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Synthesis of *ortho*-Haloaminoarenes by Aryne Insertion of Nitrogen–Halide Bonds

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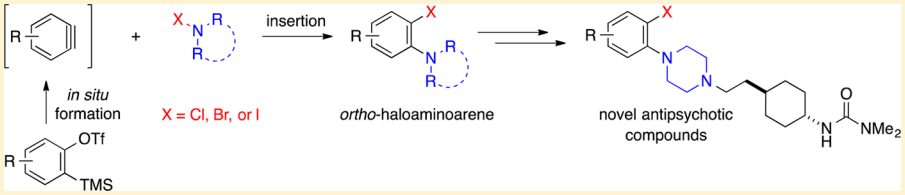
Supporting Information



ABSTRACT: A rapid and general access to *ortho*-haloaminoarenes has been developed by aryne insertion into *N*-chloramine, *N*-bromoamine, and *N*-iodoamine bonds via two complementary protocols harnessing fluoride-promoted 1,2-elimination of *ortho*-trimethylsilyl aryltriflates. Typically, electron-deficient *N*-chloramines effectively react with aryne intermediates generated at elevated temperature with CsF, while less stable *N*-haloamines are found more efficient under milder, TBAF-mediated aryne formation at room temperature. Both protocols demonstrate a good level of regioselectivity and functional group tolerance. Efforts to elucidate the mechanism of N–X insertion are also discussed. The practical value of this transformation is highlighted by rapid synthesis of novel analogues of the antipsychotic cariprazine.

INTRODUCTION

The *ortho*-haloaminoarene motif is an important pharmacophore in numerous bioactive molecules and drugs.[1] Representative examples include antipsychotics cariprazine and aripiprazole (Abilify) as well as an anti-inflammatory CXCR3 inhibitor, which all contain an *ortho*-chloro-arylpiperazine as the primary pharmacophore (Figure 1). Furthermore, *ortho*-haloaminoarenes are versatile synthetic intermediates in cross-coupling reactions, providing facile access to biologically and industrially important products.[2] Synthetic access to this class of compounds is therefore of significant interest.

Existing approaches to *ortho*-haloaminoarenes generally rely on stepwise C–N and C–X bond formation. For example, electrophilic halogenation of aminoarenes represents a straightforward strategy; however, both *ortho*- and *para*-halogenated isomers are often observed in poor regioselectivity.[3] Transition-metal catalyzed *ortho*-directed halogenations provide significant improvements in this regard, achieving excellent *ortho* selectivity with milder halide sources.[4] Despite these advances, the need for noble metals and specific directing groups limits the utility of these methods as a general synthetic strategy. Alternatively, Buchwald–Hartwig coupling reactions between *ortho*-dihaloarenes and amines can yield *ortho*-haloaminoarene products.[2b,5] However, chemoselective aminations between similarly activated aryl halides is challenging, limiting this strategy to less functionally complex arene scaffolds. The lack of an effective and general strategy remains a challenge in preparing valuable *ortho*-haloaminoarenes.

In our studies, we propose an insertion transformation between nitrogen-halide bonds (N–X) and arynes as a direct approach to this important class of *ortho*-haloaminoarene compounds (Scheme 1). This route circumvents the obstacles of previous stepwise methods through simultaneous installation of both amine and halide functionalities in an innately *ortho*-selective manner. The proposed transformation is inspired by the labile nature of N–X bonds, which could undergo an insertion reaction with highly reactive arynes without transition metals. For example, *N*-chloramines are known to cleave homolytically in the presence of acid to undergo formal intramolecular insertions across simple olefins and alkynes.[6] We expected that such an intermolecular N–X bond and aryne insertion would be general and applicable to the synthesis of a broad substrate scope of *ortho*-haloaminoarenes with a good functional group compatibility and a high level of regioselectivity, benefiting from the synthetic advantages of aryne chemistry.

Aryne intermediates have emerged as a powerful platform for the development of numerous new transformations in the past two decades.[7,8] Their reactivity is characterized by a low-lying LUMO, arising from a strained π-bond, which facilitates insertion reactions into a variety of σ-bonds for the preparation of complex *ortho*-difunctionalized arenes with predictable regioselectivity.[9] Kobayashi's work on the *ortho*-trimethylsilyl aryltriflate system,[10] has allowed for the formation of reactive aryne intermediates with mildly basic fluoride. Such mild conditions eliminate the need for strong bases or high temperatures necessary in other systems, allowing the development of aryne chemistry coupled with sensitive substrates.[11] In this study, we posited that the high reactivity of arynes could

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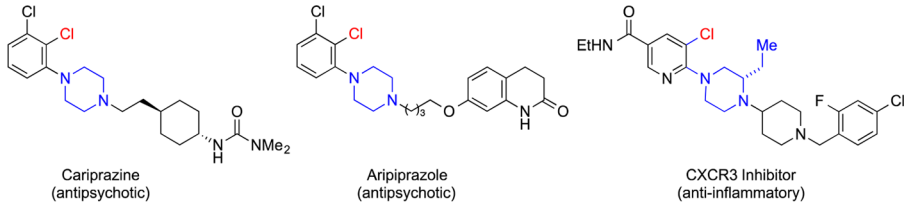
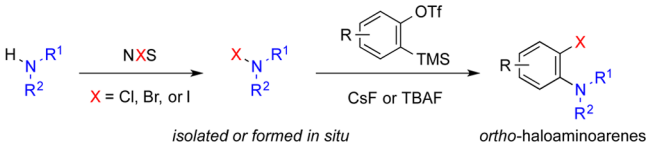


Figure 1. Representative *ortho*-haloaminoarenes in pharmaceuticals.

Scheme 1. Our Approach to *ortho*-Haloaminoarenes by Aryne Insertion of N−X Bonds



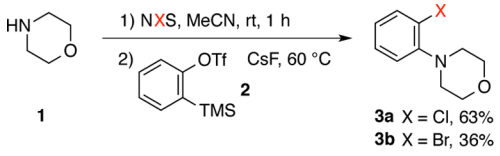
enable intermolecular amino-halogenation from labile *N*-halide bonds, yielding diverse *ortho*-haloaminoarenes under milder conditions.

In a recent communication,[12] we reported an insertion transformation between *N*-chloramines and arynes to form *ortho*-chloroaminoarenes. Preliminary results indicated that more reactive *N*-bromoamines and *N*-iodoamines were inefficient under these original conditions. Herein, we describe our continued efforts to expand this insertion strategy as a more general approach to *ortho*-haloaminoarenes, including the development of a complementary milder protocol that features improved product yields for the more reactive *N*-bromoamines and *N*-iodoamines, as well as electron-rich *N*-chloramines. Furthermore, we present extended studies to investigate the mechanism of this insertion reaction. Finally, as a brief demonstration of the utility of this method in organic synthesis and medicinal chemistry, we have also synthesized novel analogues of the antipsychotic drug cariprazine.

RESULTS AND DISCUSSION

Our studies on aryne insertion into N−X bonds began with the model substrates of morpholine **1** and benzyne precursor **2** (Scheme 2). The initial reaction optimization revealed that

Scheme 2. CsF-Promoted Benzyne Insertion of *N*-Chloro- and *N*-Bromomorpholines[a]



[a]Yields determined by ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard.

desired product **3a** formed in 63% yield upon one-pot formation of *N*-chloromorpholine, from the treatment of **1** with *N*-chlorosuccinimide, followed by exposure to **2** and CsF at 60 °C. However, these conditions were found less tolerant to analogous N−Br bond insertion, with desired *ortho*-bromoaminoarene **3b** obtained only in 36% yield.

To identify more general conditions for different *N*-halo bonds, we decided to use *N*-bromomorpholine as a standard substrate to examine additional insertion conditions (Table 1). In comparison to CsF, TBAF as the fluoride source led to the formation of **3b** in a similar 33% yield, along with protonation product **3′** in 15% yield (entries 1 and 2). When different solvents were tested, toluene and *t*-BuOH were found ineffective while THF gave a higher yield of **3′** in 27% yield, indicating a higher overall conversion of **1** to *N*-arylated product (entries 3−5). At a lower temperature (0 °C), the reaction gave a comparable yield of desired product **3b** and a reduced amount of **3′** (entry 6). Increasing the equivalence of benzyne precursor significantly improved reaction efficiency (entries 7−9). In particular, excess of **2** compared to TBAF gave markedly higher yields of **3b** and a decreased amount of byproduct **3′** (entry 8). A further increased amount of **2** could eliminate the formation of byproduct **3′**, however with no improvement for the formation of **3b** (entry 9). Finally, the use of anhydrous TBAT as the fluoride source decreased the formation of **3b** (entry 10).

With these findings, we sought to compare the efficiency of both CsF- and TBAF- mediated benzyne insertion reactions on different *N*-haloamines (Table 2). CsF-based conditions proved more effective for *N*-chloromorpholine, providing **3a** in 66% yield in comparison to 52% under TBAF-mediated conditions. Rather, more reactive *N*-bromomorpholine underwent insertion more effectively when TBAF was used, giving **3b** in 44% isolated yield compared to 29% from the CsF-mediated reaction. For highly reactive *N*-iodomorpholine, desired insertion product **3c** was formed only under TBAF-conditions, albeit in 20% yield. When an extended scope of amines was examined under both conditions, a general trend emerged from these results (Table 2), indicating more stable, electron-deficient, *N*-chloramines favored CsF-based conditions at elevated temperature while more reactive, electron-rich, substrates favored TBAF-mediated conditions at room temperature. For example, the insertion reactions between benzyne and various *N*-chloramines, including cyclic piperazines bearing an electron-withdrawing group, all successfully delivered the *ortho*-chloroaminoarene products (**4**−**9**) with comparable efficiency under CsF- and TBAF-promoted conditions. These results demonstrated good compatibility of this transformation with various functional groups such as carbamates (**4**), sulfonamides (**5**), amides (**6**−**7**), and ureas (**8**−**9**). When electronically rich cyclic amines, such as piperidine derivatives and Boc-protected diazepane were examined, significant differences were observed for the formation of desired *ortho*-chloroaminoarene products **10**−**13**, with much higher yields under TBAF-promoted reactions than the CsF-based reactions. Similar results were observed for benzyne insertions into reactive *N*-bromo- and *N*-iodoamines, in which TBAF-conditions were more effective than CsF-conditions. Although the reaction of *N*-iodoamines gave only 20% of the desired *ortho*-iodoaminoarene **17**, even under TBAF conditions, it is noteworthy that these products are inaccessible by any other method so far, to our knowledge. Note that acyclic amines were poor substrates for either TBAF or CsF conditions, with <15%

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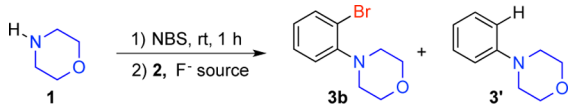
Table 1. TBAF-Mediated Benzyne Insertion into *N*-Bromomorpholine



entry	1	2	fluoride (equiv)	solvent	temp (°C)	time (h)	yield 3b[a]	yield 3′[a]
1	1	1.5	CsF (3)	MeCN	60	1	36	trace
2	1	1.5	TBAF (1.5)	MeCN	rt	1	33	15
3	1	1.5	TBAF (1.5)	toluene	rt	3	N/D	16
4	1	1.5	TBAF (1.5)	*t*-BuOH	rt	<10 min	N/D	N/D
5	1	1.5	TBAF (1.5)	THF	rt	3	36	27
6	1	1.5	TBAF (1.5)	THF	0	7	36	19
7	1.5	1	TBAF (1)	THF	rt	7	13	13
8	**1**	**2.5**	**TBAF (1.5)**	**THF**	**rt**	**24**	**52**	16
9	1	3	TBAF (1.5)	THF	rt	4	52	–
10	1	3	TBAT (1.5)	THF	rt	54	31	ND

[a]Yields determined by ^{1}H NMR spectroscopy with either CH_2Br_2 or DMF as a quantitative internal standard. TBAT = tetrabutylammonium triphenyldifluorosilicate.

desired products observed.[13] Although the insertion can be impeded by competing decomposition resulting from reactive or sterically hindered intermediates at elevated temperatures, these results prove that benzyne insertion into *N*-halo bonds is an effective strategy to rapidly access *ortho*-chloro-, *ortho*-bromo-, and *ortho*-iodoaminoarenes.

Access to more diversely substituted *ortho*-aminoarenes was next investigated with substituted aryne precursors under both CsF- and TBAF-mediated protocols (Table 3). The reactions were performed using morpholine as the model substrate with aryne precursors bearing electron-donating and electron-withdrawing functionalities at various positions. For the 3-methoxybenzyne precursor, the insertion reactions with *N*-chloro- and *N*-bromomorpholine yielded the desired *ortho*-haloaminoarenes **18** and **19** respectively under both conditions (entry 1). Notably, *ortho*-chloroaminoarene **18** was formed in a higher yield under CsF conditions than TBAF conditions while *ortho*-bromoaminoarene **19** was formed in comparable efficiency under both conditions. Similar results were observed for the insertion reaction of an asymmetric naphthylyne precursor, providing **20** and **21** with comparable efficiency in high regioselectivity (entry 2). The insertion of electron-deficient 3-chlorobenzyne gave product **22** only in low yields under either CsF or TBAF conditions, though a high regioselectivity was observed (entry 3). Distal substitutions were unable to effect regioselectivity, leading to isolation of **23** as a 1:1 mixture of isomers (entry 4). Overall, arynes bearing multiple substitutions were well tolerated, giving superb regioselectivity with both methods. A significant pattern could be observed regarding substitution effects for these substrates, as the CsF method was found to be much more effective for electron-deficient arynes (Table 3, entries 5 and 6), whereas the TBAF mediated protocol significantly favored more electron-rich arynes (entries 7 and 8). These results indicate the utility of both protocols toward accessing *ortho*-haloaminoarenes with diversely substituted aryl scaffolds.

To address the excess amount of aryne precursor used under TBAF-mediated insertion reactions, especially when these materials are not readily accessible,[10,11] we found that the isolation of the *N*-haloamines typically led to improved efficiency of aryne precursor, despite the lower overall yield of the insertion products (Scheme 3). For example, the reaction of **2** and *N*-chloromorpholine in MeCN with TBAF-effected N−Cl bond insertion in 40% yield while isolation of the intermediate *N*-bromoamine provided **3a** in 29% isolated yield. The electron-rich indolyne substrate underwent insertion of *N*-chloro-*N*′-Boc-piperazine in higher efficiency under such conditions than the CsF-mediated insertion conditions. Arynes bearing halide substituents were also tolerated, yielding **30** with excellent regioselectivity in 21% yield. Despite reduced overall yields, the synthetic utility of using isolated *N*-haloamines in the insertion reaction is substantial, especially for heteroarynes and *N*-bromoamines.

To understand the mechanism for the formation of *ortho*-chloroaminoarenes, we initially explored two possible reaction pathways: (1) a radical driven mechanism involving homolytic cleavage of the *N*-halide bond and addition to benzyne; and (2) an initial nucleophilic addition followed by electrophilic capture of the halide via a short-lived zwitterionic intermediate (Scheme 4). Previously *N*-chloramine addition across alkenes and alkynes were reported as radical mediated processes, thus an analogous radical process was suspected in this transformation.[14] When TEMPO as a radical scavenger was added to the reaction, however, no change was observed on reaction efficiency or trapping of TEMPO by an aryl radical species (Scheme 4a). An intermolecular radical cascade could be ruled out based upon these results as well as the tolerance of activated benzylic protons (e.g., **11** and **15**) in the insertion reactions. To identify whether the nitrogen or chloride of the *N*-chloramines initiated the insertion reaction, sterically hindered *N*-chloro-2,2,6,6-tetramethylpiperidine was tested with an aryne precursor; however, no reaction occurred, suggesting the dependence of the insertion on nitrogen nucleophilicity (Scheme 4b). Indeed, the regioselective outcome observed in our insertion reactions is consistent with that reported for nucleophilic additions of amines to unsymmetrical arynes,[9c−e,15] indicating that the insertion may occur in a polar pathway directed by nucleophilic addition of the nitrogen. However, it remained unclear as to the radical or polar nature of the subsequent aryl-chloride bond formation. To probe this question, an aryne precursor bearing a 3-*O*-allyl moiety was prepared as a radical trap, poised to undergo cyclization in the presence of even short-lived radicals at the 2-position. Upon exposure of this mechanism probe to *N*-chloromorpholine under TBAF-based insertion conditions in MeCN, both aminochlorination product **32** and cyclized byproduct **32**′

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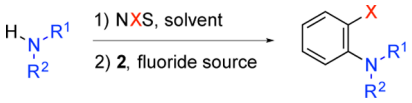
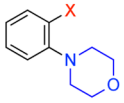
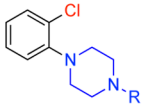
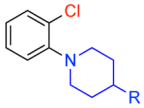
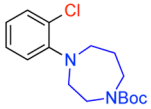
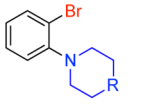
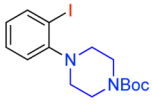
Table 2. Benzyne Insertion into Various *N*-Haloamines[a]



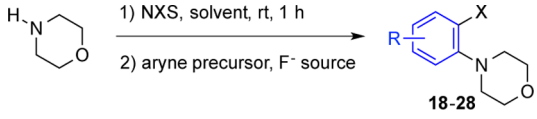
ortho-halo aminoarene product		yield (%)[a] (by CsF)	(by TBAF)
	**3a** X = Cl	66	52
	3b X = Br	29	44
	3c X = I	ND	20
	**4** R = NBoc	63	58
	5 R = NSO_2Et	66[b]	53
	6 R = N(CO)Ph	44	60
	7 R = N(CO)Cyp	53	50
	8 R= $N(CO)NEt_2$	53	53
	9 R= $N(CO)N(C_2H_4O)$	53	61
	**10** R = H	25	45
	11 R = Ph	28	60
	12 R = CO_2Et	48[c]	64
	**13**	32	47
	**14** R = NBoc	12	49
	15 R = CHPh	ND	57
	16 R = $CHCO_2Et$	ND	37
	**17**	ND	20

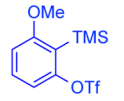
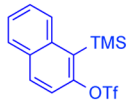
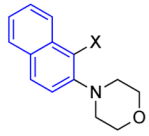
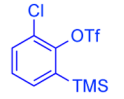
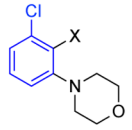
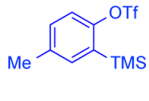
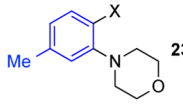
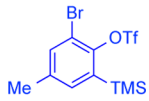
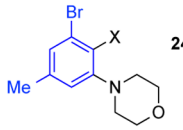
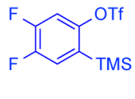
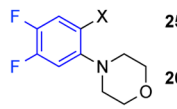
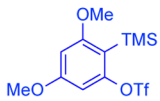
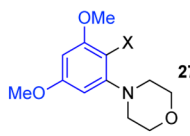
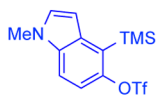
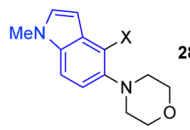
[a]Isolation yields. Reaction conditions: (step 1) amine (1.0 equiv), NXS (1.0 equiv), rt, 1 h; (step 2) CsF-conditions, **2** (1.5 equiv), CsF (3.0 equiv), 60 °C, listed as entry 1 in Table 1; TBAF-conditions, **2** (2.5 equiv), TBAF (1.5 equiv), rt, listed as entry 8 in Table 1. Results listed as products in isolation yields. ND = Not detected. [b]Average of yields from two runs. [c]90% purity.

were observed (Scheme 4c). The formation of **32′** is suggestive of some radical character at the 2-position in the insertion reaction pathway while the low efficiency of this reaction and the observed preference for C−Cl over C−C bond formation (**32** vs **32′**) prevents complete dismissal of a polar pathway.

Upon the basis of the current information, a possible mechanism is proposed (Scheme 4d): the initial nucleophilic attack of the nitrogen of the *N*-haloamine (**I**) to the electrophilic aryne would lead to the formation of activated quaternary *N*-haloamine (**II**). This intermediate (**II**) could undergo direct halogenation by the resultant *ortho*-carbanion to give the product (**V**). Alternatively, the weak *N*-halide bond can cleave homolytically, providing an aminium and halide radical (**III**), which would lead to the more stable aryl radical (**IV**) then facilitate halogenation by the previously formed halide radical to give the product (**V**).

Table 3. Aryne Scope for Insertion of *N*-Halomorpholines[j]



Entry	Aryne Precursor	Product	X	CsF	TBAF
1			**18** Cl	76%[a]	41%[b]
			19 Br	35%[a]	38%[c]
2			**20** Cl	63%	47%[d]
			21 Br	47%	50%
3			**22** Cl	22%[e]	18%[f]
4			**23** Cl	48%[g]	47%[g]
5			**24** Cl	59%	11%[h]
6			**25** Cl	54%	25%
			26 Br	37%	27%
7			**27** Cl	34%	41%
8			**28** Cl	25%[i]	39%

[a]rs = 5:1. [b]rs = 3:1. [c]rs = 12:1. [d]rs = 10:1. [e]rs = 9:1. [f]rs = 6:1. [g]rs = 1:1. [h]Yield determined by ^{1}H NMR spectroscopy. [i]rs = 8:1. [j]Reaction conditions: (step 1) amine (1 equiv), NXS (1 equiv), MeCN, rt, 1 h; (step 2) CsF- or TBAF-promoted insertion conditions (listed as entry 1 and 8 in Table 1, respectively). Isolation yields. Major isomer is shown. Regioselectivity (rs) is determined by ^{1}H NMR spectroscopy.

Given the synthetic value and operational simplicity of this facile approach to access highly substituted *ortho*-haloaminoarenes, we next prepared several novel analogues of the antipsychotic cariprazine as part of our ongoing interest in neurologically active aminoarenes (Scheme 5). Starting from commercially available *N*-Boc-piperazine, the insertion reactions in Scheme 3 led to the formation of **29** and **30** as two novel *ortho*-chloroaminoarenes. Thus, the preparation of the new cariprazine analogues **34** and **35** was readily achieved by the removal of the Boc group followed by reductive amination

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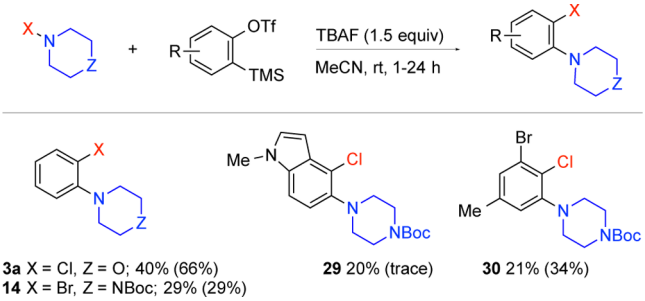
Scheme 3. Insertion of *N*-Haloamines with Aryne Precursor in Stoichiometric Amount[a]



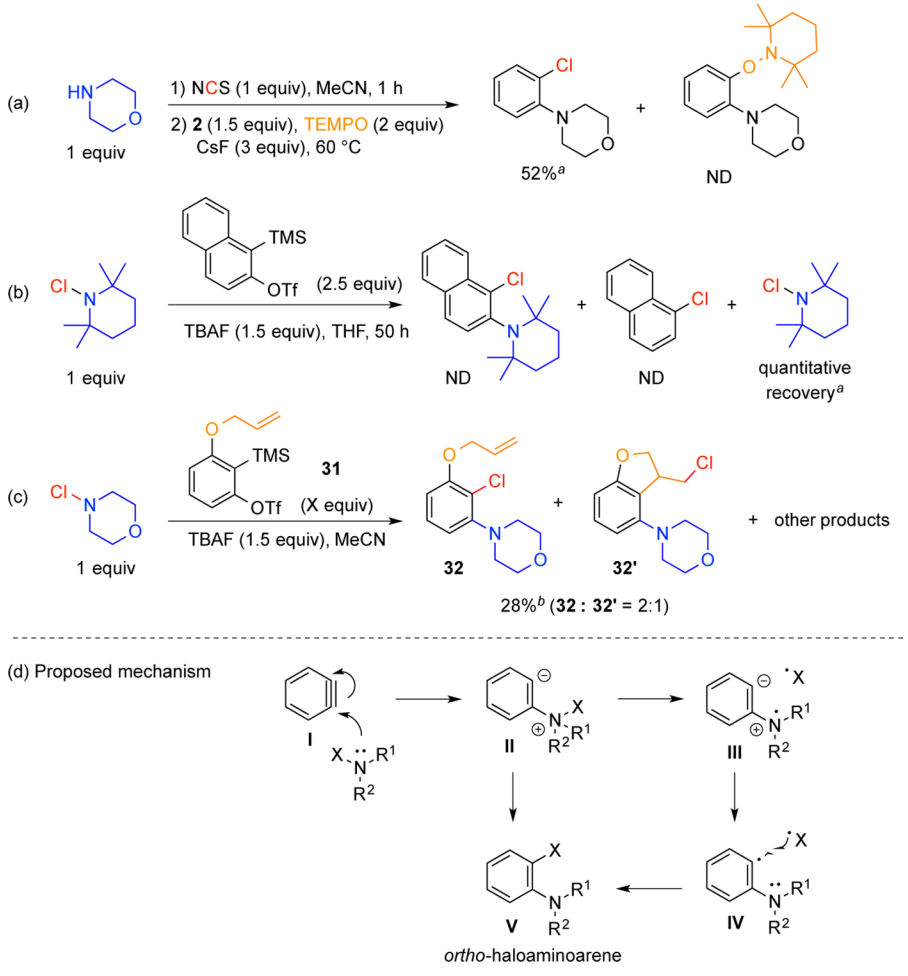
[a]Reaction conditions: *N*-chloro or *N*-bromoamine (1 equiv), aryne precursor (1 equiv), TBAF (1.5 equiv), MeCN, rt. Isolated yields shown. As a comparison, the yields indicated in the parentheses are those obtained under the CsF-based one-pot method (aryne precursor 1.5 equiv).

with **33**. Note that both **34** and **35** would be particularly difficult to access otherwise. This example demonstrated aryne insertion reaction of *N*-haloamines as a valuable method for the rapid synthesis of pharmaceutically important *ortho*-haloaminoarenes and its synthetic utility in medicinal chemistry and drug discovery. Future structure−activity relationship studies of these novel analogues will provide valuable information toward the discovery of novel antipsychotic properties.

CONCLUSION

A transition-metal-free aryne insertion of nitrogen-halide bonds has been described for the synthesis of *ortho*-haloaminoarene compounds. This formal *ortho*-haloamination of arynes can be achieved as a one-pot protocol directly starting from amines, by a facile halogenation with *N*-halosuccinimides. Insertion of the corresponding *N*-chloro, *N*-bromo, or *N*-iodoamines with aryne intermediates formed *in situ* provide the *ortho*-haloaminoarene products in moderate to good yields. Two complementary conditions have been established to effect this insertion on a broad scope of amine and aryne substrates, employing either CsF or TBAF to promote 1,2-elimination of *ortho*-trimethylsilyl aryltriflates for the *in situ* formation of arynes. Reactions with electron-deficient *N*-chloramines are more efficient under CsF-mediated aryne forming conditions, whereas more reactive *N*-chloramines, as well as *N*-bromo- and *N*-iodoamines strongly prefer mild TBAF-mediated conditions. Both CsF and TBAF protocols demonstrated good compatibility with various functional groups such as halides, carbamates, amides, ureas, and esters. Mechanism studies indicated that the reaction is initiated by the nitrogen moiety, while the presence of a short-lived aryl radical was identified as a partial contributor in the

Scheme 4. Mechanistic Studies



[a]Yields determined by ^{1}H NMR spectroscopy with CH_2Br_2 as a quantitative internal standard. [b]Isolation yield of a mixture.

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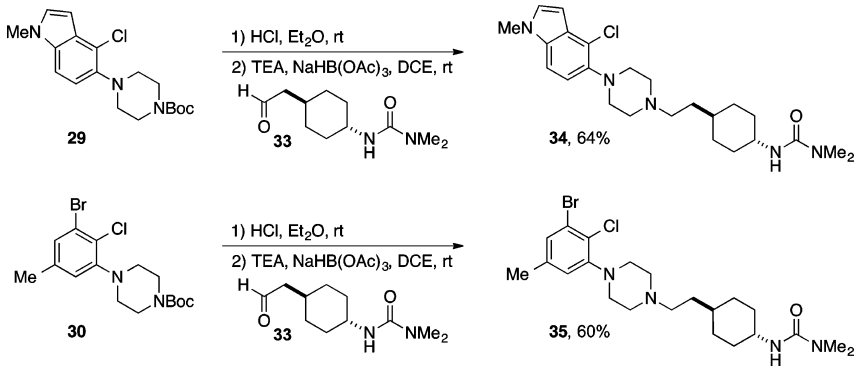
Scheme 5. Rapid Synthesis of Novel Analogues of the Antipsychotic Cariprazine



reaction mechanism by an intramolecular mechanism probe. Furthermore, the modular synthesis of novel analogues of antipsychotic cariprazine demonstrated the synthetic value and potential of this transformation in medicinal chemistry and drug discovery.

EXPERIMENTAL SECTION

General Experimental Information. Unless otherwise noted, reactions were performed without exclusion of air or moisture. All commercially available reagents and solvents were used as received unless otherwise stated. *N*-Chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS) were recrystallized from boiling water then dried under a vacuum and stored in a desiccator. *N*-Iodosuccinimide (NIS) was recrystallized from boiling 1,4-dioxane with CCl_4 then dried under a vacuum and stored in a desiccator. Analytical thin-layer chromatography (TLC) was performed using aluminum plates precoated with 0.25 mm of 230−400 mesh silica gel impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light and/or exposure to $KMnO_4$ or vanillin stain. Organic solutions were concentrated *in vacuo* using a rotary evaporator. Column chromatography was performed with silica gel (60 Å, standard grade). Nuclear magnetic resonance spectra were recorded at ambient temperature (unless otherwise stated) on 400 or 500 MHz spectrometers. All values for proton chemical shifts are reported in parts per million (δ) and are referenced to the residual protium in $CDCl_3$ (δ 7.26). All values for carbon chemical shifts are reported in parts per million (δ) and are referenced to the carbon resonances in $CDCl_3$ (δ 77.0). NMR data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad), coupling constant (Hz), and integration. Infrared spectroscopic data are reported in wavenumbers (cm^{-1}) with only select peaks shown. High-resolution mass spectra were obtained using a liquid chromatography-electrospray ionization and time-of-flight mass spectrometer.

General Procedure for CsF-Mediated *N*-Haloamination of Arynes. To a solution of the amine (0.20 mmol, 1 equiv) in MeCN (2.0 mL) in a 1-dram vial, was added *N*-halosuccinimide (0.20 mmol, 1.0 equiv). The mixture was stirred in the dark at room temperature for 1 h, after which aryne precursor (0.30 mmol, 1.5 equiv) and CsF (91 mg, 0.60 mmol, 3.0 equiv) were added. The resulting mixture was placed on a preheated 60 °C hot plate and stirred vigorously. The reaction was monitored by TLC analysis for complete consumption of *N*-chloramine (typically 1−2 h). Then the reaction mixture was filtered through a pad of Celite, and washed with dichloromethane. The filtrate was concentrated and the resulting residue was redissolved in organic solvent (dichloromethane or ethyl acetate, 15 mL) and washed with a saturated aqueous solution of Na_2CO_3 (5 mL). The aqueous layer was extracted with organic solvent of choice (dichloromethane or ethyl acetate, 10 mL × 3). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo*. The crude material was purified by flash column chromatography. Occasionally, further purification was performed by recrystallization using hot hexanes or kugelrohr distillation (as indicated).

General Procedure for TBAF-Mediated *N*-Haloamination of Arynes. To a solution of the amine (0.20 mmol, 1.0 equiv) in anhydrous THF, was added *N*-halosuccinimide (0.20 mmol, 1.0 equiv) under nitrogen. The mixture was stirred in the dark for 1 h at room temperature. Aryne precursor (0.50 mmol, 2.5 equiv) was then added followed by the dropwise addition of a solution of TBAF (1.0 M, THF, 0.30 mL, 0.30 mmol, 1.5 equiv). After stirring in the dark at room temperature for 24 h, the reaction was quenched with a saturated aqueous solution of Na_2CO_3 (5 mL) and diluted in dichloromethane (15 mL). The aqueous layer was extracted with dichloromethane (5 mL × 2). The combined organic layers were dried over Na_2SO_4 and then filtered. The filtrate was added directly onto silica gel without prior concentration, and the resulting silica mixture was purified by flash column chromatography. Occasionally, further purification was performed by recrystallization from hot hexanes or kugelrohr distillation (as indicated).

TBAF-Mediated *ortho*-Haloamination Protocol Using Isolated *N*-Haloamines (Scheme 3). To a solution of *N*-haloamine (0.40 mmol, 1.0 equiv) in anhydrous THF, was added aryne precursor (0.40 mmol, 1.0 equiv) followed by the dropwise addition of a solution of TBAF (1.0 M, THF, 0.6 mL, 0.6 mmol, 1.5 equiv). After stirring in the dark at room temperature for 24 h, the reaction was quenched with a saturated aqueous solution of Na_2CO_3 (5 mL) and diluted in dichloromethane (15 mL). The aqueous layer was extracted with dichloromethane (5 mL × 2). The combined organic layers were dried over Na_2SO_4 and then filtered. The filtrate was added directly onto silica gel without prior concentration and the resulting silica mixture was purified by flash column chromatography. Occasionally, further purification was performed by recrystallization from hot hexanes or kugelrohr distillation (as indicated).

*4-(2-Chlorophenyl)-morpholine (**3a**).* Isolation by flash column chromatography (10% ethyl acetate−hexanes). The title compound was obtained as a white solid (130.8 mg, 66%) from the CsF promoted conditions, as a clear oil (20.4 mg, 52%) from the one-pot TBAF conditions, and as a clear oil (31.8 mg, 40%) from the procedure using isolated *N*-chloramine: R_f = 0.32 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, J = 8.0, 1.2 Hz, 1H), 7.26 (ddd, J = 8.0, 1.2, 0.8 Hz, 1H), 7.05 (dd, J = 8.0, 1.6 Hz, 1H), 7.01 (ddd, J = 8.0, 1.6, 0.8 Hz, 1H), 3.90 (t, J = 4.6 Hz, 4H), 3.08 (t, J = 4.6 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 130.7, 128.7, 127.6, 123.9, 120.2, 67.1, 51.6; FTIR (thin film), cm^{-1} 2853, 1479, 1115, 1069, 761; HRMS-ESI (m/z) Calcd for ($C_{10}H_{13}ClNO$) ([M + H]$^+$) 198.0680, found 198.0681.

*4-(2-Bromophenyl)morpholine (**3b**).* Isolation by flash column chromatography (5% ethyl acetate−hexanes). The title compound was obtained as a colorless oil (14.0 mg, 29%) from the CsF promoted conditions and as a white solid (21.5 mg, 44%) from the one-pot TBAF conditions: R_f = 0.35 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.0 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 3.89 (t, J = 4.4 Hz, 4H), 3.05 (t, J = 4.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

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150.1, 133.7, 128.2, 124.4, 120.7, 119.7, 67.0, 51.9; FTIR (thin film), cm^{-1} 2817, 1473, 1225, 1110, 1038, 931, 757; HRMS-ESI (m/z) Calcd for ($C_{10}H_{13}BrNO$) ([M + H]$^+$) 242.0175, found 242.0175.

4-(2-Iodophenyl)morpholine (**3c**). Isolated by flash column chromatography (5% ethyl acetate−hexanes). The title compound was obtained as a clear oil (11.7 mg, 20%) from the one-pot TBAF conditions: R_f = 0.55 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 6.4 Hz, 1 H), 7.35−7.31 (m, 1H), 7.04 (d, J = 6.4 Hz, 1H), 6.82 (t, J = 6.4 Hz, 1H), 3.89 (s br, 4H), 2.99 (s br, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 140.1, 129.2, 125.6, 121.0, 98.1, 67.2, 52.7; FTIR (thin film), cm^{-1} 2957, 1578, 1468, 1114, 1013, 932, 760; HRMS-ESI (m/z) Calcd for ($C_{10}H_{13}INO$) ([M + H]$^+$) 290.0036, found 290.0037.

4-(2-Chlorophenyl)piperazine-1-tert-butyl-carboxylate (**4**). Isolation by flash column chromatography (15% ethyl acetate−hexanes). The title compound was obtained as a yellow solid (32.5 mg, 63%) from the CsF promoted conditions and as a yellow solid (34.6 mg, 58%) from the one-pot TBAF conditions: R_f = 0.64 (30% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 8.0, 1.6 Hz, 1H), 7.22 (ddd, J = 8.0, 7.2, 1.6 Hz, 1H), 7.01 (dd, J = 7.6, 1.6 Hz, 1H), 6.98 (ddd, J = 7.6, 7.2, 1.6 Hz, 1H), 3.59 (t, J = 4.8 Hz, 4H), 2.98 (t, J = 4.8 Hz, 4H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 154.9, 1493, 130.7, 129.1, 127.6, 124.0, 120.6, 79.7, 51.3, 44.1, 28.5; FTIR (thin film), cm^{-1} 2974, 1693, 1479, 1246, 1169, 1036, 760; HRMS-ESI (m/z) Calcd for ($C_{15}H_{22}ClN_2O_2$) ([M + H]$^+$) 297.1364, found 297.1357.

1-(2-Chlorophenyl)-4-(ethylsulfonyl)piperazine (**5**). Isolation by flash column chromatography (20% ethyl acetate−hexanes). The title compound was obtained as a white solid (31.2 mg, 54%, and 45.2 mg 78% on two individual runs) from the CsF promoted conditions and as a white solid (30.7 mg, 53%) from the one-pot TBAF conditions: R_f = 0.72 (50% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, J = 8,0, 1.6 Hz, 1H), 7.24 (ddd, J = 8.0, 7.2, 0.8, 1H), 7.03−6.99 (m, 2H), 3.48 (t, J = 4.8 Hz, 4H), 3.11 (t, J = 4.8 Hz, 4H), 3.01 (q, J = 7.6 Hz, 2H), 1.41 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.5, 130.7, 128.9, 127.7, 124.4, 120.7, 51.2, 46.1, 43.8, 7.8; FTIR (thin film), cm^{-1} 2827, 1479, 1323, 1144, 949, 748; HRMS-ESI (m/z) Calcd for ($C_{12}H_{18}ClN_2O_2S$) ([M + H]$^+$) 289.0772, found 289.0772.

(4-(2-Chlorophenyl)piperazin-1-yl)(phenyl)methanone (**6**). Isolation by flash column chromatography (20% ethyl acetate−hexanes). The title compound was obtained as a yellow solid (26.5 mg, 44%) from the CsF promoted conditions and as a yellow solid (36.1 mg, 60%) from the one-pot TBAF conditions: R_f = 0.26 (30% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (m, 5H), 7.37 (dd, J = 7.6, 1.2 Hz, 1H), 7.23 (ddd, J = 7.6, 7.2, 1.6 Hz, 1H), 7.02−6.98 (m, 2H), 3.38 (br d, 4H), 3.05 (br d, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 148.6, 135.7, 130.7, 129.7, 128.9, 128.5, 127.6, 127.1, 124.3, 120.5; ^{13}C NMR (125 MHz, $C_6D_5CD_3$, 80 °C) 51.5, 45.2; FTIR (thin film), cm^{-1} 2918, 1628, 1478, 1227, 1039, 1011, 761; HRMS-ESI (m/z) Calcd for ($C_{17}H_{18}ClN_2O$) ([M + H]$^+$) 301.1102, found 301.1105.

(4-(2-Chlorophenyl)piperazin-1-yl)(cyclopropyl)methanone (**7**). Isolation by flash column chromatography (30% ethyl acetate−hexanes). The title compound was obtained (1:1 ratio of two conformers) as a yellow oil (26.5 mg, 53%) from the CsF promoted conditions and as a clear oil (26.3 mg, 50%) from the one-pot TBAF conditions: R_f = 0.56 (50% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.36 (m, 1H), 7.23 (ddd, J = 8.8, 8.0, 1.6 Hz, 1H), 7.0 (m, 2H), 3.83 (br d, 4H), 3.04 (br d, 4H), 1.78 (tt, J = 8.0, 4.8 Hz, 1H), 1.03−1.00 (m, 2H), 0.80−0.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 148.7, 130.7, 128.9, 127.6, 124.2, 120.5, 51.7, 51.0, 45.8, 42.4, 11.0, 7.4; FTIR (thin film), cm^{-1} 2819, 1636, 1479, 1227, 1032, 760; HRMS-ESI (m/z) Calcd for ($C_{14}H_{18}ClN_2O$) ([M + H]$^+$) 265.1102, found 265.1102.

4-(2-Chlorophenyl)-N,N-diethylpiperazine-1-carboxamide (**8**). Isolation by flash column chromatography (30% ethyl acetate−hexanes). The title compound was obtained as a yellow oil (31.2 mg, 53%) from the CsF promoted conditions and as a yellow oil (31.1 mg, 53%) from the one-pot TBAF conditions: R_f = 0.30 (30% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 8.0, 1.6 Hz, 1H), 7.22 (ddd, J = 8.0, 7.6, 1.6 Hz, 1H), 7.02 (dd, J = 8.0, 1.6 Hz, 1H), 6.98 (ddd, J = 8.0, 7.6, 1.6 Hz, 1H), 3.41 (t, J = 4.8 Hz, 4H), 3.23 (q, J = 7.2 Hz, 4H), 3.04 (t, J = 4.8 Hz, 4H), 1.14 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 149.0, 130.6, 128.8, 127.6, 123.9, 120.5, 51.1, 47.2, 41.8, 13.2; FTIR (thin film), cm^{-1} 2920, 1641, 1479, 1229, 1038, 760; HRMS-ESI (m/z) Calcd for ($C_{15}H_{23}ClN_3O$) ([M + H]$^+$) 296.1524, found 296.1524.

(4-(2-Chlorophenyl)piperazin-1-yl)(morpholino)methanone (**9**). Isolation by flash column chromatography (ethyl acetate) followed by kugelrohr distillation. The title compound was obtained as a white solid (32.9 mg, 53%) from the CsF promoted conditions and as a white solid (37.4 mg, 61%) from the one-pot TBAF conditions: R_f = 0.35 (ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, J = 8.0, 1.6 Hz, 1H), 7.22 (ddd, J = 8.0, 7.2, 1.6 Hz, 1H), 7.00 (m, 2H), 3.70 (t, J = 4.8 Hz, 4H), 3.47 (t, J = 4.8 Hz, 4H), 3.30 (t, J = 4.8 Hz, 4H), 3.03 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 148.9, 130.7, 127.6, 124.1, 120.5, 66.6, 51.1 47.4, 46.9; FTIR (thin film), cm^{-1} 2850, 1639, 1410, 1226, 1113, 1026, 760; HRMS-ESI (m/z) Calcd for ($C_{15}H_{21}ClN_3O_2$) ([M + H]$^+$) 310.1317, found 310.1318.

1-(2-Chlorophenyl)piperidine (**10**). Isolation by flash column chromatography (10% dichloromethane−hexanes). The title compound was obtained as a colorless oil (9.7 mg, 25%) from the CsF promoted conditions and as a colorless oil (17.4 mg, 45%) from the one-pot TBAF conditions: R_f = 0.27 (10% dichloromethane−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J = 8.0, 1.6 Hz, 1H), 7.20 (ddd, J = 8.0, 7.6, 1.6 Hz, 1H), 7.04 (dd, J = 8.0, 1.6 Hz, 1H), 6.93 (ddd, J = 8.0, 7.6, 1.6 Hz, 1H), 2.97 (t, J = 2.8 Hz, 4H), 1.75 (quin., J = 2.8 Hz, 4H), 1.58 (quin., J = 2.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 130.5, 128.9, 127.4, 123.2, 120.4, 52.9, 26.2, 24.3; FTIR (thin film), cm^{-1} 2937, 1588, 1479, 1233, 756; HRMS-ESI (m/z) Calcd for ($C_{11}H_{15}ClN$) ([M + H]$^+$) 196.0888, found 196.0888.

1-(2-Chlorophenyl)-4-phenylpiperidine (**11**). Isolation by flash column chromatography using a gradient of (5% dichloromethane−hexanes to 5% ethyl acetate−hexanes). The title compound was obtained as a white solid (15.0 mg, 28%) from the CsF promoted conditions and as a white solid (34.2 mg, 60%) from the one-pot TBAF conditions: R_f = 0.26 (5% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.30 (m, 5H), 7.26−7.21 (m, 2H), 7.11 (d, J = 7.2 Hz, 1H), 6.98 (t, J = 7.8 Hz, 1H), 3.53 (d, J = 12.0 Hz, 2H), 2.79 (t, J = 10.8 Hz, 2H), 2.67 (tt, J = 11.8, 4.2 Hz, 1H), 2.08−1.92 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) 150.4, 146.2, 130.6, 128.9, 128.4, 127.5, 126.9, 126.2, 123.4, 120.5, 52.6, 42.5, 33.7; FTIR (thin film), cm^{-1} 2934, 1586, 1478, 1382, 758, 700; HRMS-ESI (m/z) Calcd for ($C_{17}H_{19}ClN$) ([M + H]$^+$) 272.1201, found 272.1202.

Ethyl-1-(2-chlorophenyl)piperidine-4-carboxylate (**12**). Isolation by flash column chromatography (5% hexanes−ethyl acetate). The title compound was obtained as a colorless oil (25.0 mg, 90% purity, 42%) from the CsF promoted conditions and as a colorless oil (34.5 mg, 64%) from the one-pot TBAF conditions: R_f = 0.38 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, J = 8.0, 1.2 Hz, 1H), 7.20 (ddd, J = 8.0, 7.6, 1.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.37 (d, J = 11.6 Hz, 2H), 2.71 (td, J = 11.6, 2.8 Hz, 2H), 2.44 (tt, J = 10.4, 4.6 Hz, 1H), 2.01−1.96 (m, 4H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 149.8, 130.5, 129.0, 127.4, 123.5, 120.5, 115.7, 60.4, 51.2, 40.9, 28.5, 14.2; FTIR (thin film), cm^{-1} 2953, 1730, 1588, 1480, 1310, 1169, 1041, 757; HRMS-ESI (m/z) Calcd for ($C_{14}H_{19}ClNO_2$) ([M + H]$^+$) 268.1099, found 268.1098.

4-(2-Chlorophenyl)-1,4-diazepane-1-tert-butyl-carboxylate (**13**). Isolation by flash column chromatography (5% ethyl acetate−hexanes). The title compound was obtained as a colorless oil (20.2 mg, 32%) from the CsF promoted conditions and as a colorless oil (28.9 mg, 47%) from the one-pot TBAF conditions: R_f = 0.52 (20% ethyl acetate−hexanes); ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ 7.34 (d, J = 7.5 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 7.5 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 3.61 (s br, 4H), 3.22−3.17 (m, 4H), 2.03−2.01 (m, 2H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 50 °C) As a mixture of conformers δ 155.5, 151.1, 130.6, 129.1, 127.4, 123.4, 122.2, 79.4, 55.5, 54.6, 54.4, 48.3, 48.0, 46.2, 45.3, 28.6; FTIR (thin film),

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cm^{-1} 2972, 1690, 1480, 1157, 1088, 753; HRMS-ESI (m/z) Calcd for ($C_{16}H_{24}ClN_2O_2$) ([M + H]$^+$) 311.1521, found 311.1526.

*4-(2-Bromophenyl)piperazine-1-tert-butyl-carboxylate (**14**).* Isolated by flash column chromatography (5% ethyl acetate−hexanes). The title compound was obtained as a colorless oil (8.5 mg, 12%) from the CsF promoted conditions, as a colorless oil (33.2 mg, 49%) from the one-pot TBAF conditions, and as a colorless oil (20.4 mg, 29%) from the isolated *N*-bromoamine procedure: R_f = 0.65 (30% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.93 (t, J = 8.0 Hz, 1H), 3.60 (t, J = 4.6 Hz, 4H), 2.97 (t, J = 4.6 Hz, 4H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 154.9, 150.4, 133.8, 128.3, 124.6, 121.0, 120.0, 79.8, 51.6, 28.4; FTIR (thin film), cm^{-1} 2923, 1689, 1585, 1474, 1163, 757; HRMS-ESI (m/z) Calcd for ($C_{15}H_{22}BrN_2O_2$) ([M + H]$^+$) 341.0859, found 341.0860.

*1-(2-bromophenyl)-4-phenylpiperidine (**15**).* Isolated by flash column chromatography using a gradient of (5% dichloromethane−hexanes to 5% ethyl acetate−hexanes). The title compound was obtained as an orange solid (36.2 mg, 57%) from the one-pot TBAF conditions: R_f = 0.26 (5% ethyl acetate−hexanes) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 1H), 7.35−7.20 (m, 6H), 7.09 (d, J = 8.0 Hz, 1H), 3.49 (d, J = 11.6 Hz, 2H), 2.69 (td, J = 11.6, 2.4 Hz, 2H), 2.65 (tt, J = 8.0, 4.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 151.4, 146.2, 133.7, 128.4, 128.1, 126.9, 126.2, 124.0, 121.0, 120.1, 53.0, 42.5, 33.7; FTIR (thin film), cm^{-1} 2933, 1586, 1474, 1382, 759, 699; HRMS-ESI (m/z) Calcd for ($C_{17}H_{19}BrN$) ([M + H]$^+$) 316.0695, found 316.0695.

*Ethyl-1-(2-bromophenyl)piperidine-4-carboxylate (**16**).* Isolated by flash column chromatography (5% ethyl acetate−hexanes). The title compound was obtained as a colorless oil (23.0 mg, 37%) from the one-pot TBAF conditions: R_f = 0.38 (10% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 8.0, 1.6 Hz, 1H), 7.25 (ddd, J = 8.0, 7.2, 1.6 Hz, 1H), 7.03 (dd, J = 8.0, 1.6 Hz, 1H) 6.89 (ddd, J = 8.0, 7.2, 1.6 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.35 (d, J = 12.0 Hz, 2H), 2.70 (td, J = 12.0, 3.6 Hz, 2H), 2.43 (tt, J = 10.4, 4.8 Hz, 1H), 2.05−1.92 (m, 4H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 151.2, 133.7, 128.1, 124.2, 121.0, 120.1, 60.4, 51.7, 40.9, 28.5, 14.2; FTIR (thin film), cm^{-1} 2952, 1726, 1586, 1474, 1166, 1043, 756; HRMS-ESI (m/z) Calcd for ($C_{14}H_{19}BrNO_2$) ([M + H]$^+$) 312.0594, found 312.0593.

*4-(2-Iodophenyl)piperazine-1-tert-butyl-carboxylate (**17**).* Isolated by flash column chromatography (5% ethyl acetate−hexanes). The title compound was obtained as a clear oil (15.8 mg, 20%) from the one-pot TBAF conditions: R_f = 0.55 (20% ethyl acetate−hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, J = 8.0, 1.5 Hz, 1H), 7.34−7.30 (m, 1H), 7.01 (d, J = 7.5 Hz, 1H), 6.82 (td, J = 7.5, 1.5 Hz, 1H), 3.63 (s br, 4H), 2.93 (s br, 4H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) 155.0, 153.4, 140.2, 129.2, 125.7, 121.2, 98.5, 79.7, 52.4, 44.3, 28.5; FTIR (thin film), cm^{-1} 2924, 1696, 1469, 1417, 1245, 1170; HRMS-ESI (m/z) Calcd for ($C_{15}H_{22}IN_2O_2$) ([M + H]$^+$) 389.0720, found 389.0727.

*4-(2-Chloro-6-methoxyphenyl)morpholine (**18**) and 4-(2-Chloro-3-methoxyphenyl)-morpholine (**18′**).* Isolation by flash column chromatography (10% ethyl acetate−hexanes). The title compound was obtained as a white solid (34.9 mg, 76%, a 5:1 mixture) from the CsF promoted conditions and as a white solid (18.8 mg, 41%, a 3:1 mixture) from the one-pot TBAF conditions: R_f = 0.44 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.6 Hz, 1H, **18**) 7.19 (t, J = 8.2 Hz, 1H, **18′**), 6.71−6.68 (m, 2H, **18**), 6.58 (d, J = 2.8 Hz, 1H, **18′**), 6.53 (dd, J = 8.6, 2.8 Hz, 1H, **18**), 3.89 (s, 3H, **18′**), 3.88 (t, J = 4.8 Hz, 4H, **18** and **18′**), 3.78 (s, 3H, **18**), 3.05 (t, J = 4.8, 4H, **18** and **18′**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 150.5, 130.9, 127.3, 117.0, 112.5, 108.1, 107.2, 106.9, 67.2, 67.1, 56.3, 55.5, 51.8, 51.6; FTIR (thin film), cm^{-1} 2852, 1472, 1270, 1115, 1093, 1044, 777; HRMS-ESI (m/z) Calcd for ($C_{11}H_{14}ClNO_2$) ([M + H]$^+$) 228.0786, found 228.0785.

*4-(2-Bromo-3-methoxyphenyl)morpholine (**19**) and 4-(2-Bromo-6-methoxyphenyl)-morpholine (**19′**).* Isolated by flash column chromatography (5% ethyl acetate−hexanes). The title compound was obtained as a colorless oil (19.3 mg, 35%, a 5:1 mixture) from the CsF promoted conditions and as a colorless oil (21.0 mg, 38%, a 12:1 mixture): R_f = 0.44 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44, (d, J = 8.6 Hz, 1H, **19′**), 7.24 (t, J = 8.0 Hz, 1H, **19**), 6.71 (d, J = 8.0 Hz, 1H, **19**), 6.62 (d, J = 8.0 Hz, 1H, **19**), 6.61 (d, J = 2.6 Hz, 1H, **19′**), 6.50 (dd, J = 8.6, 2.6 Hz, 1H, **19′**), 3.89 (s, 3H, **19**), 3.88 (t, J = 4.4 Hz, 4H, **19** and **19′**), 3.78 (s, 3H, **19′**), 3.05 (t, J = 4.4 Hz, 4H, **19** and **19′**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 157.1, 151.9, 151.2, 134.0 (2C), 128.3, 113.2, 110.1, 109.1, 109.0, 107.8, 107.2, 67.2, 56.4, 55.5, 52.2, 52.0; FTIR (thin film), cm^{-1} 2852, 1469, 1267, 1114, 1091, 1045, 776; HRMS-ESI (m/z) Calcd for ($C_{11}H_{15}BrNO_2$) ([M + H]$^+$) 272.0281, found 272.0285.

*4-(1-Chloronaphthalen-2-yl)morpholine (**20**).* Isolation by flash column chromatography (10% ethyl acetate−hexanes). The title compound was obtained as a white solid (31.0 mg, 63%) from the CsF promoted conditions and as a white solid (23.2 mg, 47%, a 10:1 mixture) from the one-pot TBAF conditions: R_f = 0.42 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.58−7.54 (m, 1H), 7.46−7.42 (m, 1H), 7.34 (d, J = 8.8 Hz, 1H), 3.95 (t, J = 4.4 Hz, 4H), 3.18 (t, J = 4.4 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.2, 132.0, 131.0, 127.9, 127.7, 127.2, 125.0, 124.2, 124.0, 119.5, 67.3, 51.8; FTIR (thin film), cm^{-1} 2852, 1503, 1367, 1114; HRMS-ESI (m/z) Calcd for ($C_{14}H_{15}ClNO$) ([M + H]$^+$) 248.0836, found 248.0837.

*4-(1-Bromonaphthalen-2-yl)morpholine (**21**).* Isolation by flash column chromatography (5% ethyl acetate−hexanes). The title compound was obtained as a pink solid (27.3 mg, 47%) from the CsF promoted conditions and as a pink solid (29.3 mg, 50%) from the one-pot TBAF conditions: R_f = 0.42 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (d, J = 8.0 Hz, 1H), 7.80 (t, J = 8.0 Hz, 2H), 7.56 (ddd, J = 8.0, 6.8, 1.2 Hz, 1H), 7.46−7.42 (m, 1H), 7.35 (d, J = 8.8 Hz, 1H), 3.95 (t, J = 4.4 Hz, 4H), 3.16 (t, J = 4.4 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0, 133.3, 131.5, 128.7, 127.9, 127.5, 127.0, 125.2, 120.1, 118.6, 67.3, 52.3; FTIR (thin film), cm^{-1} 2851, 1499, 1252, 1114, 987, 810, 749; HRMS-ESI (m/z) Calcd for ($C_{14}H_{15}BrNO$) ([M + H]$^+$) 292.0332, found 292.0340.

*4-(2,3-Dichlorophenyl)morpholine (**22**) and 4-(2,6-Dichlorophenyl)morpholine (**22′**).* Isolation by flash column chromatography (10% ethyl acetate−hexanes). The title compound was obtained as a colorless oil (10.3 mg, 22%, a 9:1 mixture) from the CsF promoted conditions and as a colorless oil (8.4 mg, 18%, a 6:1 mixture) from the one-pot TBAF conditions: R_f = 0.36 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.14 (m, 2H, **22** and **22′**), 6.95 (dd, J = 7.0, 2.6 Hz, 1H, **22**), 3.88 (t, J = 4.8 Hz, 4H, **22** and **22′**), 3.16 (t, J = 4.8 Hz, 4H, **22′**), 3.04 (t, J = 4.8 Hz, 4H, **22**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 134.1, 127.5, 124.8, 118.5, 67.1, 66.6, 51.7, 49.0; FTIR (thin film), cm^{-1} 2854, 1578, 1446, 1237, 1117, 956, 779; HRMS-ESI (m/z) Calcd for ($C_{10}H_{12}Cl_2NO$) ([M + H]$^+$) 232.0290, found 232.0292.

*4-(2-Chloro-5-methylphenyl)morpholine (**23**) and 4-(2-Chloro-4-methylphenyl)morpholine (**23′**).* Isolation by flash column chromatography (10% ethyl acetate−hexanes). The title compound was obtained as a colorless oil (20.3 mg, 48%, a 1:1 mixture) from the CsF promoted conditions and as a colorless oil (19.8 mg, 47%, a 1:1 mixture) from the one-pot TBAF conditions: R_f = 0.53 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.0 Hz, 1H, **23**), 7.20 (d, J = 1.6 Hz, 1H, **23′**), 7.03 (dd, J = 8.0, 1.6 Hz, 1H, **23′**), 6.93 (d, J = 8.4 Hz, 1H, **23**), 6.84 (s, 1H, **23**), 6.80 (d, J = 8.0 Hz, 1H, **23′**), 3.87−3.86 (m, 8H, **23** + **23′**), 3.04 (t, J = 4.4 Hz, 4H, **23′**), 3.02 (t, J = 4.8 Hz, 4H, **23**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 146.5, 137.6, 131.1, 128.2, 124.6, 121.0, 120.0, 67.2, 51.8, 51.7, 21.1, 20.4; FTIR (thin film), cm^{-1} 2852, 1496, 1135, 1115, 1039; HRMS-ESI (m/z) Calcd for ($C_{11}H_{15}ClNO$) ([M + H]$^+$) 212.0837, found 212.0836.

*4-(3-Bromo-2-chloro-5-methylphenyl)morpholine (**24**).* solated by flash column chromatography (10% ethyl acetate−hexanes). The title compound was obtained as a white solid (34.5 mg, 59%) from the CsF promoted conditions: R_f = 0.35 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 1.2 Hz, 1H), 6.78 (d, J = 1.2 Hz, 1H), 3.87 (t, J = 4.6 Hz, 4H), 3.02 (t, J = 4.6 Hz, 4H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 138.2, 128.6, 126.2,

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123.9, 120.1, 67.1, 51.8, 20.9; FTIR (thin film), cm^{-1} 2852, 1441, 1250, 1113, 883; HRMS-ESI (m/z) Calcd for ($C_{11}H_{14}BrClNO$) ([M + H]$^+$) 289.9942, found 289.9937.

*4-(2-Chloro-4,5-difluorophenyl)morpholine (**25**).* Isolation by flash column chromatography (10% ethyl acetate−hexanes). The title compound was obtained as a pale yellow solid (25.0 mg, 54%) from the CsF promoted conditions and as a white solid (11.7 mg, 25%) from the one-pot TBAF conditions: R_f = 0.54 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (dd, J = 9.8, 8.0 Hz, 1H), 7.87 (dd, J = 11.8, 8.0 Hz, 1H), 3.86 (t, J = 4.4 Hz, 4H), 3.98 (t, J = 4.4 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.2 (dd, J_{C-F} = 250, 12.5 Hz), 145.9 (dd, J = 250, 12.5 Hz), 145.8, 123.4 (d, J = 12.5 Hz), 119.2 (d, J = 12.5 Hz), 109.3 (d, J = 12.5 Hz), 66.9, 51.7; FTIR (thin film), cm^{-1} 2856, 1494, 1200, 1165, 1115, 799; HRMS-ESI (m/z) Calcd for ($C_{10}H_{11}ClF_2NO$) ([M + H]$^+$) 234.0492, found 234.0491.

*4-(2-Bromo-4,5-difluorophenyl)morpholine (**26**).* Isolated by flash column chromatography (5% ethyl acetate−hexanes). The title compound was obtained as a white solid (21.1 mg, 37%) from the CsF promoted conditions and as a white solid (15.3 mg, 27%) from the one-pot TBAF conditions: R_f = 0.54 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 9.6, 8.4 Hz, 1H), 6.89 (dd, J = 11.8, 7.4 Hz, 1H), 3.87 (t, J = 4.4 Hz, 4H), 2.97 (t, J = 4.4 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.7 (dd, J_{C-F} = 250, 12.5 Hz), 147.2, 146.2 (dd, J_{C-F} = 250, 12.5 Hz), 122.1 (d, J_{C-F} =12.5 Hz), 113.1, 109.8 (d, J_{C-F} = 12.5 Hz), 67.0, 52.1; FTIR (thin film), cm^{-1} 2855, 1493, 1199, 1115, 896; HRMS-ESI (m/z) Calcd for ($C_{10}H_{11}BrF_2NO$) ([M + H]$^+$) 277.9987, found 277.9992.

*4-(2-Chloro-3,5-dimethoxyphenyl)morpholine (**27**).* Isolation by flash column chromatography (10% ethyl acetate−hexanes). The title compound was obtained as a white solid (17.4 mg, 34%) from the CsF promoted conditions and as a white solid (21.2 mg, 41%) from the one-pot TBAF conditions: R_f = 0.32 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (d, J = 2.6 Hz, 1H), 6.25 (d, J = 2.6 Hz, 1H), 3.88−3.86 (m, 7H), 3.81 (s, 3H), 4.04 (t, J = 4.4 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 156.7, 150.8, 108.7, 98.1, 94.1, 67.1, 56.2, 55.4, 51.7; FTIR (thin film), cm^{-1} 2957, 1455, 1202, 1113, 1043; HRMS-ESI (m/z) Calcd for ($C_{12}H_{17}ClNO_3$) ([M + H]$^+$) 258.0899, found 258.0886.

*4-(4-Chloro-1-methyl-1H-indol-5-yl)morpholine (**28**) and 4-(5-Chloro-1-methyl-1H-indol-4-yl)morpholine (**28′**).* Isolation by flash column chromatography (5% ethyl acetate−hexanes). The title compound was obtained as a white solid (25.3 mg, 25%, an 8:1 mixture) from the CsF promoted conditions and as a white solid (19.6 mg, 39%) from the one-pot TBAF conditions: R_f = 0.36 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (dd, J = 8.8, 0.4 Hz, 1H, **28**), 7.15 (d, J = 7.6 Hz, 1H, **28′**), 7.07 (d, J = 2.8 Hz, 1H, **28**), 7.05 (d, J = 8.8 Hz, 1H, **28**), 7.01 (d, J = 3.2 Hz, 1H, **28′**), 6.60 (d, J = 7.6 Hz, 1H, **28′**), 6.56 (dd, J = 2.8, 0.4 Hz, 1H, **28**), 6.46 (dd, J = 3.2, 0.4 Hz, 1H, **28′**, 3.95 (t, J = 4.8 Hz, 4H, **28′**), 3.92 (t, J = 4.6 Hz, 4H, **28**), 3.78 (s, 3H, **28′**), 3.77 (s, 3H, **28**), 3.24 (t, J = 4.8 Hz, 4H, **28′**, 3.06 (t, J = 4.6 Hz, 4H, **28**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3 (2C), 134.2 (2C), 129.9, 128.6, 127.3, 122.2, 120.5 (2C), 114.9, 108.0 (2C), 106.1, 104.3, 99.8, 67.5 (2C), 52.6 (2C), 51.9 (2C), 33.1 (2C); FTIR (thin film), cm^{-1} 2852, 1478, 1253, 1252, 1114; HRMS-ESI (m/z) Calcd for ($C_{13}H_{16}ClN_2O$) ([M + H]$^+$) 251.0946, found 251.0946.

*4-(3-Bromo-2-chloro-5-methylphenyl)piperazine-1-tert-butylcarboxylate (**29**).* Isolation by flash column chromatography (5% ethyl acetate−hexanes) followed by kugelrohr distillation. The title compound was obtained as a waxy white solid (66.5 mg, 34%) from the CsF promoted conditions and as a colorless oil (33.9 mg, 21%) from the isolated *N*-chloramine protocol: R_f = 0.60 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 6.75 (s, 1H), 3.58 (t, J = 4.4 Hz, 4H), 2.95 (t, J = 4.4 Hz, 4H), ^{13}C NMR (100 MHz, $CDCl_3$, one carbon did not resolve) δ 154.7, 150.4, 138.1, 128.6, 126.2, 123.7, 120.3, 79.7, 51.3, 28.4, 20.8; FTIR (thin film), cm^{-1} 2974, 1686, 1478, 1418, 1233, 1121; HRMS-ESI (m/z) Calcd for ($C_{16}H_{23}BrClN_2O_2$) ([M + H]$^+$) 389.0626, found 389.0626.

*4-(4-Chloro-1-methyl-1H-indol-5-yl)piperazine-1-tert-butyl-carboxylate (**30**).* Isolation by flash column chromatography (5% ethyl acetate−hexanes) followed by recrystallization from hot hexanes. The title compound was obtained as a yellow solid (87.2 mg, 20%) from the isolated *N*-chloramine protocol: R_f = 0.63 (50% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 8.8 Hz, 1H), 7.06 (d, J = 3.2 Hz, 1H), 7.01 (d J = 8.8 Hz, 1H), 6.56 (d, J = 3.2 Hz, 1H), 3.77 (s, 3H), 3.63 (t, J = 4.4 Hz, 4H), 2.99 (t, J = 4.4 Hz, 4H). 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 154.9, 141.4, 134.4, 129.8, 128.6, 120.7, 115.2, 107.9, 99.9, 79.4, 52.2, 44.4, 32.8, 28.5; FTIR (thin film), cm^{-1} 2974, 1686, 1478, 1418, 1233, 1121; HRMS-ESI (m/z) Calcd for ($C_{18}H_{25}ClN_3O_2$) ([M + H]$^+$) 350.1630, found 350.1631.

Synthesis of Aryne Precursors. Known aryne precursors were synthesized as previously described.[16]

*3-(Allyloxy)-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (**31**).* To a vigorously stirring solution of 1-allyloxy-2-bromoresorcinol[17] (1.14 g, 5.00 mmol, 1.0 equiv) in THF (10 mL), was added dropwise HMDS (0.806 g, 5.00 mmol, 1.0 equiv) under nitrogen. The reaction mixture was heated to reflux for 4 h until gas evolution had fully ceased. Upon cooling down to room temperature, the reaction mixture was concentrated to remove remaining HMDS and ammonia. Without further purification, the crude material was dissolved in THF (35 mL), cooled down to −94 °C, and added dropwise *n*-BuLi (2.2 mL, 2.5 M, 5.50 mmol, 1.1 equiv) over 10 min at −94 °C. The reaction was allowed to slowly warm to −78 °C over 40 min, cooled back down to −94 °C and next added dropwise Tf_2O (1.69 g, 6.00 mmol, 1.2 equiv) over 10 min. Upon the complete addition, the reaction was again allowed to warm to −78 °C over 40 min. Then the reaction mixture was quenched with the slow addition of a mixture of saturated aqueous solution of $NaHCO_3$ and H_2O (5 mL, 1:1) at −78 °C, and upon further warmed up to room temperature, followed by another addition of saturated aqueous solution of $NaHCO_3$ and H_2O (20 mL, 1:1) and Et_2O (70 mL). The aqueous layer was extracted with Et_2O (50 mL × 3). The combined organic layers were dried over $MgSO_4$, and filtered. The filtrate was concentrated. The resulting residue was purified by flash column chromatography (10% dichloromethane−hexanes) to yield **31** as a clear oil (1.10 g, 62% yield): R_f = 0.58 (5% ethyl acetate−hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, J = 8.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 6.04 (ddt, J = 17.5, 10.5, 5.5 Hz, 1H), 5.41 (ddd, J = 17.5, 3.0, 1.5 Hz, 1H), 5.31 (ddd, J = 10.5, 3.0, 1.0 Hz, 1H), 4.56 (ddd, J = 5.5, 1.5, 1.0 Hz, 2H), 0.38 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 154.7, 132.5, 131.6, 121.0, 118.8 (q, J_{C-F} = 318 Hz), 118.1, 112.9, 110.5, 69.5, 0.8; FTIR (thin film), cm^{-1} 2956, 1595, 1418, 1204, 1138, 833; HRMS-ESI (m/z) Calcd for ($C_{13}H_{16}F_3O_4SSi$) ([M − H]$^-$) 353.0496, found 353.0496.

*4-(3-(Allyloxy)-2-chlorophenyl)morpholine (**32**) and 4-(3-(Chloromethyl)-2,3-dihydrobenzofuran-4-yl)morpholine (**32′**).* Synthesized from *N*-chloromorpholine (36.4 mg, 0.300 mmol) based on the TBAF method. Isolated by column chromatography (5% ethyl acetate−hexanes) to give **32** and **32′** (a 2:1 mixture) as a colorless oil (21.4 mg, 28%): R_f = 0.59 (20% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, J = 8.0 Hz, 1H, **32**), 7.14 (t, J = 8.0 Hz, 1H, **32′**), 6.70 (dd, J = 8.0, 1.2 Hz, 1H, **32**), 6.67 (dd, J = 8.0, 1.2 Hz, 1H, **32**), 6.55 (d, J = 8.0 Hz, 1H, **32′**), 6.52 (d, J = 8.0 Hz, 1H, **32′**), 6.06 (ddt, J = 17.2, 10.4, 5.2 Hz, 1H, **32**), 5.46 (ddd, J = 17.2, 2.8, 1.6, 1H, **32**), 5.30 (ddd, J = 10.4, 2.8, 1.6 Hz, 1H, **32**), 4.64−4.53 (m, **32** 2H, **32′** 4H), 4.18 (dd, J = 10.8, 3.2 Hz, 1H, **32′**), 3.88 (t, J = 4.8 Hz, 4H, **32**), 3.86−3.78 (m, 1H, **32′**), 3.50 (t, J = 10.8 Hz, 1H, **32′**), 3.18 (ddd, J = 12.0, 6.0, 3.2 Hz, 4H, **32′**), 3.05 (t, J = 4.8 Hz, 4H), 2.86 (ddd, J = 9.2, 6.4, 2.8 Hz, 2H, **32′**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 155.6, 150.9, 150.5, 133.1, 130.7, 127.4, 118.5, 118.0, 112.9, 110.6, 109.0, 108.9, 105.7, 74.8, 70.1, 67.5 (2C), 45.6, 44.9; FTIR (thin film), cm^{-1} 2853, 1589, 1470, 1448, 1269, 1233, 1115; HRMS-ESI (m/z) Calcd for ($C_{13}H_{17}ClNO_2$) ([M + H]$^+$) 254.0942, found 254.0942.

Synthesis of Cariprazine Analogues. *1,1-Dimethyl-3-((trans)-4-(2-oxoethyl)cyclohexyl)urea (**33**).* To an oven-dried round bottomed flask was added ethyl 2-(*trans*-4-aminocyclohexyl)acetate hydrochloride[18] (0.500 g, 2.26 mmol, 1.0 equiv), dichloromethane (12 mL) and triethylamine (0.46 g, 4.51 mmol, 2.0 equiv) under nitrogen. After the reaction mixture turned into a solution, dimethylcarbamoyl

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chloride was added slowly (0.49 g, 4.51 mmol, 2.0 equiv). The mixture was stirred at room temperature for 24 h and then quenched with a 5% NH_4OH aqueous solution (25 mL) followed by the addition of dichloromethane (25 mL). The aqueous layer was extracted with dichloromethane (25 mL × 3). The combined organic layers were washed with an aqueous HCl solution (0.5 M, 25 mL × 4) followed by brine (30 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*, providing pure ethyl 2-((*trans*)-4-(3,3-dimethylureido)cyclohexyl)-acetate as a white solid (0.554 g, 96%): R_f = 0.23 (100% ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (q, J = 7.2 Hz, 2H), 3.61−3.52 (m, 1H), 2.87 (s, 6H), 2.18 (d, J = 6.8 Hz, 2H), 2.03−1.97 (m, 2H), 1.78−1.63 (m, 4H), 1.24 (t, J = 7.2 Hz, 3H), 1.11 (t, J = 10.0 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 157.6, 59.8, 49.2, 41.2, 35.8, 33.9, 33.3, 31.5, 14.0; FTIR (thin film), cm^{-1} 3312, 2917, 1730, 1624, 1531, 1032; HRMS-ESI (m/z) Calcd for ($C_{13}H_{25}N_2O_3$) ([M + H]$^+$) 257.1860, found 257.1862. An anhydrous solution of ethyl 2-((*trans*)-4-(3,3-dimethylureido)cyclohexyl)acetate (0.500 g, 1.95 mmol, 1.0 equiv) in toluene (20 mL) was sparged with nitrogen at room temperature for 15 min and cooled down to −78 °C followed by dropwise addition of a solution of DIBAL (1.0 M in hexanes, 3.9 mL, 3.90 mmol, 2.0 equiv) over 10 min under nitrogen. The reaction mixture was stirred at −78 °C for 3 h and was quenched by slow addition of toluene/MeOH (15 mL, 2:1 ratio). The mixture was warmed to room temperature followed by the addition of Na_2SO_4 (2.00 g). The resulting slurry was allowed to stir at room temperature overnight. The solids were removed by filtration and the resulting filtrate was concentrated *in vacuo*. The yellow solid residue was purified by column chromatography (100% ethyl acetate) to yield **33** as a white waxy solid (0.159 g, 39%): R_f = 0.23 (100% ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (t, J = 2.0 Hz, 1H), 4.22−4.07 (m, 1H), 3.64−3.50 (m, 1H), 2.67 (s, 6H), 2.32 (dd, J = 6.4, 2.0 Hz, 2H), 2.07−1.96 (m, 2H), 1.15−1.10 (m, 3H), 1.18−1.07 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 157.7, 50.7, 49.3, 36.1, 33.6, 31.8 (2C); FTIR (thin film), cm^{-1} 3319, 2927, 1725, 1628, 1541, 1222; HRMS-ESI (m/z) Calcd for ($C_{11}H_{21}N_2O_2$) ([M + H]$^+$) 213.1598, found 213.1598.

General Procedure for the Synthesis of Cariprazine Analogues by Boc-Deprotection and Reductive Amination.[19] To a 1-dram reaction vial containing the Boc-protected starting material (1.0 equiv) was added a solution of HCl in Et_2O (2.0 M, 20 equiv). The mixture was stirred vigorously for 24 h, yielding a white suspension. Product was collected by vacuum filtration, rinsed with copious Et_2O followed by hexanes, then washed into a separate flask using copious amounts of methanol. Solvent was removed under reduced pressure and the resulting aryl-piperazinyl hydrochloride salt was used in the next step without further purification.

To a suspension of aryl-piperazinyl hydrochloride salt (1.0 equiv) in 1,2-dichloroethane (0.25 M), was added dropwise triethylamine (1.1 equiv) followed by $NaHB(OAc)_3$ (1.5 equiv). The mixture was allowed to stir at room temperature for 24 h. The reaction was then diluted in dichloromethane (25 mL) and washed with an aqueous solution of K_2CO_3 (1.0 M, 10 mL × 3) followed by brine (10 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was dissolved in minimal hot ethyl acetate, and filtered while hot. Hexanes was then carefully layered on top of the hot filtrate. The mixture was allowed to cool down, promoting slow precipitation of pure product upon standing. This process was repeated as necessary for full recovery of product.

*3-((trans)-4-(2-(4-(4-Chloro-1-methyl-1H-indol-5-yl)piperazin-1-yl)ethyl)cyclohexyl)-1,1-dimethylurea (**34**).* Starting from **29** (87.2 mg, 0.249 mmol), the title compound **34** was obtained as a tan solid (71.1 mg, 63% over two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, J = 8.8 Hz, 1H), 7.06 (d, J = 8.8 Hz, 1 H), 7.05 (d, J = 2.8 Hz, 1H), 6.53 (d, J = 2.8 Hz, 1H), 4.12 (d, J = 7.2 Hz, 1H), 3.75 (s, 3H), 3.63−3.54 (m, 1H), 3.09 (s br, 4H), 2.87 (s, 6H), 2.67 (s br, 4H), 2.54 (t, J = 8.0 Hz, 2H), 2.02 (s br, 2H), 1.77 (s br, 2H), 1.46 (dt, J = 9.2, 6.4 Hz, 2H), 1.15 (s br, 1H), 1.11−1.02 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 141.4, 134.0, 129.7, 128.4, 120.1, 114.9, 107.9, 99.6, 56.7, 53.7, 52.1, 49.7, 36.0, 35.6, 33.9, 33.0, 32.0; FTIR (thin film), cm^{-1} 3342, 2921, 1626, 1512, 1233, 904, 724; HRMS-ESI (m/z) Calcd for ($C_{24}H_{37}ClN_5O$) ([M + H]$^+$) 446.2681, found 446.2681.

*3-((trans)-4-(2-(4-(3-Bromo-2-chloro-5-methylphenyl)piperazin-1-yl)ethyl)cyclohexyl)-1,1-dimethylurea (**35**).* Starting from **30** (66.2 mg, 0.169 mmol), the title compound was obtained as a white solid (50.2 mg, 60% over two steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (d, J = 1.3 Hz, 1H), 6.76 (d, J = 1.3 Hz, 1H), 4.12 (d, J = 7.5 Hz, 1H), 3.59−3.49 (m, 1H), 3.02 (s br, 4H), 2.85 (s, 6H), 2.59 (s br, 4H), 2.25 (s, 3H), 2.02−1.90 (m, 2H), 1.80−1.71 (m, 2H), 1.42 (dt, J = 9.0, 6.5 Hz, 2H), 1.23 (s br, 1H), 1.11−1.01 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 150.7, 138.1, 128.2, 126.0, 123.7, 120.1, 56.6, 53.3, 51.3, 49.8, 36.1, 35.6, 34.0, 33.8, 32.0, 20.9; FTIR (thin film), cm^{-1} 3343, 2924, 1628, 1533; HRMS-ESI (m/z) Calcd for ($C_{22}H_{35}BrClN_4O$) ([M + H]$^+$) 485.1677, found 485.1673.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Additional screening data and copies of ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Oshiro, Y.; Sato, S.; Kurahashi, N.; Tanaka, T.; Kikuchi, T.; Tottori, K.; Uwahodo, Y.; Nishi, T. *J. Med. Chem.* **1998**, *41*, 658. (b) Agai-Csongor, E.; Domany, G.; Nogradi, K.; Galambos, J.; Vago, I.; Keseru, G. M.; Greiner, I.; Laszlovszky, I.; Gere, A.; Schmidt, E.; Kiss, B.; Vastag, M.; Tihanyi, K.; Saghy, K.; Laszy, J.; Gyertyan, I.; Zajer-Balazs, M.; Gemesi, L.; Kapas, M.; Szombathelyi, Z. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 3437. (c) Kiss, B.; Horvath, A.; Nemethy, Z.; Schmidt, E.; Laszlovszky, I.; Bugovics, G.; Fazekas, K.; Hornok, K.; Orosz, S.; Gyertyan, I.; Agai-Csongor, E.; Domany, G.; Tihanyi, K.; Adham, N.; Szombathelyi, Z. *J. Pharmacol. Exp. Ther.* **2010**, *333*, 328.

(2) (a) Hartwig, J. F. *Nature* **2008**, *455*, 314. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (c) Fan, X.-H.; Yang, L.-M. *Eur. J. Org. Chem.* **2011**, *2011*, 1467. (d) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679. (e) Heck, R. *Org. React.* **1982**, *27*, 345.

(3) (a) Gassman, P. G.; Campbell, G.; Frederick, R. *J. Am. Chem. Soc.* **1968**, *90*, 7377. (b) Gassman, P. G.; Campbell, G. A. *J. Am. Chem. Soc.* **1971**, *93*, 2567. (c) Nickson, T. E.; Rochedolson, C. A. *Synthesis* **1985**, 669. (d) Shen, H.; Vollhardt, K. P. C. *Synlett* **2012**, 208.

(4) (a) Wan, X. B.; Ma, Z. X.; Li, B. J.; Zhang, K. Y.; Cao, S. K.; Zhang, S. W.; Shi, Z. J. *J. Am. Chem. Soc.* **2006**, *128*, 7416. (b) Bedford, R. B.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 5524. (c) Schroder, N.; Wencel-Delord, J.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 8298.

(5) Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.

(6) (a) Neale, R. S. *J. Org. Chem.* **1967**, *32*, 3263. (b) Neale, R. S.; Marcus, N. L. *J. Org. Chem.* **1967**, *32*, 3273.

(7) Selected reviews, see: (a) Heaney, H. *Chem. Rev.* **1962**, *62*, 81. (b) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701. (c) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502. (d) Worlikar, S. A.; Larock, R. C. *Curr. Org. Chem.* **2011**, *15*, 3214.

DOI: 10.1021/jo502541t
J. Org. Chem. 2015, 80, 1059−1069

(e) Bhojgude, S. S.; Biju, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 1520. (f) Bhunia, A.; Yetra, S. R.; Biju, A. T. *Chem. Soc. Rev.* **2012**, *41*, 3140. (g) Gampe, C. M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3766. (h) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *112*, 3550. (i) Yoshida, H.; Takaki, K. *Synlett* **2012**, 1725.

(8) Selected examples, see: (a) Nakayama, J.; Tajiri, T.; Hoshino, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2907. (b) Yoshida, H.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247. (c) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112. (d) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340. (e) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292. (f) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2005**, *46*, 6729. (g) Pena, D.; Perez, D.; Guitian, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579. (h) Yoshida, H.; Mimura, Y.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 2405. (i) Yoshida, H.; Watanabe, M.; Morishita, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 1505. (j) Liu, Y. L.; Liang, Y.; Pi, S. F.; Li, J. H. *J. Org. Chem.* **2009**, *74*, 5691. (k) Biju, A. T.; Glorius, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 9761. (l) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168. (m) Biswas, K.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 4946. (n) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2011**, *13*, 4136. (o) Laczkowski, K. Z.; Garcia, D.; Pena, D.; Cobas, A.; Perez, D.; Guitian, E. *Org. Lett.* **2011**, *13*, 960. (p) Okuma, K.; Matsunaga, N.; Nagahora, N.; Shioji, K.; Yokomori, Y. *Chem. Commun.* **2011**, *47*, 5822. (q) Hoye, T. R.; Baire, B.; Niu, D. W.; Willoughby, P. H.; Woods, B. P. *Nature* **2012**, *490*, 208. (r) Kim, J.; Stoltz, B. M. *Tetrahedron Lett.* **2012**, *53*, 4994. (s) Rodriguez-Lojo, D.; Cobas, A.; Pena, D.; Perez, D.; Guitian, E. *Org. Lett.* **2012**, *14*, 1363. (t) Saito, N.; Nakamura, K.; Shibano, S.; Ide, S.; Minami, M.; Sato, Y. *Org. Lett.* **2013**, *15*, 386. (u) Yoshida, S.; Hosoya, T. *Chem. Lett.* **2013**, *42*, 583. (v) Baire, B.; Niu, D. W.; Willoughby, P. H.; Woods, B. P.; Hoye, T. R. *Nat. Protoc.* **2013**, *8*, 501.

(9) (a) Rondan, N. G.; Domelsmith, L. N.; Houk, K. N.; Bowne, A. T.; Levin, R. H. *Tetrahedron Lett.* **1979**, 3237. (b) Im, G. Y. J.; Bronner, S. M.; Goetz, A. E.; Paton, R. S.; Cheong, P. H. Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, *132*, 17933. (c) Cheong, P. H. Y.; Paton, R. S.; Bronner, S. M.; Im, G. Y. J.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 1267. (d) Garr, A. N.; Luo, D. H.; Brown, N.; Cramer, C. J.; Buszek, K. R.; VanderVelde, D. *Org. Lett.* **2010**, *12*, 96. (e) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *Synlett* **2011**, 2599. (f) Goetz, A. E.; Garg, N. K. *Nat. Chem.* **2013**, *5*, 54.

(10) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.

(11) Bronner, S. M.; Garg, N. K. *J. Org. Chem.* **2009**, *74*, 8842.

(12) Hendrick, C. E.; McDonald, S. L.; Wang, Q. *Org. Lett.* **2013**, *15*, 3444.

(13) See the Supporting Information for details on additional amine substrates.

(14) Neale, R. S. *J. Org. Chem.* **1967**, *32*, 3263.

(15) (a) Liu, Z. J.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198. (b) Morishita, T.; Fukushima, H.; Yoshida, H.; Ohshita, J.; Kunai, A. *J. Org. Chem.* **2008**, *73*, 5452.

(16) (a) Pena, D.; Cobas, A.; Perez, D.; Guitian, E. *Synthesis* **2002**, 1454. (b) Bronner, S. M.; Bahnck, K. B.; Garg, N. K. *Org. Lett.* **2009**, *11*, 1007.

(17) Kirsop, P.; Storey, J. M. D.; Harrison, W. T. A. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2004**, *60*, 1147.

(18) Shonberg, J.; Herenbrink, C. K.; Lopez, L.; Christopoulos, A.; Scammells, P. J.; Capuano, B.; Lane, J. R. *J. Med. Chem.* **2013**, *56*, 9199.

(19) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

DOI: 10.1021/jo502541t
J. Org. Chem. 2015, 80, 1059−1069