Aryne-Mediated Amination of Aryl Halides Enabled by Solvent-Separated Ion Pairs

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Arynes are versatile synthetic intermediates in organic chemistry. Traditionally, arynes have been formed via methods including dehalogenative elimination and desilylative elimination (as with the Kobayashi aryne precursor).[1,2] In this work, we present a novel approach to dehalogenative elimination that generates arynes and hetero-arynes under mild conditions and in a cost-effective manner. This method enables aryne formation from commercially available aryl halides in a single step, without the use of toxic additives.

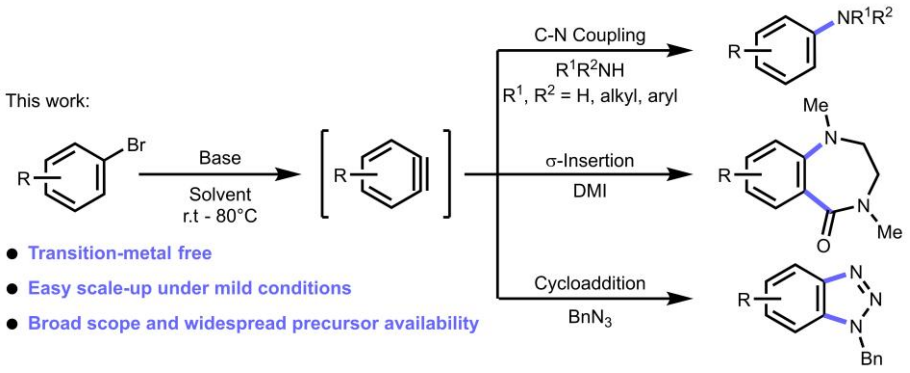

Figure 1. Novel method for aryne formation enables amination, σ-insertion, and cycloaddition reactions under mild conditions.

We showcase the utility of arynes as intermediates for C-N coupling between aryl halides and amines. Furthermore, aryne-based σ-insertion and cycloaddition reactions also proved fruitful (Figure 1). The scope of our C-N couplings encompasses a wide array of hereo-aryl halides as aryne precursors (including several previously inaccessible arynes), and aliphatic and heterocyclic amines. Interestingly, in our methodology, the aryl halide intermediates of some drug-like molecules were shown to form unconventional regioisomers. Computational studies provided a framework to understand experimentally observed patterns of selectivity. The selectivity of aryne formation (in cases where two arynes can form from the same aryl halide) and product regioselectivity can both be accurately predicted. Thus, we achieved regiocontrol over C-N coupling products solely based on the choice of aryl halide. Due to its simplicity, low cost, and high-boiling solvent, this methodology is especially valuable for High-Throughput Experimentation (HTE), process chemistry, and other applications.

1 N. Kim, M. Choi, S.-E. Suh, D. M. Chenoweth, *Chemical Reviews* **2024**, *124(20)*, 11435.

2 Y. Himeshima, T. Sonda, H. Kobayashi, *Chemical Letters* **1983**, *12(8)*, 1211.