For instance, the A-values obtained for several cyclic and acyclic amines correlate with the nucleophilicity (N) parameters previously determined by Mayr (**2b**, **2d**, **2f**, **2h**, **2i**; Figure 1a).[9] This is also consistent with the fact that Garg and Mayr used N-parameters to determine the electrophilicity of several arynes (Scheme 1b).[5] Nucleophilicity parameters are not relevant or known for arynophiles that react through cycloaddition reactions or formal σ-bond insertion.

HOMO-LUMO interactions are often correlated with reaction rates of cycloaddition reactions.[10] As such, we calculated the $HOMO_{energy}$ (eV) of the arynophiles that react with cycloaddition and observed a linear trend with A-values for **2a**, **2k**, **2l**, **2p**, and **2s** (Figure 1b). Pentamethylcyclopentadiene **2m** was an outlier in this trend, possibly due to steric effects of the five methyl groups, which are not well accounted for in the $HOMO_{energy}$ calculation. Collectively, these 10 arynophiles span the range of A-values deter-

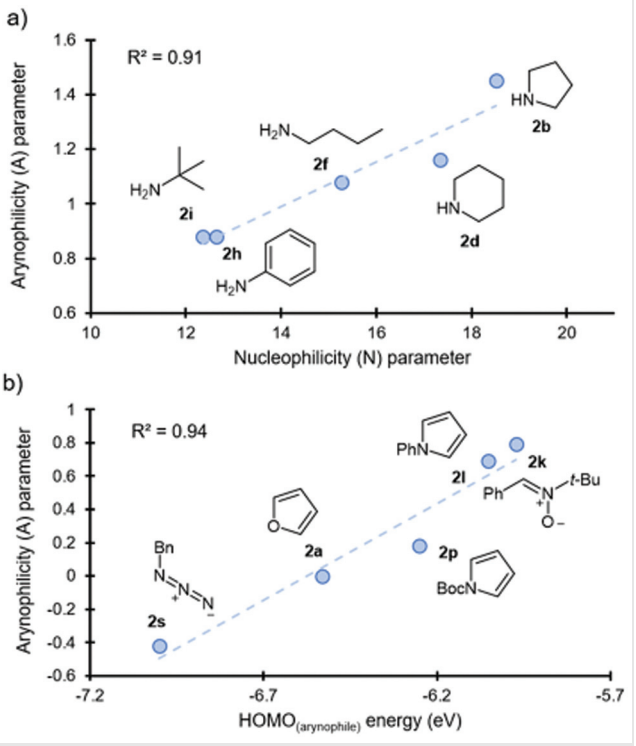


Figure 1 Correlation of A-values with other reactivity parameters. (a) Nucleophilicity (N) parameter; (b) $HOMO_{energy}$ of the arynophile.

mined here **2b**, A = 1.45 and **2s**, A = –0.42 (Scheme 3 and Figure 1).

In order to demonstrate the generality of the A-parameters derived here, we applied them to other iodonium and non-iodonium aryne precursors. Specifically, we used **1b**, bearing a mesityl iodonium leaving group, and **1c**, the venerable Kobayashi-type reagent (Figure 2). As in Scheme 3, we performed one-pot competition experiments between the reference arynophile **2a** and several representative arynophiles that undergo nucleophilic addition (**2b** and **2f**), cycloaddition (**2l** and **2p**), and σ-bond insertion (**2j**) and the correlation with A-values are shown in Figure 2. Aryne precursors **1b** and **1c** extrude the same aryne, 3-chlorobenzyne, as **1a** and so competitive trapping with arynophiles should follow the same trends.

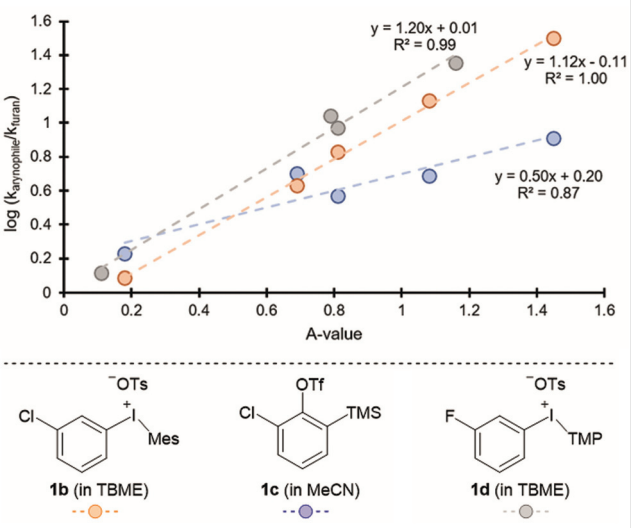
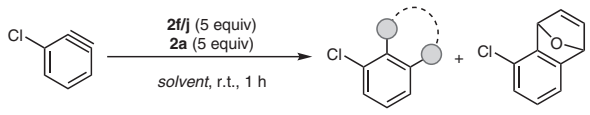


Figure 2 Correlation of A-values with different aryne precursors

However, there are some small distinctions that are worth pointing out. When aryne precursor **1b** was subjected to competition experiments (Figure 2, orange circles) a slope of 1.12 was obtained, indicating that a nearly identical response was observed as with **1a**. However, when aryne precursor **1c** was subjected to competition experiments the linear free-energy relationship was conserved, but a slope of 0.50 was observed. This difference may be explained by a change in solvent from TBME for **1a** to MeCN for **1c** and a rate enhancement for the reference arynophile furan in the more polar solvent.[11] To test this hypothesis, we used **1a** in competition experiments between arynophiles **2f** and **2j** with reference arynophile **2a** in MeCN instead of TBME as solvent (Table 1). We observed a decrease in the $\log(k_{arynophile}/k_{furan})$ values for **1a** when the competition experiments were conducted in MeCN, consistent with our hypothesis. Moreover, the $\log(k_{arynophile}/k_{furan})$ values obtained for **1a** in MeCN were very similar to those obtained for **1c** in MeCN (Table 1). Finally, we also performed competition experiments with aryne precursor **1d**, bearing a fluoro substituent (grey circles, Figure 2). The LFER was also observed in this case, demonstrating that this trend extends to other substituted arynes as well.

Table 1 Comparison of Competition Experiments in TBME and MeCN[a]



Aryne precursor/arynophile	Solvent	$\log(k_{arynophile}/k_{furan})$
1a/**2f**	TBME	1.08
1a/**2f**	MeCN	0.72
1c/**2f**	MeCN	0.69
1a/**2j**	TBME	0.81
1a/**2j**	MeCN	0.57
1c/**2j**	MeCN	0.63

[a] Conditions for **1a**: **1a** (0.1 mmol, 1 equiv), **2f**/**j** (0.5 mmol, 5 equiv), **2a** (0.5 mmol, 5 equiv), NaO*t*-Bu (0.15 mmol, 1.5 equiv), solvent (see table, 0.5 mL), r.t., 1 h. Conditions for **1c**: **1c** (0.085 mmol, 1 equiv), **2f**/**j** (0.425 mmol, 5 equiv), **2a** (0.425 mmol, 5 equiv), CsF (0.425 mmol, 5 equiv), MeCN (0.41 mL), r.t., 1 h.

In conclusion, we have developed an arynophilicity parameter (A-value) that describes the relative reactivity in trapping arynes and includes three different reaction pathways. The A-values for arynophiles that act as nucleophiles correlate with known nucleophilicity parameters. Additionally, the A-values for arynophiles that participate in cycloaddition reactions correlate with $HOMO_{energy}$ of the arynophile. Comparison of arynophiles from these groups, and from other substrate classes that are not described by nucleophilicity or $HOMO_{energy}$, are now possible as they are unified by a single A-value scale. The A-values were developed with diaryliodonium salts as aryne precursors, but are also compatible with the more common (2-trimethylsilyl)aryl triflate reagents. Further parameterization of other arynophiles, development of a related scale for arynes, and use of the A-values in other related reactions are ongoing in our laboratory.

Commercially available reagents and solvents were used without further purification unless otherwise stated. The percentage of active oxidant for *m*-CPBA was determined by iodometric titration prior to use.[12] (3-Chlorophenyl)(2,4,6-trimethoxyphenyl)iodonium tosylate **1a**,[13] (3-chlorophenyl)(mesityl)iodonium tosylate **1b**,[14] 2-chloro-6-(trimethylsilyl)phenyl trifluoromethanesulfonate **1c**,[15] (3-fluorophenyl)(2,4,6-trimethoxyphenyl)iodonium tosylate **1d**,[13] *N*-*tert*-butyl-α-phenyl nitrone **2k**,[16] *N*-phenylpyrrole **2l**,[17] chloroazepane **2o**,[18] *N*-Boc pyrrole **2p**,[19] and aryne adducts **3a**,[7] **3j**,[7] **3k**,[7] **3o**,[7] **4a**,[20] **4b**,[21] and **4c**[22] have been previously characterized. Reactions performed above room temperature (ca. 23 °C) were done so in an oil bath or aluminum block heated externally. Reactions performed below ambient room

temperature were done so in an ice, or dry-ice-acetone bath. Crude reaction mixtures were analyzed by ^{1}H NMR spectroscopy or thin-layer chromatography (TLC) on Sigma–Aldrich Al Foils Flexible TLC plates (silica gel 60 Å F-254) and visualized by UV irradiation, iodine, anisaldehyde, or permanganate stain. Crude material was purified by flash column chromatography on SilicaFlash P60 silica gel. Product distributions for competition experiments were obtained by integration of peaks known for the analyte molecules, see the Supporting Information for competition reaction spectra. ^{1}H and ^{13}C{^{1}H} spectra were recorded in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as an internal standard on a Bruker Avance II 400 MHz or Bruker Avance III 600 MHz spectrometer; the following notation is used: br – broad, s – singlet, d – doublet, t – triplet, q – quartet, m – multiplet, dd – doublet of doublets, dt – doublet of triplets, and ddd – doublet of doublet of doublets. FTIR spectra were recorded on a Thermo Scientific Nicolet iS5 Infra-red spectrometer. High-resolution mass spectrometry (HRMS) data were recorded on a Thermo Scientific Q-exactive mass spectrometer by electrospray ionization with an Orbitrap mass-analyzer (ESI-Orbitrap). Melting points were recorded on a Mel-Temp (Thermo scientific) and are reported as uncorrected.

General Procedure to Obtain Analytically Pure Samples of Aryne Adducts 3a–s

Iodonium salt **1a** (0.5 mmol, 1 equiv) was weighed out in air and added to a 12 mL vial. A magnetic stir bar, TBME (2.5 mL) and arynophile (1–5 equiv) were added sequentially, forming a slurry. NaO^{t}Bu (0.0721 g, 0.75 mmol, 1.5 equiv or as indicated) was weighed out in air and added to the vial with constant stirring in one portion. The vial was sealed with a cap, and the reaction mixture was vigorously stirred at room temperature, or as indicated, for one hour. The reaction was quenched with ammonium chloride solution (7 mL) and extracted with EtOAc (3 × 3 mL). The combined organic phases were dried with $MgSO_4$. The drying agent was removed by vacuum filtration, and the crude reaction mixture was concentrated under reduced pressure using a rotary evaporator. The crude mixture was further purified by flash chromatography on silica gel using EtOAc or diethyl ether in hexanes.

1-(3-Chlorophenyl)pyrrolidine (3b)

Prepared from **1a** and pyrrolidine **2b** (0.1066 g, 1.5 mmol, 3 equiv) on a 0.5 mmol scale according to the general procedure with the following modification: the crude product was purified by filtration through a pad of silica and obtained in an isolated yield of 18% (0.0166 g, 0.09 mmol) as a mixture of regioisomers (1:0.1) appearing as a clear oil. Characterization of the major regioisomer is provided below. Spectral data are consistent with previous reports.[23]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.10 (t, J = 8.07 Hz, 1 H), 6.60 (dd, J_1 = 7.83 J_2 = 1.2 Hz, 1 H), 6.51 (t, J = 2.2 Hz, 1 H), 6.41 (dd, J_1 = 8.4 J_2 = 2.3 Hz, 1 H), 3.26–3.23 (m, 4 H), 2.01–1.98 (m, 4 H).

^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ = 148.9, 134.9, 130.0, 115.1, 111.4, 109.8, 47.6, 25.5.

1-(3-Chlorophenyl)azepane (3c)

Prepared from **1a** and azepane **2c** (0.112 mL, 1 mmol, 2 equiv) on a 0.5 mmol scale according to the general procedure with the following modifications: 3 equivalents of NaO^{t}Bu (0.1440 g, 1.5 mmol) and the product was obtained in an isolated yield of 48% (0.0498 g, 0.36 mmol) as a clear liquid.

R_f = 0.85 (hexanes/EtOAc, 1:0.2).

IR (ATR): 2922, 2851, 1589, 1490, 1233, 1197, 1099, 1001, 752 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.09 (t, J = 8.1 Hz, 1 H), 6.63 (t, J = 2.2 Hz, 1 H), 6.59–6.52 (m, 2 H), 3.43–3.40 (m, 4 H), 1.77 (br, 4 H), 1.55–1.52 (m, 4 H).

^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ = 165.8, 162.1, 159.6, 148.3(2), 148.3(0), 131.9, 131.7.

HRMS (ESI): m/z [$C_{12}H_{16}ClN$ $^+$+H]$^+$ calcd: 210.1050; found: 210.1042.

1-(3-Chlorophenyl)piperidine (3d)

Prepared from **1a** and piperidine **3d** (98 uL, 0.5 mmols, 1 equiv) on a 0.5 mmol scale according to general procedure A with the following modifications: the reaction was conducted at 50 °C for 90 min using 1.1 equivalents of NaO^{t}Bu (0.0528 g, 0.55 mmol). The product was obtained in an isolated yield of 48% (0.0469 g, 0.37 mmol) as a light-yellow oil. Spectral data are consistent with previous reports.[24]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.13 (t, J = 8.11 Hz, 1 H), 6.88–6.86 (m, 1 H), 6.79–6.74 (m, 2 H), 3.17–3.14 (m, 4 H), 1.71–1.65 (m, 4 H), 1.60–1.54 (m, 2 H).

^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ = 153.1, 134.8, 129.9, 118.6, 116.0, 114.3, 50.1, 25.6, 24.2.

3-Chloro-*N*-methyl-*N*-phenylaniline (3e)

Prepared from **1a** and *N*-methylaniline **2e** (0.1071 g, 0.5 mmol, 1 equiv) on a 0.5 mmol scale according to the general procedure and obtained in an isolated yield of 38% (0.0410 g, 0.19 mmol) as a clear liquid. Spectral data are consistent with previous reports.[25]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.33 (t, J = 7.9 Hz, 2 H), 7.14–7.06 (m, 4 H), 6.88 (t, J = 2.1 Hz, 1 H), 6.82 (dd, J_1 = 7.88, J_2 = 1.1 Hz, 1 H), 6.77 (dd, J_1 = 8.3, J_2 = 2.2 Hz, 1 H), 3.29 (s, 3 H).

^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ = 150.2, 148.2, 134.8, 129.9, 129.6, 123.5, 123.4, 119.5, 117.4, 115.8, 40.3.

N-Butyl-3-chloroaniline (3f)

Prepared from **1a** and *N*-butylamine **2f** (147 µL, 1.5 mmol, 3 equiv) on a 0.5 mmol scale according to the general procedure with the following modifications: 3 equivalents of NaO^{t}Bu (1.5 mmol, 0.144 g) was used. The product was obtained in an isolated yield of 7% (0.0064 g, 0.035 mmol) as a clear liquid.

R_f = 0.73 (hexanes/EtOAc, 1:0.2).

IR (ATR): 2956, 2924, 2850, 1598, 1541, 1326, 1279, 1027, 762 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.05 (t, J = 8.0 Hz, 1 H), 6.63 (dd, J_1 = 7.8, J_2 = 1.1 Hz, 1 H), 6.56 (t, J = 2.1 Hz, 1 H), 6.45 (dd, J_1 = 8.2 J_2 = 1.6 Hz, 1 H), 3.73 (br, 1 H), 3.08 (t, J = 7.2 Hz, 2 H), 1.63–1.56 (m, 3 H), 1.47–1.38 (m, 3 H), 0.96 (t, J = 7.1 Hz, 3 H).

^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ = 149.6, 135.0, 130.1, 116.8, 112.1, 111.0, 43.5, 31.5, 29.7, 20.2, 13.9.

HRMS (ESI): m/z [$C_{10}H_{14}ClN$ + H]$^+$ calcd: 184.0893; found: 184.0889.

3-Chloro-*N*-cyclohexylaniline (3g)

Prepared from **1a** and cyclohexylamine **2g** (171 µL, 1.5 mmol, 3 equiv) on a 0.5 mmol scale according to the general procedure with the following modifications: 3 equivalents of NaO^{t}Bu (0.1440 g, 1.5 mmol) was used. The product was obtained in an isolated yield of 15% (0.0164 g, 0.08 mmol) as a clear liquid. Spectral data are consistent with previous reports.[26]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.03 (t, *J* = 8.0 Hz, 1 H), 6.60 (d, *J* = 7.8 Hz, 1 H), 6.54 (t, *J* = 2.0 Hz, 1 H), 6.43 (dd, J_1 = 8.2, J_2 = 2.0 Hz, 1 H), 3.60 (br, 1 H), 3.24–3.19 (m, 1 H), 2.05–2.02 (m, 2 H), 1.76 (dt, J_1 = 12.9, J_2 = 3.8 Hz, 2 H), 1.65 (dt, *J* = 12.4 Hz, J_2 = 3.7 Hz, 2 H), 1.42–1.32 (m, 2 H), 1.26–1.20 (m, 1 H), 1.19–1.10 (m, 2 H).

^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ = 148.5, 135.0, 130.2, 116.5, 112.5, 111.4, 51.6, 33.3, 25.8, 24.9.

3-Chloro-*N*-phenylaniline (3h)

Prepared from **1b** and aniline **2h** (91.3 µL, 1 mmol, 2 equiv) on a 0.5 mmol scale according to the general procedure and obtained in an isolated yield of 23% (0.023 g, 0.115 mmol) as a clear liquid. Spectral data are consistent with previous reports.[27]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.30 (t, *J* = 7.8 Hz, 2 H), 7.15 (dd, *J* = 8.4 Hz, 1 H), 7.10 (d, *J* = 7.8 Hz, 2 H), 7.04 (s, 1 H), 7.00 (t, *J* = 7.4 Hz, 1 H), 6.90–6.84 (m, 2 H), 5.71 (br, 1 H).

^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ = 144.8, 141.9, 135.0, 130.3, 129.5, 122.1, 120.5, 119.0, 116.6, 115.1.

N-(*tert*-Butyl)-3-chloroaniline (3i)

Prepared from **1a** and *tert*-butylamine **2i** (0.1097 g, 1.5 mmol, 3 equiv) on a 0.5 mmol scale according to general procedure A with the following modifications: 3 equivalents of NaO^{t}Bu (0.144 g, 1.5 mmol) was used. The product was obtained in an isolated yield of 72% (0.0666 g, 0.36 mmol) as a clear liquid. Spectral data are consistent with previous reports.[28]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.04 (t, *J* = 8.0 Hz, 1 H), 6.70 (t, *J* = 2.1 Hz, 1 H), 6.68 (dd, J_1 = 1.9, J_2 = 0.8 Hz, 1 H), 6.66 (dd, J_1 = 1.9, J_2 = 0.8 Hz), 6.57 (dd, J_1 = 2.3, J_2 = 0.9 Hz, 1 H), 6.55 (dd, J_1 = 2.3, J_2 = 0.8 Hz, 1 H), 3.57 (br, 1 H), 1.34 (s, 9 H).

^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ = 148.1, 134.5, 129.9, 117.5, 115.9, 114.6, 51.4, 29.9.

5-Chloro-9-phenyl-1,4-dihydro-1,4-epiminonaphthalene (3l)

Prepared from **1a** and *N*-phenylpyrrole **2l** (0.1432 g, 1 mmol, 2 equiv) on a 0.5 mmol scale according to the general procedure and obtained as a mixture of the title compound and trimethoxyphenyl-iodide. The crude reaction mixture was further purified after column chromatography to 79% (21% TMP-I, 0.0530 g crude mass) by crystallization of TMP-I from toluene. The impure mixture was obtained as a brown oil.

R_f = 0.66 (hexanes/EtOAc, 1:0.2).

IR (ATR): 3059, 3020, 2926, 1581, 1492, 1450, 1296, 1157, 764 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.17 (t, *J* = 7.9 Hz, 2 H), 7.11 (dd, J_1 = 6.1 Hz, J_2 = 1.4 Hz, 1 H), 7.00 (s, 2 H), 6.88–6.81 (m, 5 H), 5.61 (s, 1 H), 5.45 (s, 1 H).

Trimethoxyphenyl iodide impurity; δ = 6.14 (s, 2 H), 3.86 (s, 6 H), 3.82 (s, 3 H).[29]

^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ = 150.8, 146.7, 146.4, 142.4, 141.4, 128.9, 128.0, 126.7, 125.5, 121.1, 119.8, 117.9, 70.2, 67.6.

Trimethoxyphenyl iodide impurity; δ = 162.1, 159.8, 91.2, 66.7, 56.4, 55.5.

HRMS (ESI): *m*/*z* [$C_{16}H_{12}ClN^{+}$+Na]$^+$ calcd: 254.0737 Found; 254.0726.

5-Chloro-1,2,3,4,9-pentamethyl-1,4-dihydro-1,4-methanonaphthalene (3m)

Prepared from **1a** and pentamethylcyclopentadiene **2m** (0.243 mL, 1.5 mmol, 3 equiv) according to the general procedure on a 0.5 mmol scale and obtained in an isolated yield of 38% (0.0470 g, 0.19 mmol) as a white crystalline solid. This compound was further purified by crystallization after column chromatography by slow evaporation from hexanes.

Mp 51–53 °C; R_f = 0.91 (hexanes/EtOAc, 1:0.16).

IR (ATR): 3057, 2957, 2926, 2903, 2867, 1571, 744 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.92 (dd, *J* = 5.0, 2.9 Hz, 1 H), 6.85–6.82 (m, 2 H), 2.22 (q, *J* = 6.4 Hz, 1 H), 1.60 (s, 6 H), 1.49 (d, *J* = 1.2 Hz, 3 H), 1.33 (s, 3 H), 0.81 (d, *J* = 6.4 Hz, 3 H).

^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ = 159.4, 150.7, 140.8(1), 140.8(2), 127.1, 126.0, 125.2, 116.4, 77.0(2) (overlaps with solvent residual peak), 61.3, 58.6, 13.1, 11.8, 11.2, 11.0, 9.3.

HRMS (ESI): *m*/*z* [$C_{16}H_{19}Cl$ + H]$^+$ calcd: 247.1248; found: 247.1246.

N-(3-Chlorophenyl)-2,4,6-trimethylaniline (3n)

Prepared from **1a** and 2,4,6-trimethylaniline **2n** (0.1352 µL, 0.5 mmol, 1 equiv) on a 0.5 mmol scale according to the general procedure and obtained in an isolated yield of 83% (0.1000 g, 0.4150 mmol) as a yellow solid. Spectral data are consistent with previous reports.[30]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.04 (t, *J* = 7.0 Hz, 1 H), 6.94 (s, 2 H), 6.69–6.66 (m, 1 H), 6.42 (t, *J* = 2.1 Hz, 1 H), 6.38–6.35 (m, 1 H), 5.13 (br, 1 H), 2.30 (s, 3 H), 2.16 (s, 6 H).

^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ = 148.0, 136.1, 136.0, 135.1, 134.6, 130.2, 129.3, 117.7, 112.8, 111.4, 20.9, 18.2.

tert-Butyl 5-Chloro-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate (3p)

Prepared from **1a** and *N*-Boc-pyrrole **2p** (83.5 µL, 0.5 mmol, 1 equiv) on a 0.5 mmol scale according to the general procedure and obtained in an isolated yield of 74% (0.103 g, 0.37 mmol) as a clear oil.

R_f = 0.63 (hexanes/EtOAc, 1:0.2).

IR (ATR): 2976, 2933, 2828, 1707, 1585, 1327, 1156, 1027, 739 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.13 (br, 1 H), 7.00 (br, 2 H), 6.93–6.87 (m, 2 H), 5.64 (br, 1 H), 5.51 (s, 1 H), 1.37 (s, 9 H).

^{13}C{H} NMR ($CDCl_3$, 101 MHz): δ = 155.0 (br-1C), 150.9 (br-1C), 146.5, 143.5 (br-1C), 143.0 (br1-C), 141.7 (br), 126.7, 125.6, 119.5–118.9 (br)-1C, 81.0, 66.9 (br), 65.6 (br), 28.1.

Note: Broad peaks are observed for this compound due to the presence of Boc-Group rotamers, spectral data are consistent with previous reports of *N*-Boc-epiminonphthalene type compounds.

HRMS (ESI): *m*/*z* [$C_{15}H_{16}ClNO_2^{+}$+Na]$^+$ calcd: 300.0762; found: 300.0753.

7-Chloro-1,5-dimethyl-2,3,4,5-tetrahydrobenzo[*b*][1,5]diazocin-6(1*H*)-one (3q)

Prepared from **1a** and DMPU **2q** (0.187 mL, 1.5 mmol, 3 equiv) according to the general procedure on a 0.5 mmol scale with the following modifications: The reaction was performed using LiHMDS (1 M in toluene, 0.5 mL, 1 equiv) as base and toluene (2 mL) as the reaction solvent. The reaction was allowed to stir for 40 min. The product was obtained in an isolated yield of 59% (0.0704 g, 0.30 mmol) as a white solid. Spectral data are consistent with previous reports.[25]

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.08 (t, *J* = 8.2 Hz, 1 H), 6.78 (dd, *J* = 7.8, 0.7 Hz, 1 H), 6.58 (d, *J* = 8.6 Hz, 1 H), 3.64–3.56 (m, 2 H), 3.19–3.16 (m, 1 H), 3.02–3.00 (m, overlaps with singlet at 2.99 and 3.03, 1 H), 3.03 (s, 3 H), 2.99 (s, 3 H), 1.88–1.78 (m, 2 H).

$^{13}C\{H\}$ NMR ($CDCl_3$, 101 MHz): δ = 170.9, 149.1, 133.3, 129.8, 121.6, 118.7, 112.7, 48.8, 48.0, 42.2, 33.6, 26.72.

_N_-(3-Chlorophenyl)-_N_-phenylacetamide (3r)

Prepared from **1a** and acetanilide (0.1351 g, 1 mmol, 2 equiv) on a 0.5 mmol scale according to the general procedure and obtained in an isolated yield of 21% (0.0256 g, 0.105 mmol) as a brown oil. Spectral data are consistent with previous reports.[31]

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.52–7.12 (m, 9 H), 2.06 (s, 3 H).

$^{13}C\{H\}$ NMR ($CDCl_3$, 101 MHz): δ = 170.4, 129.8, 128.4, 126.4, 23.9.

1-Benzyl-4-chloro-1*H*-benzo[*d*][1,2,3]triazole (3s)

Prepared from **1a** and benzylazide **2s** (0.5 mmol, 68 µL, 1 equiv) according to the general procedure on a 0.5 mmol scale for 1 hour with the following modification: the reaction was conducted at 0 °C. The product was obtained in an isolated yield of 59% (0.0714 g, 0.295 mmol) as an off-white solid. Spectral data are consistent with previous reports.[15]

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.37–7.30 (m, 5 H), 7.28–7.23 (m, 3 H), 5.86 (s, 2 H).

$^{13}C\{H\}$ NMR ($CDCl_3$, 101 MHz): δ = 144.1, 134.3, 134.1, 129.1, 128.7, 127.9, 127.6, 125.5, 123.8, 108.5, 52.69.

6-Fluoro-1,4-dimethyl-1,2,3,4-tetrahydro-5*H*-benzo[*e*][1,4]diazepin-5-one (4a)

Prepared from **1d** and DMI **2j** (0.166 mL, 1.5 mmol, 3 equiv) on a 0.5 mmol scale according to the general procedure and obtained in an isolated yield of 43% (0.045 g, 0.215 mmol) as a white solid.

Mp 110–114 °C; R_f = 0.09 (hexanes/acetone, 1:0.2).

IR (ATR): 3063, 2995, 2883, 2820, 1641, 1607, 1457, 1172, 803 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.31–7.25 (m, 1 H), 6.72 (t, J = 8.6 Hz, 1 H), 6.66 (d, J = 8.4 Hz), 3.45 (t, J = 5.7 Hz, 2 H), 3.24 (t, J = 5.7, 2 H), 3.19 (s, 3 H), 2.80 (s, 2 H).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, 376 MHz): δ = –113.06.

$^{13}C\{H\}$ NMR ($CDCl_3$, 101 MHz): δ = 165.8, 160.9 (d, J_{C-F} = 252.1 Hz), 148.3 (d, J_{C-F} = 5.4 Hz), 131.8 (d, J_{C-F} = 10.9 Hz), 117.6 (d, J_{C-F} = 14.0 Hz), 113.3 (d, J_{C-F} = 2.9 Hz), 109.5 (d, J_{C-F} = 22.2 Hz), 57.4, 47.7, 40.3, 33.6.

HRMS (ESI): m/z $[C_{11}H_{13}FN_2O+H]^+$ calcd: 209.1085; found: 209.1088.

***tert*-Butyl 5-Fluoro-1,4-dihydro-1,4-epiminonaphthalene-9-carboxylate (4b)**

Prepared from **1d** and *N*-Boc-pyrrole **2p** (83.5 uL, 0.5 mmols, 1 equiv) on a 0.5 mmol scale according to the general procedure and obtained in an isolated yield of 37% (0.0492 g, 0.185 mmol) as a clear oil.

R_f = 0.61 (hexanes/EtOAc, 1:0.2).

IR (ATR): 3063, 2995, 2883, 2820, 1641, 1607, 1457, 1172, 803 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.07 (br d, J = 6.4 Hz, 1 H), 7.00 (br, 1 H), 6.97–6.92 (m, 1 H), 6.68 (t, J = 8.4 Hz, 1 H), 5.73 (br, 1 H), 5.51 (br, 1 H), 1.38 (s, 9 H).

$^{19}F\{^1H\}$ NMR ($CDCl_3$, 376 MHz): δ = –120.55, –121.69.

$^{13}C\{H\}$ NMR ($CDCl_3$, 101 MHz): δ = 154.8, 152.0 (d, J = 4.5 Hz), 143.5–141.8 (br), 133.0 (d, J = 20.3 Hz), 127.3 (d, J = 6.2 Hz), 117.2 (br), 113.6 (d, J = 21.7 Hz), 80.92, 66.4 (br), 63.4 (br), 28.1.

Note: Broad peaks are observed for this compound due to the presence of Boc-group rotamers, spectral data is consistent with previous reports of *N*-Boc-epiminonaphthlalene type compounds.

HRMS (ESI): m/z $[C_{15}H_{16}FNO_2+Na]^+$ calcd: 284.1063; found: 284.1052.

General Procedure for Competition Experiments to Determine A-Values

A 3 mL vial containing a magnetic stir bar was charged with arynophile **2b–s** (0.5 mmol, 5 equiv), TBME (0.5 mL) and furan **2a** (36 µL, 0.5 mmol, 5 equiv). The aryne precursor **1a–c** (0.1 mmol, 1 equiv) was weighed out in air and added to the vial. NaO^{t}Bu (0.0144 g, 0.15 mmol, 1.5 equiv) was weighed out in air and added to the vial with vigorous stirring in one portion. The vial was sealed with a cap, and the reaction mixture was allowed to stir at room temperature for 1 hour. The reaction was quenched with ammonium chloride solution (2 mL) and extracted with EtOAc (3 × 1 mL). The combined organic phases were filtered through a Pasteur pipette containing a cotton plug and $MgSO_4$, drying agent into a 20 mL scintillation vial. The solvent is then removed by rotary evaporation. $CDCl_3$ with tetramethylsilane as an internal standard (1 mL) was added to the vial, and the NMR sample was prepared. The spectral data was acquired with a Bruker Avance II 400 MHz spectrometer with a D1 relaxation time of 30 seconds. Select arynophile competition reactions were run in triplicate, and the computed A values represent an average, with standard deviation reported as ± values.

Procedure for Competition Experiments with Kobayashi Reagents

A 3 mL vial containing a magnetic stir bar was charged with **1c** (0.085 mmol, 0.02828 g), MeCN (0.41 mL), the arynophile (0.425 mmol, 5 equiv), and furan (31 µL, 0.425 mmol, 5 equiv). CsF (0.06455 g, 0.425 mmol, 5 equiv) was weighed out in air and quickly added to the vial with vigorous stirring in one portion. The vial was sealed with a cap, and the reaction mixture was allowed to stir at room temperature for 4 hours. The reaction mixture was filtered through a small plug of silica with 10 mL EtOAc as the eluent. The solvent was then removed by rotary evaporation. $CDCl_3$ with tetramethylsilane as an internal standard (1 mL) was added to the vial, and the NMR sample was prepared. The spectral data was acquired with a Bruker Avance II 400 MHz spectrometer with a D1 relaxation time of 30 seconds.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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