ADVANCES IN NONCLASSICAL BENZENE BIOISOSTERE SYNTHESIS AND FUNCTIONALIZATION

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INTRODUCTION

Bioisosteres are exchangeable chemical moieties which exhibit similar biological effects while possessing distinct physicochemical properties.[1] Medicinal chemists leverage bioisosteres to enhance potency, selectivity, and metabolic stability in drug optimization campaigns.[1] Additionally, bioisosteric replacements can be employed to assert intellectual property claims. In contrast to classical bioisosteres, modern nonclassical bioisosteres differ substantially in electronic, physicochemical, and steric parameters from their parent structures. The increasing prevalence of small, strained polycyclic benzene bioisosteres (**Figure 1**) has motivated the development of new synthetic methods to access sp^3-rich space, and advances in process chemistry have enabled kilogram-scale production of certain motifs.

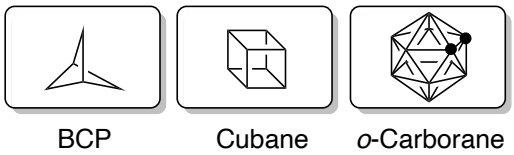

Figure 1. Nonclassical benzene bioisosteres

BICYCLO[1.1.1]PENTANES

Bicyclo[1.1.1]pentanes (BCPs) have been extensively validated as benzene bioisosteres.[2] BCPs substituted at the bridgehead positions mimic *mono*- and *para*-substituted benzene rings and are readily accessed by single- or two-electron transfer processes across the "spring-loaded" central bond of [1.1.1]propellane (**Figure 2a**). In 2016, the Baran group reported a strain-release amination strategy for the introduction of *mono*-aminated strained ring systems through the reaction of magnesium amide nucleophiles, termed "turbo amides", with high energy C-C and C-N bonds.[1] In 2019, the Anderson group reported a general strategy to access 1,3-disubstituted BCPs via photoredox-catalyzed reactions of sp^2 and sp^3 alkyl halides with [1.1.1]propellane.[2] In contrast to the bridgehead positions, there are few synthetically useful methods for functionalizing the BCP backbone. Qin recently reported a strategy for the construction of (C1, C2, and C3)- multisubstituted BCPs via intramolecular coupling of cyclobutene-tethered sulfonylhydrazones and boronates (**Figure 2b**).[3] Notably, this method provides bioisosteres of 1,3,4-trisubstituted benzene rings.

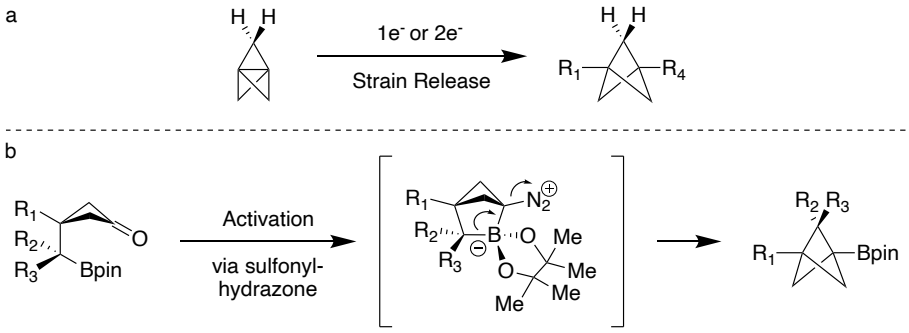

Figure 2. BCP synthetic strategies a) strain-release and b) intramolecular coupling

SECOND-GENERATION SATURATED BENZENE BIOISOSTERES

Despite a few exceptions, the BCP scaffold primarily provides access to *para*-disubstituted benzene mimics. Recently, bicyclo[2.1.1]hexane and 2-oxabicyclo[2.1.1]hexane cores were developed as *ortho*- and *meta*-disubstituted benzene bioisosteres, respectively (**Figure 3**).[4,5] Notably, molecules containing the 2-oxabicyclo[2.1.1]hexane core also demonstrated a dramatic improvement in aqueous solubility relative to those containing the BCP scaffold.

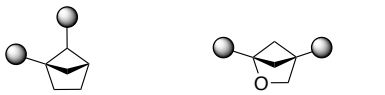

Figure 3. Saturated *ortho*- and *meta*-disubstituted benzene bioisosteres

CUBANES

Cubane was only recently validated as a benzene bioisostere,[6] but it has noteworthy potential for accessing novel chemical space through substitution of its vertices lying above and below the plane of a phenyl ring. Recent advances in process chemistry have facilitated pilot-scale production and commercial availability of dimethyl 1,4-cubanedicarboxylate,[7] a precursor to numerous functionalized building blocks for the replacement of *para*-disubstituted benzene rings. Although preliminary methods for installing variable substitution patterns exist, there is an unmet need for general cubane vertex differentiation and functionalization strategies.

CARBORANES

Carboranes are carbon-boron molecular clusters that can act as three-dimensional benzene analogues (**Figure 4**). The volume of a carborane cage approximates the rotational volume of a benzene ring.[8] Additionally, carboranes share common features with benzene rings including aromaticity and high thermal and chemical stability.[8] Unlike the previously discussed bioisosteres, carboranes are inexpensive and commercially available in bulk. The orthogonal reactivity of carborane C-H and B-H bonds enables differential functionalization of the C-H vertices, but it is notably more difficult to selectively functionalize a singular B-H vertex among 10 similar B-H bonds. Recent advances in methods for regioselective functionalization, including B-H borylation,[8] are contributing to the use of carborane systems as emerging benzene bioisosteres.

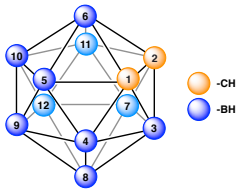

Figure 4. *o*-Carborane numbering system

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