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Synthesis of *meta*-Substituted Arene Bioisosteres from [3.1.1]propellane
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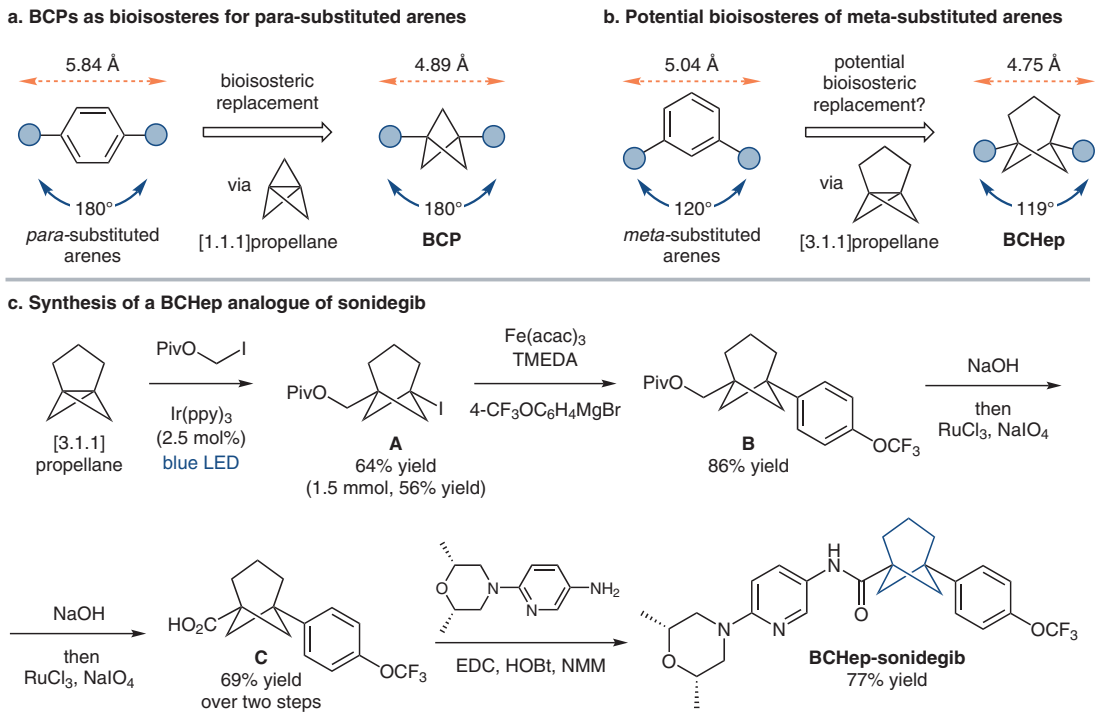
Bicycloheptanes as *meta*-Substituted Arene Bioisosteres



Significance: Over the past decade, bicyclopentanes (BCPs) have emerged as arene bioisosters in medicinal chemistry. However, BCPs are limited to serve as bioisosteric replacements for unsubstituted and *para*-substituted arenes. To address this, Anderson and co-workers have developed a synthesis of a variety of bicycloheptanes (BCHeps) and have demonstrated their value as bioisosteric replacements for *meta*-substituted arenes.

Comment: Anderson and co-workers have demonstrated ring-opening difunctionalization of [3.1.1]propellane via several reaction conditions including photoredox- and metallaphotoredox-catalyzed cross-couplings. Reaction products such as intermediate **A** could be further functionalized through Kumada coupling (shown) or lithium–halogen exchange/electrophile capture. The synthesis of BCHep analogues of sonidegib (**BCHep-sonidegib**) and URB597 (not shown) were exemplified. In line with the outlined hypothesis, the BCHep analogues of these active pharmaceutical ingredients (APIs) were shown to provide similar vector projections and physicochemical properties with improvements in in vitro clearance and membrane permeability in comparison to the parent *meta*-substituted arene APIs.

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