Aromatic halogenation using carborane catalyst

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Abstract

Halogenated organic compounds have been appreciated as one of the most fundamental and versatile building blocks in the modern chemistry field. Moreover, the remarkable development of metal-catalyzed coupling techniques has greatly reinforced their utility. Although classical halogenation using Lewis/Brønsted acid activators is still a promising tool, it suffers from handling difficulties, low selectivity, and limited functional group tolerance. We herein introduce carborane-based sulfide catalysts for aromatic halogenation using N-halosuccinimides. The developed reaction system was readily applicable to the late-stage functionalization of drug molecules and the efficient synthesis of multi-halogenated aromatics.

Background & Results

Haloarenes have been an important class of chemicals in the modern organic chemistry field because the halide functionality offers numerous possible transformations into valuable building blocks. Although classical halogenation using molecular halogens (mainly Cl_2 and Br_2) and acid activators is still a promising protocol, it suffers from low regioselectivity and limited practical application in fine-chemical synthesis. To address this issue, the development of highly active yet efficiently selective halogenation methods has long been desired. In this work, we have developed carborane-based sulfide catalysts for aromatic halogenation. Carboranes ($C_2B_{10}H_{12}$) are three-dimensional aromatic molecules with icosahedral geometry, high thermal and chemical stabilities, and unique electronic effects. We envisioned that these boron clusters would be a handle to modulate the electronic property of halonium species, whereas their spherical shape exerts a negligible change in steric factor. As a specific design, we synthesized a series of sulfur-substituted carboranes and systematically studied their activity. Density functional theory (DFT) calculations revealed that the m-carborane scaffold was most suitable for 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.

Significance of the research and Future perspective

The reaction system was readily applicable to sensitive substrates (epoxide, diselenide, azide, alkene, alkyne, etc.) and highly deactivated electron-deficient arenes. 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. Depending on the synthetic challenge, the introduced catalyst system could become a more efficient and selective alternative to existing methods both in academic research and the chemical industry.

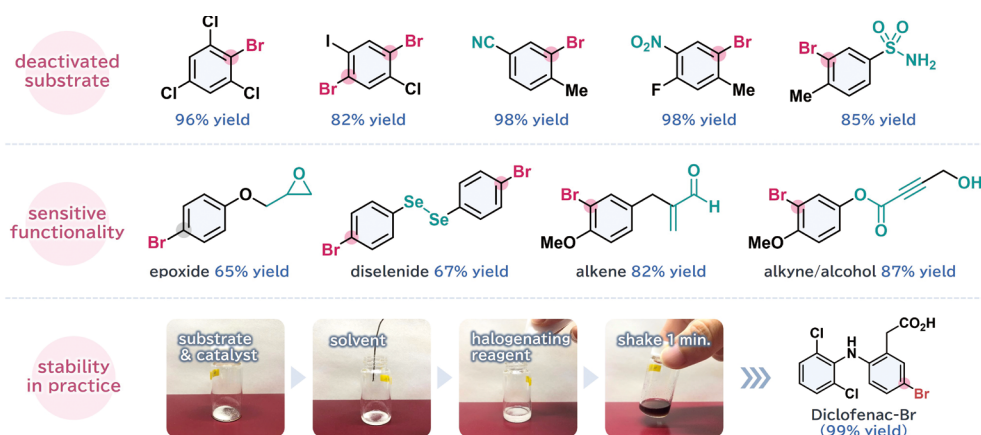**Carborane-SMe Catalyst**
- bench-stable crystalline solid
- improved activity & selectivity
- tunable new catalyst platform

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(left) X-ray crystal structure, (right) space-fill model

Fig. 1

deactivated substrate: 96% yield · 82% yield · 98% yield · 98% yield · 85% yield

sensitive functionality: epoxide 65% yield · diselenide 67% yield · alkene 82% yield · alkyne/alcohol 87% yield

stability in practice: substrate & catalyst → solvent → halogenating reagent → shake 1 min. → Diclofenac-Br (99% yield)

Fig. 2