Carborane-Based Lewis Base Catalysts for Aromatic Halogenation

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Abstract: Haloarenes have been an important class of chemicals in modern organic chemistry field because the halide functionality offers numerous possible transformations. Classical electrophilic aromatic halogenation using molecular halogens and Lewis/Brønsted acid activators is still a promising synthetic tool; however, it suffers from handling difficulties, low selectivity, and limited functional group tolerance. We herein introduce carborane-based Lewis base catalysts for the aromatic halogenation using *N*-halosuccinimides. The developed reaction system was readily applicable to late-stage functionalization of drug molecules and efficient synthesis of multi-halogenated aromatics. The *m*-carborane scaffold was most suitable for the catalysis, and the possible fine-tuning by decorating the cluster vertices was important for modulating the electronic property of halonium species to maximize the catalytic performance.

For more than 150 years since the structure of benzene was proposed by August Kekulé, aromatic molecules have been privileged compounds both in academic research and industrial chemistry. Currently, by virtue of the remarkable development of transition-metal-catalyzed coupling techniques over the past decades, we can readily design and synthesize various functional aromatic compounds.[1,2] Haloarenes have been an important class of chemicals in modern organic chemistry field because the halide functionality offers numerous possible transformations into valuable building blocks. The versatile applications of aryl halides in pharmaceuticals,[3,4] material science,[5] and imaging technic[6,7] have also reinforced their synthetic importance. The electrophilic aromatic halogenation has been the most practical and straightforward synthetic method.[8] Although classical halogenation using molecular halogens (mainly Cl_2 and Br_2) and Lewis/Brønsted acid activators is still a promising protocol, it suffers from handling difficulties, low regioselectivity, and limited functional group tolerance (Fig. 1a). Moreover, the late-stage halogenation of complex molecules has been regarded as a challenging task.[9] To address this issue, the development of highly active yet efficiently selective halogenation methods has long been desired.
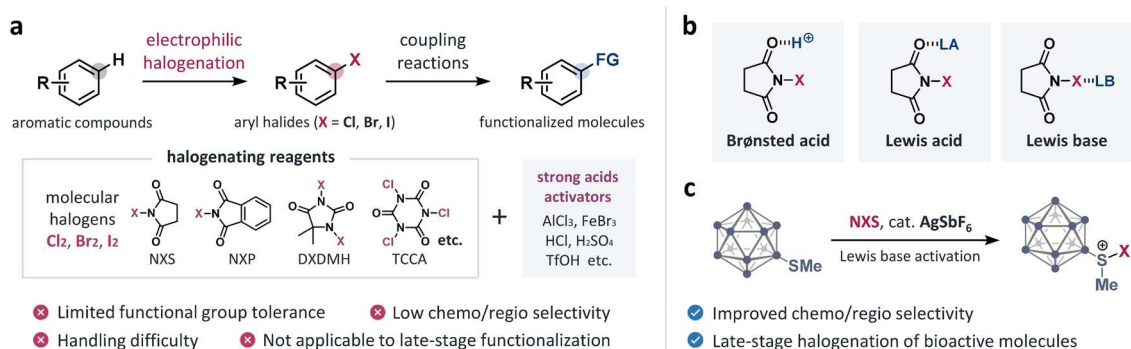
Fig. 1. Catalytic Aromatic Electrophilic Halogenation. (**a**) A schematic presentation for the conventional aromatic halogenation. (**b**) General activation models of *N*-halosuccinimides. (**c**) This work: development of new carborane-based Lewis base catalysts.

N-Halosuccinimides (NXS) are particularly useful halogenating reagents due to their stability, low-cost, and ease of handling. Since NXS as well as relevant N–X type compounds solely are substantially less active reagents that can halogenate only electron-rich (activated) arenes, they are generally used in combination with strong acids to enhance the reactivity (Fig. 1b). For example, FeCl₃,[10] triflic acid (TfOH),[11] HCF₂CF₂SO₃H (TFESA),[12] and BF₃·H₂O[13] were adopted to achieve halogenation of electron-deficient (deactivated) aromatics; however, these harsh conditions would offer limited synthetic applications. A few pioneering catalytic systems with relatively mild reaction conditions have been established for the halogenation of deactivated arenes. Wang reported an AuCl₃-catalyzed halogenation using NXS, where arylgold species formed through the direct metalation of C–H bonds were assumed to be reactive nucleophiles.[14] Recently, Song and Jiao utilized nitrobenzenesulfonic acid (NBSA) as a catalyst[15] in combination with HFIP (hexafluoro-2-propanol) solvent.[16,17]

Meanwhile, Lewis basic molecules have also been used to catalytically activate halogenating reagents by forming halonium complexes (Fig. 1b).[18,19] It should be noted that Lewis base catalysts have attracted significant interest as a practical tool for halonium-induced cyclization (cation-π cyclization).[20,21,22,23,24,25,26,27,28,29,30] The Lewis base activation is generally much less powerful than the acid catalysis, and thereby is only effective for the aromatic halogenation of electron-rich substrates.[31,32,33,34,35,36,37,38,39,40,41,42,43] As a milestone, we recently developed Trip-SMe (Trip = 9-triptycenyl) for the catalytic halogenation of unactivated aromatics using NXS.[44,45,46] However, this designed sulfide catalyst was still insufficiently effective to achieve halogenation of electron-deficient arenes because the triptycene moiety was preferentially halogenated to reduce its activity. Moreover, functionalized triptycene derivatives are not readily accessible, making it difficult to systematically tune their catalytic performance. To address these issues, we began a quest for a suitable structural platform to establish highly practical reaction systems.

Carboranes (C₂B₁₀H₁₂) are an interesting class of 3D aromatic molecules with icosahedral geometry, high thermal and chemical stabilities, and unique electronic effects.[47,48,49] We envisioned that these
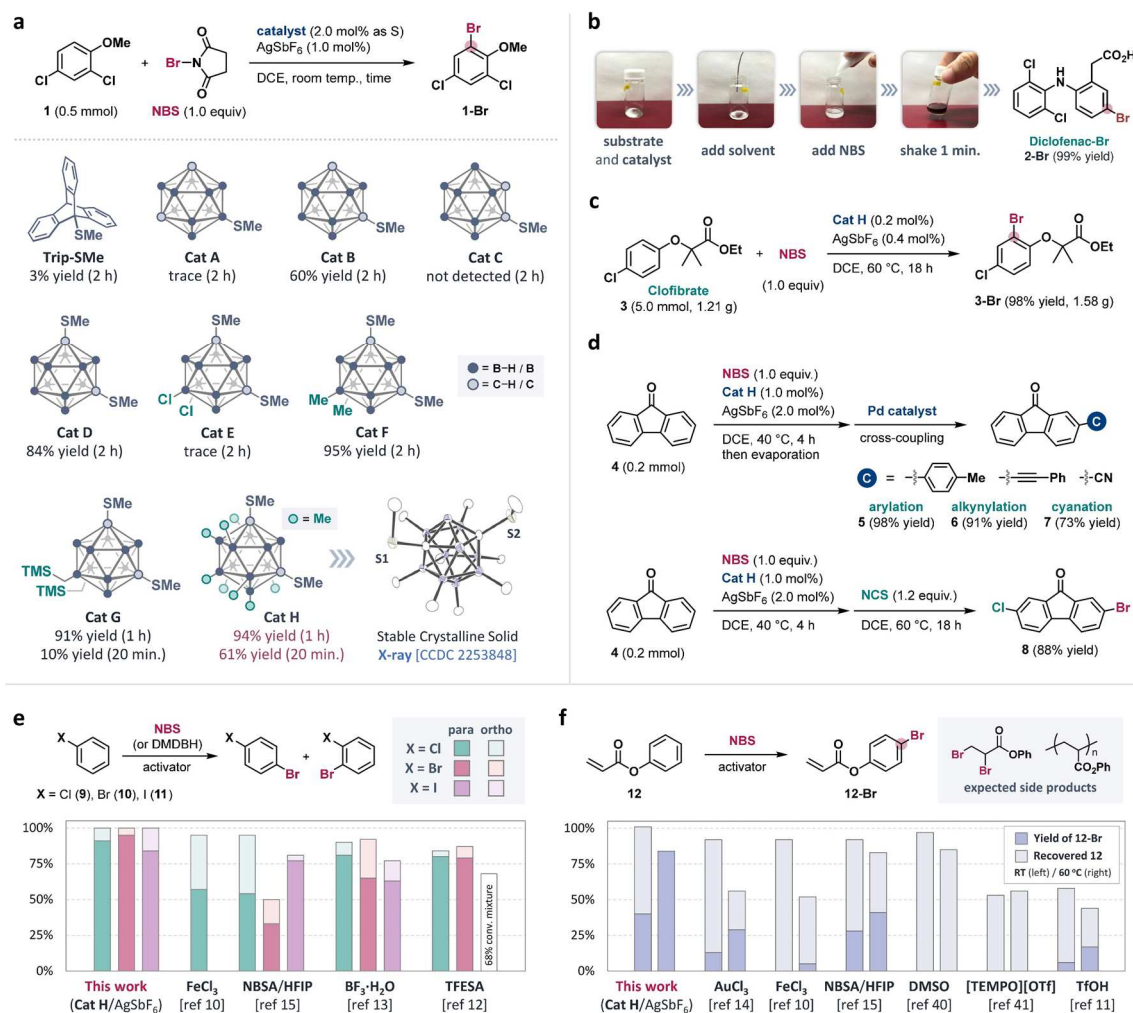
boron clusters would be a handle to modulate the electronic property of halonium species,[50,51,52] whereas their spherical shape exert a negligible change in steric factor (Fig. 1c). As a specific design, we synthesized a series of functionalized carboranes and systematically studied their activity. To our delight, several carborane-based sulfide catalysts exhibited significantly improved activity and chemo/regioselectivities. The developed catalytic system was applicable not only to bromination but also to more challenging chlorination and iodination. [53] Potential synthetic applications are demonstrated by late-stage halogenation of bioactive compounds and straightforward synthesis of multi-halogenated compounds.

Catalyst Development

At the outset we evaluated the activity of designed carborane catalysts for the bromination of 2,4-dichloroanisole (**1**) with NBS at room temperature with $AgSbF_6$ co-catalyst (Fig. 2a). Trip-SMe catalyst was insufficiently effective for this transformation. To our delight, *m*-carborane catalyst bearing an SMe group at the C1 vertex (**Cat A**) exhibited enhanced activity to afford the desired product **1-Br** in 60% yield under the same conditions. In sharp contrast, relocation of the SMe group onto the B9 vertex (**Cat B**) or changing the cluster structure to an isomeric *o*-carborane (**Cat C**) resulted in significant drop in productivity. By introducing two SMe groups at both C1 and C7 positions (**Cat D**), the catalyst loading could be reduced while maintaining high product yield (84%). Accordingly, we envisioned improving the catalytic activity by installing functionalities onto B9 and B10 vertices. Chlorination substantially deactivated the catalyst (**Cat E**) whereas methylation improved the yield to 95% (**Cat F**). A relatively strong electron donating (trimethylsilyl)methyl substituent[54] further improved the productivity to give **1-Br** in 91% yield in 1 h (**Cat G**). Based on these results, we synthesized an octamethyl carborane catalyst (**Cat H**), which exhibited the highest activity among the examined catalysts. Notably, we examined the bromination of **1** adopting several activators described in literatures, but the product **1-Br** was obtained in moderate yields only when strong acids were used (see Table S1).

The carborane catalyst **Cat H** is an bench-stable crystalline solid prepared from commercially available *m*-carborane in two steps. To demonstrate the robustness and practicality, bromination of diclofenac (**2**) was conducted in a glass vial under air: completed in 1 minute shaking at room temperature to give **2-Br** in 99% yield (Fig. 2b). For the gram scale reaction of clofibrate (**3**) with NBS, the catalyst amount could be reduced to 0.2 mol% **Cat H** and 0.4 mol% $AgSbF_6$, producing 1.58 g (98% yield) of **3-Br** (Fig. 2c). Additionally, we examined one-pot halogenation and palladium-catalyzed coupling reactions (Fig. 2d). Fluorenone (**4**) was cleanly converted to 2-bromo-9-fluorenone within 4 h at 40 °C. After removal of the solvent, the crude material was subjected to Suzuki-Miyaura coupling, Sonogashira coupling, and cyanation conditions, which were all compatible with the developed halogenation to afford the corresponding products **5**, **6**, and **7** in high yields, respectively.

Besides, consecutive bromination/chlorination of fluorenone (**4**) was successful to produce 2-bromo-7-chloro-fluorenone (**8**) in 88% yield.

Fig. 2. Catalyst development and activity evaluation. (**a**) Evaluation of the catalytic activity. (**b**) Reaction setup for the bromination of diclofenac. (**c**) Gram scale reaction of clofibrate. (**d**) One-pot reactions. (**e**) Selectivity for the bromination of halobenzenes. (**f**) Aromatic halogenation of phenyl acrylate.

The ortho/para selectivity is not a trivial issue for the electrophilic halogenation of halobenzenes,. We then examined the bromination of chlorobenzene (**9**), bromobenzene (**10**), and iodobenzene (**11**) with NBS under the standard conditions (Fig. 2e). The starting materials were fully converted to the corresponding dihalobenzenes with high para selectivity (91:9 for **9-Br**, 95:5 for **10-Br**, 84:16 for **11-Br**). Such an effective regiocontrol has been difficult to achieve with strong acid activators, which have been used for the halogenation of electron deficient arenes. In fact, as summarized in Fig. 2e, considerable amount of ortho isomers were usually produced, and it was also difficult to suppress

over-reaction.

The developed catalytic system was effective for sensitive substrates. As a particular example, phenyl acrylate (**12**) is prone to oligomerize in the presence of radical initiators, and its alkene moiety may undergo 1,2-dibromination[55] or aza-Michael addition/halogenation;[56] thereby, no example is reported for the aromatic halogenation of **12**. Intriguingly, the corresponding haloarene **12**-**Br** was isolated in 81% yield (84% NMR yield) using NBS under the standard conditions at 60 °C (Fig. 2f). We also examined the same transformation with several activators reported in literatures, but all these entries ended up with low substrate conversion and/or poor mass balance (see Table S2).

Scope and Limitation

Next, we evaluated the scope and limitation for the bromination (Fig. 3). Electron deficient arenes such as methyl benzoate, 1,3-difluorobenzene, 1,2-dichlorobenzene, and 4-methylbenzotrifluoride were applicable to give the corresponding aryl bromides in moderate yields (**13**–**16**). Unfortunately, methyl benzenes with a strong deactivating CN or NO_2 group (**18**, **19**) were not reactive, and an electron-donating OMe group was necessary to facilitate the halogenation (**19**–**21**). Strong acid activators would remain more powerful for highly deactivated aromatics. Looking at the bright side, the sufficiently mild reaction conditions realized excellent functional group tolerance including aldehyde (**22**), terminal epoxide (**23**), glycol ether (**24**), alkyl halide (**25**, **43**), azide (**26**), boronic ester (**27**), thiocyanate (**28**), sulfide (**29**), imide (**30**, **31**), sulfanyl imide (**32**), diselenide (**33**), and alcohol (**42**). It should be highlighted that the labile Se–Se bond of **33** remained untouched during the reaction. As similar to the reaction of phenyl acrylate described above (Fig. 2f), alkene (**34**, **44**) and alkyne (**35**–**44**) fragments conjugated with carbonyl were well-tolerated in the present system reaction.

Late-Stage Halogenation

To demonstrate potential synthetic applications of the developed methodology, we examined the late-stage halogenation of bioactive compounds (Fig. 4). A series of approved drugs bearing various functional groups were successfully brominated to afford the corresponding products **45**–**55** with excellent yield and regioselectivity. It is notable that, even in the absence of potent directors, single isomers were produced by the bromination of zaltoprofen and flurbiprofen (**51**, **52**). The two possible reaction sites within loxoprofen benzene ring have fairly similar electronic and steric environments; however, the product **54** was obtained with high level of regiocontrol. Atovaquone underwent the reaction smoothly to give **55** with moderate selectivity. To our delight, the present catalytic system was also applicable to the more challenging aromatic chlorination (**56**–**62**) and iodination (**63**–**66**). Various functional groups including cyclopropane (**46**, **57**, **64**), isoxazole (**47**, **48**, **58**), carbamate (**49**), enolizable ketone (**51**, **54**), acyl pyrrolidone (**53**), and naphthoquinone (**55**) were readily tolerated. For the bromination of leflunomide (**47**, **48**) and the chlorination of clofibrate (**61**, **62**), both mono- and di-halogenated products were obtained in high yields by simply changing the amount of NBS and NCS used, respectively.
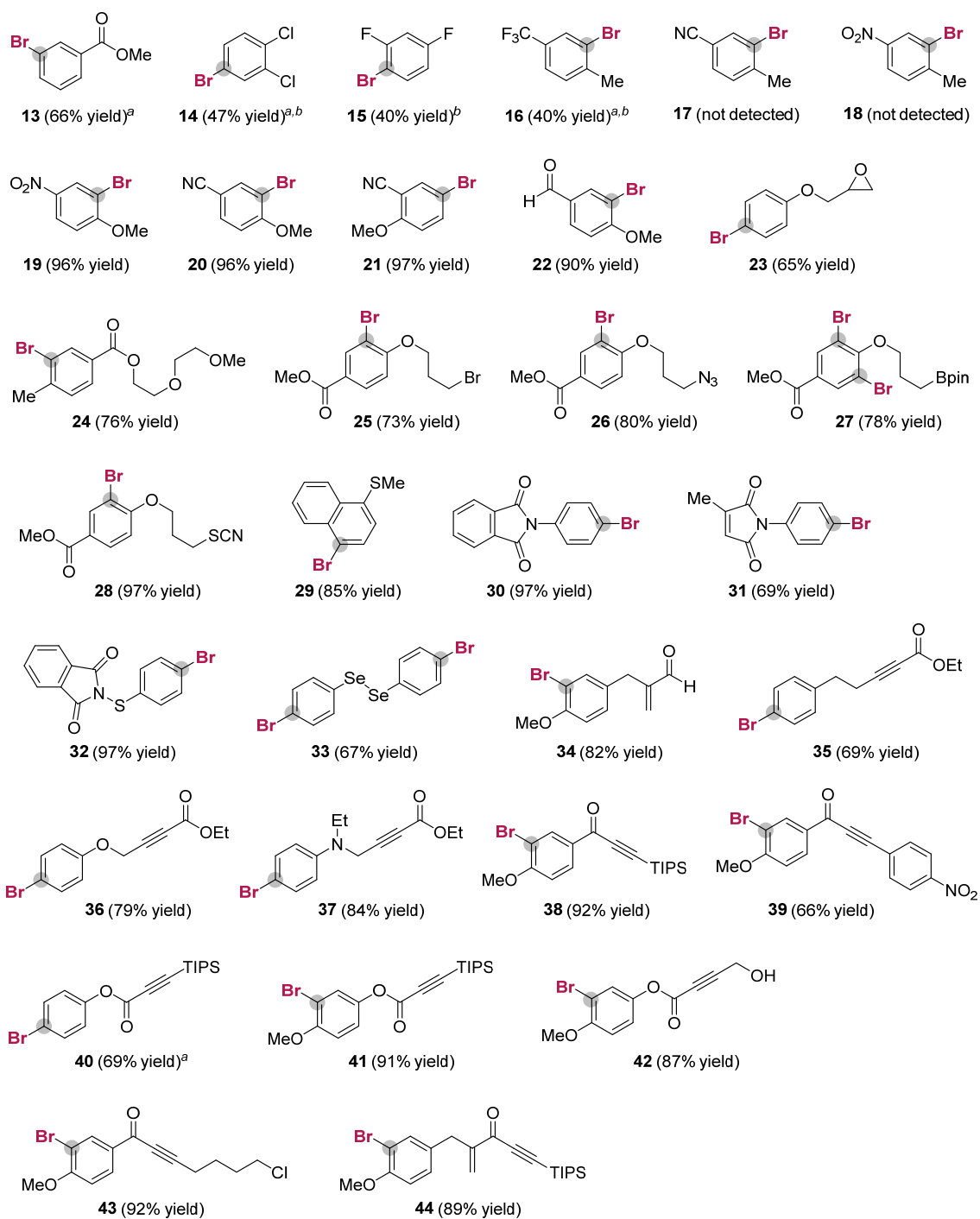
13 (66% yield)[a]   **14** (47% yield)[a,b]   **15** (40% yield)[b]   **16** (40% yield)[a,b]   **17** (not detected)   **18** (not detected)

19 (96% yield)   **20** (96% yield)   **21** (97% yield)   **22** (90% yield)   **23** (65% yield)

24 (76% yield)   **25** (73% yield)   **26** (80% yield)   **27** (78% yield)

28 (97% yield)   **29** (85% yield)   **30** (97% yield)   **31** (69% yield)

32 (97% yield)   **33** (67% yield)   **34** (82% yield)   **35** (69% yield)

36 (79% yield)   **37** (84% yield)   **38** (92% yield)   **39** (66% yield)

40 (69% yield)[a]   **41** (91% yield)   **42** (87% yield)

43 (92% yield)   **44** (89% yield)

Fig. 3. Scope of catalytic electrophilic bromination. Yields are of isolated, purified materials otherwise noted. Detail reaction conditions are summarized in the Supplementary Information. [a] **Cat D** was used instead of **Cat H**. [b] NMR yield.
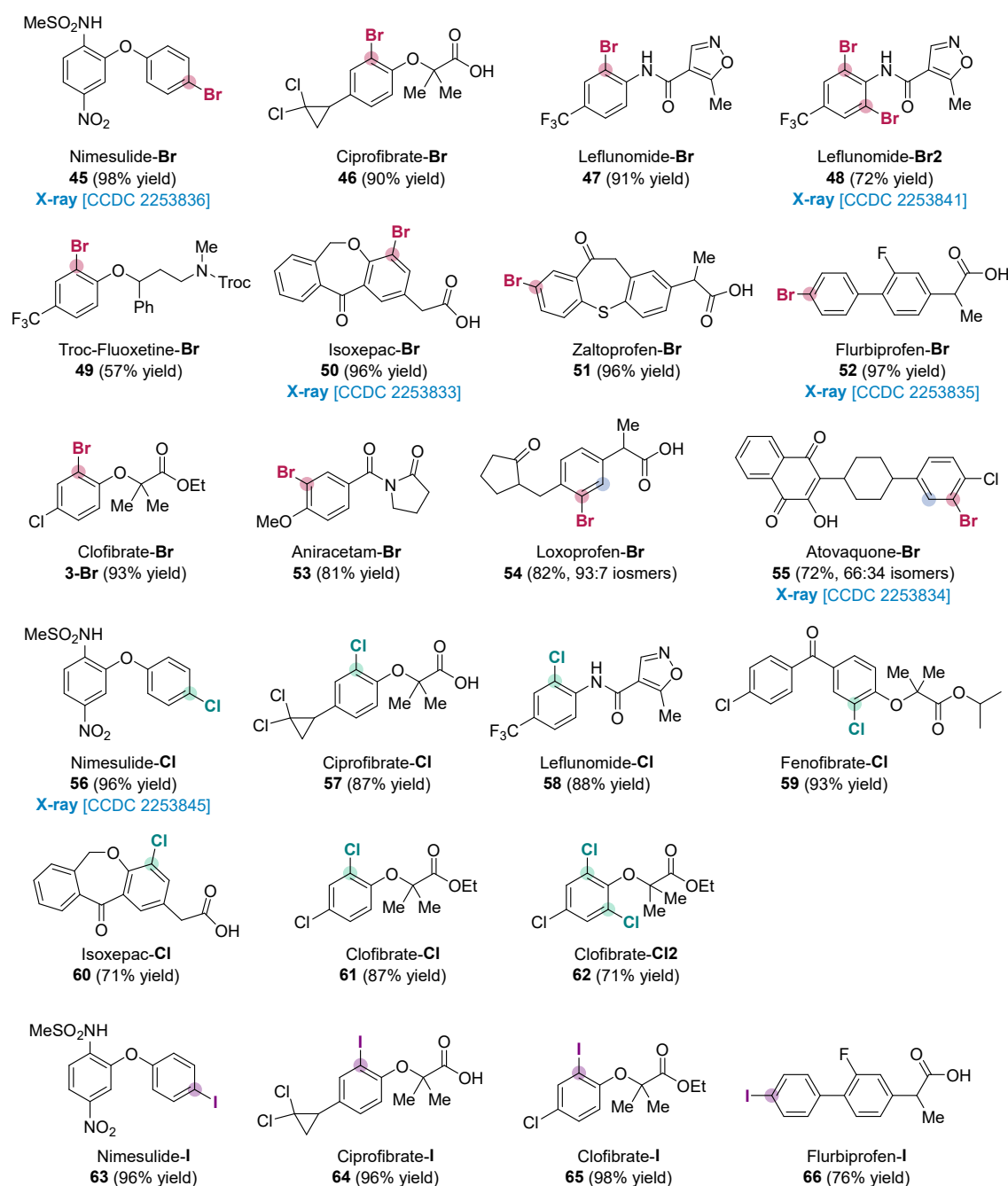
Fig. 4. Late-stage halogenation of bioactive compounds. Yields are of isolated, purified materials otherwise noted. Detail reaction conditions are summarized in the Supplementary Information.

Synthesis of Multi-Halogenated Arenes

To further expand the scope, we examined the synthesis of multi-halogenated compounds, which have been increasingly valuable building blocks for synthesizing densely functionalized aromatics and nanocarbon materials. However, harsh reaction conditions required for achieving multiple halogenations practically lack selectivity in the position and the number of halogens to be installed. As a particular example, the direct and selective synthesis of halogenated *o*-terphenyl derivatives has been unsuccessful to date because

the reaction with bromine produces complex mixture of isomers.[57] In the present system, di- (**67**), tri-(**68**), and tetra-bromination (**69**) products were all obtained in high yields by adjusting the NBS stoichiometry (Fig. 5a). Additional examples are showcased in Fig.5b. Fluorenone, tetraphenylmethane, and hexaphenylbenzene were cleanly halogenated under the standard conditions, affording the target compounds **70–74** in excellent yields. Naphthalene underwent complete α-chlorination (**75**) upon treatment with 4.0 equiv of NCS, whereas the reaction with 3.5 equiv of NBS gave 1,4,6-tribromonaphthalene (**76**). In a similar manner, 1,5-dibromonaphthalene was converted to the α-halogenated product **77**. Unexpectedly, when 2,6-dibromonaphthalene was reacted with 2.0 equiv of NCS, the sterically congested positions were preferentially chlorinated to give **78** as a major product. Under more forceful conditions with 4.0 equiv of NCS at 60 °C, the tri-chlorination product **79** was obtained in 65% yield. On the other hand, bromination with 2.0 equiv of NBS produced a mixture of isomers (**80a + 80b**) and both were isolated in moderate yields. For the reaction of 2,7-dibromonaphthalene, the di-chlorination (**81**) and mono-bromination (**82**) products were obtained in high yields. The C9–C10 double bond within phenanthrene readily undergo 1,2-dihalogenation to give the corresponding saturated compounds, and the subsequent H–X elimination may afford 9-halophenanthrene;[58,59] however, the present protocol with 2.0 equiv of NCS produced 9,10-dichlorophenanthrene (**83**) in 79% yield. Moreover, the penta-chlorination product **84** was obtained in synthetically useful 49% yield using 5.0 equiv of NCS. Reaction continued further if excess NCS was used until the hexa-chlorination product **85** eventually formed. For the reaction of chrysene with 2.0 equiv of halogenating reagents, 6,12-dichlochrysene (**86**) and 6,12-dibromochrysene (**87**) were obtained in moderate yields. We also examined the multiple chlorination of chrysene and successfully isolated the hexa-chlorination product **88** in 19% yield.

Mechanistic Consideration

We assume that the reaction mechanism is essentially similar to that of the Trip-SMe catalyst.[44] A sulfonium complex consists of carborane-S(Me)Br and a weakly coordinating SbF_6 anion would form as an active species, which then deliver a halogen cation to the aromatic substrate (Fig. 6a). The generated sigma complex is deprotonated by succinimide anion to liberate the halogenated product and $AgSbF_6$. To gain experimental support for this surmise, we synthesized a relevant sulfonium salt and examined its reactivity (Fig. 6b). The carborane **Cat H** was sequentially treated with bromine and $SbCl_5$ at −40 °C to give the corresponding adduct **89** in 75% yield,[60,61] and the structure was unambiguously determined by an X-ray analysis. When the bromination of **1** was conducted using a catalytic amount of **89** and NBS at room temperature, **1**-**Br** was obtained in reasonably high 93% yield in the absence of $AgSbF_6$; $HSbBrCl_5$ probably acted as the co-catalyst in this case.
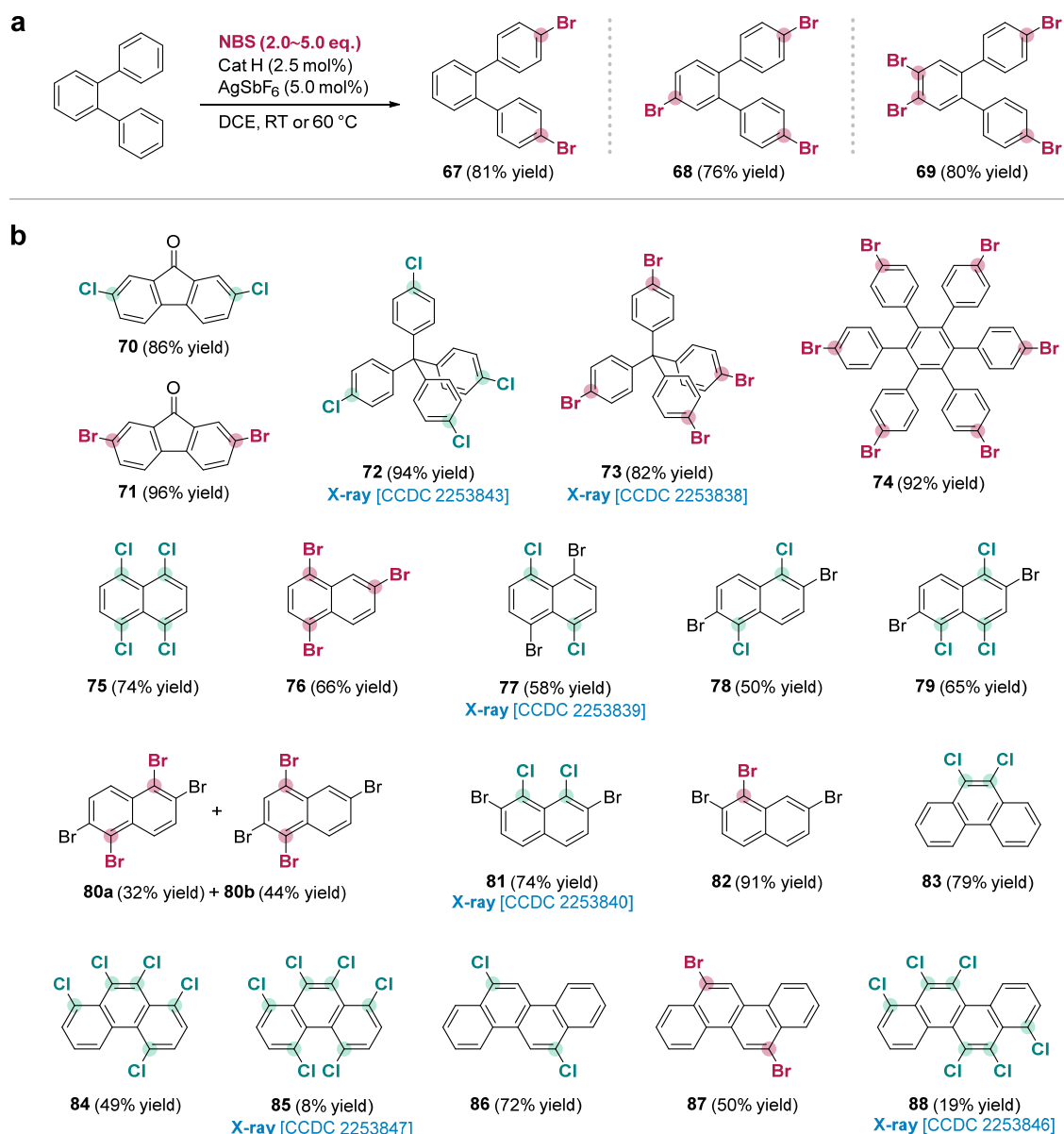
Fig. 5. Synthesis of multi-halogenated aromatic compounds. (a) Controlled bromination of *o*-terphenyl. **(b)** Scope of multi-halogenation. Yields are of isolated, purified materials otherwise noted.

As summarized in Fig. 2a, the catalytic activity drastically changed depending on the position of SMe substituent (**Cat A** vs **Cat B**) and the carborane isomerism (**Cat B** vs **Cat C**). Considering the negligible steric effect of the spherical carborane framework, it would be reasonable to regard the electronic effect as a key factor for the reactivity. We thus conducted a computational study focusing on two representative parameters (Fig. 6c). We assembled seven carborane derivatives bearing one SMe group (**I–VII**), Trip-SMe, and SMe$_2$ as a model system for calculations. Additionally, the corresponding [R-S(Me)Br][PF$_6$] type complexes were calculated as the expedient active species (see Fig. S17). The first parameter is the nucleophilicity of the sulfur atom, which is represented by N-

index value.[62] The SMe group attached to the B9 atom of *m*-carborane exhibited high nucleophilicity (**I**: 2.82 eV) comparable to that of SMe$_2$ (2.87 eV). In contrast, the remaining six carboranes bearing an SMe group at the C1 vertex (**II**–**VII**) have lower nucleophilicity (1.99~2.53 eV) than Trip-SMe (2.57 eV). This trend reflects the inherent dichotomy of the carborane cluster: substituents experience either a strong electron-withdrawing effect on the C1 position or strong electron-donating effect on the B9 position. The lowest N-index value was given to the C1-functionalized *o*-carborane (**III**: 1.99 eV) because its C1 atom is directly connected to the electron deficient C2 atom. The second parameter is the energy level of molecular orbital correspond to the σ-hole,[63] electropositive region developed along the S–Br axis, within the sulfonium complexes. In the halogenation reaction, this S–Br σ* orbital accepts π electrons of the aromatic substrate to form the corresponding arenium ion intermediate. We expect that lower level of the σ* orbital and higher nucleophilicity of the SMe group would be favorable for the activity. These two parameters are generally in a trade-off relationship, so that catalysts with a right balance should be identified in practice. When two parameters are plotted on a graph, the active catalysts (**II**, **V**, **VI**, **VII**, see Fig. 2a) were found to occupy a specific area. We concluded that the electronic properties of *m*-carborane skeleton was most suitable to hit this hot spot, and the possible fine-tuning by decorating the cluster vertices was important for maximizing the catalytic performance.
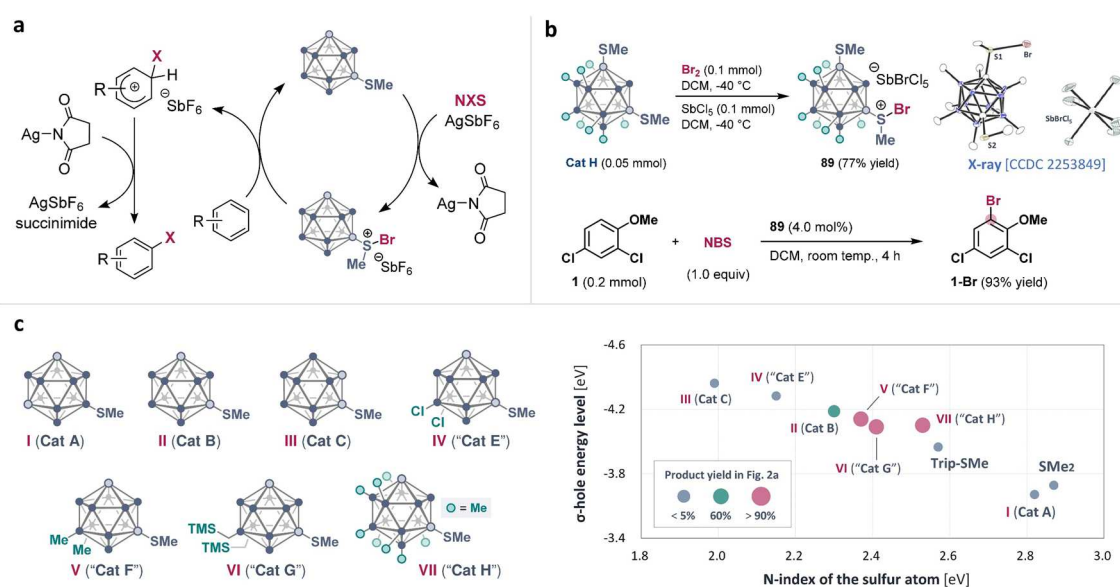

Fig. 6. Mechanistic study. (**a**) Proposed reaction mechanism. (**b**) Synthesis and catalytic activity of a sulfonium complex **89**. (**c**) Summary of DFT calculations.

Conclusion

In this work, we have developed new carborane-based Lewis base catalysts for the aromatic halogenation using *N*-halosuccinimides under mild conditions. The reaction system was readily

applicable to electron-deficient arenes and sensitive substrates. Its potential synthetic applications were demonstrated by the regioselective halogenation of drug molecules and multi-halogenation of aromatic hydrocarbons. The proposed reaction mechanism was supported by the isolation of a sulfonium complex **89**. DFT calculations revealed that the electronic properties of *m*-carborane skeleton was the most suitable for the catalysis, and further chemical functionalization of the cluster vertices was highly important to enhance the catalytic activity.

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