BNCT, Medical & healthcare, Drug discovery, Functional materials

Quick and scalable synthesis of carborane-substituted arenes via a dump-and-stir cuprate reagent: Unlocking applications in BNCT, drug design, and functional materials

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Abstract

We have developed a novel and practical method for introducing ortho-carborane units into a wide range of (hetero)aryl compounds. By synthesizing an isolable lithium bis(ortho-carboranyl)cuprate complex (**Li/Cu-1**), we achieved efficient C–C bond formation with aryl bromides and chlorides through a simple "mix and heat" protocol. This approach overcomes the limitations of conventional methods, which require complex multi-step procedures and hazardous reagents. The new technique enables scalable synthesis of carborane-substituted arenes, paving the way for their application in medicinal chemistry, materials science, and beyond.

Background & Results

Carboranes are unique polyhedral clusters composed of carbon and boron atoms, known for their exceptional thermal and chemical stability, three-dimensional aromaticity, neutron-capturing capability, and bioisosteric similarity to benzene. Carborane-substituted arenes (carboranyl arenes) are promising molecular frameworks that combine 2D and 3D aromaticity for next-generation pharmaceuticals and functional materials. However, existing synthetic methods suffer from critical limitations: low reproducibility due to the complex equilibrium of multiple copper species, restricted substrate scope requiring expensive aryl iodides, operational complexity involving multi-step procedures at low temperatures (−78℃ to 0℃), and safety concerns with unstable intermediates. To address these challenges, we developed lithium bis(ortho-carboranyl) cuprate (**Li/Cu-1**), a stable and isolable reagent that can be synthesized on a multi-decagram scale (>30 mmol) and stored under an inert atmosphere. This reagent enables direct coupling with readily available aryl bromides and chlorides through a simple "dump-and-stir" protocol: mixing with substrates in the presence of isophthalonitrile and heating in toluene at 100℃. Using this method, we synthesized over 30 diverse carboranyl arenes in high yields with excellent reproducibility, including multiple-carborane-substituted structures and carborane-fused π-systems. Notably, we demonstrated the bioisosteric replacement of the benzene ring in flurbiprofen, a non-steroidal anti-inflammatory drug (NSAID), highlighting the potential for structure optimization in drug design.

Significance of the research and Future perspective

This work represents a major breakthrough in carborane chemistry, offering a user-friendly and scalable synthetic tool for introducing carborane units into organic molecules. In the medical field, the method facilitates the development of boron-containing drugs for boron neutron capture therapy (BNCT), a promising cancer treatment that selectively destroys tumor cells using neutron irradiation. Additionally, it enables structural optimization of existing pharmaceuticals through bioisosteric substitution of benzene rings with carborane units, potentially improving drug stability and efficacy. In materials science, the unique properties of carboranes—including three-dimensional aromaticity and exceptional thermal stability—can be harnessed to create advanced luminescent materials for organic light-emitting diodes (OLEDs) and charge-transport materials for high-performance electronic devices.

The simplicity, high reproducibility, and large-scale applicability of the carboranyl cuprate reagent are expected to democratize access to carborane chemistry, lowering the barrier for researchers and companies across disciplines to explore its potential. This "dump-and-stir" approach could accelerate innovation in both academic research and industrial manufacturing, opening new avenues for sustainable chemical synthesis.

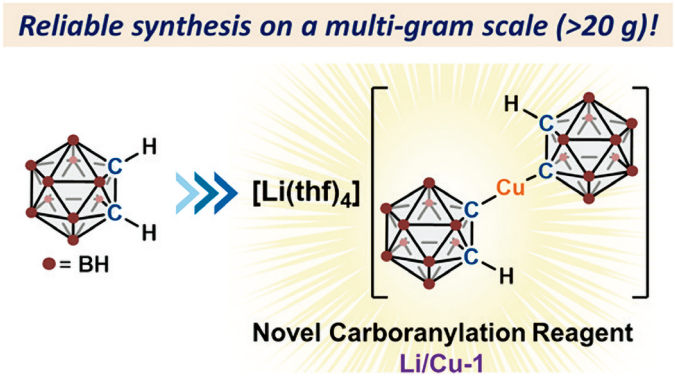

Fig. 1. A novel carbonylation reagent, lithium bis-carboranyl cuprate (**Li/Cu-1**).

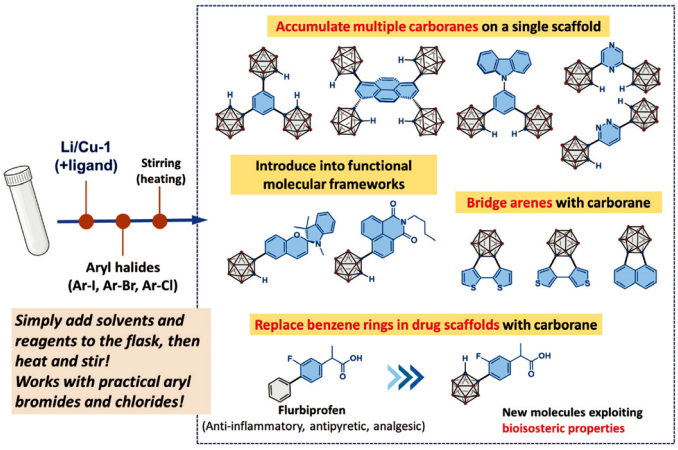

Fig 2. A dump-and-stir synthesis of versatile carboranyl arenes

Patent	Japanese Patent Application No.2025-130009
Treatise	Hisata,Yusei; Morishita, Daina; Hoshimoto, Yoichi. An isolated lithium ortho-carboranyl cuprate complex for the synthesis of multiple-carborane-substituted arenes from (hetero)aryl bromides and chlorides. J. Am. Chem. Soc. 2025, 147(41), 37677-37687. doi: 10.1021/jacs.5c13004
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