RECENT ADVANCES OF THE HEXADEHYDRO-DIELS-ALDER REACTION IN BENZYNE CHEMISTRY

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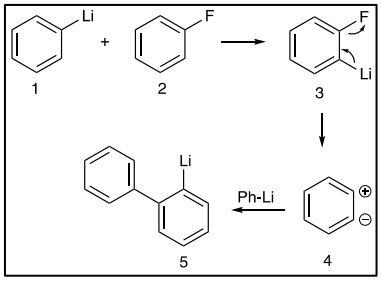
INTRODUCTION

Benzynes are highly reactive and strained molecules that owe their reactivity to a non-traditional cyclic triple bond that results from the weak overlap of sp^2 orbitals. The first experimental evidence of the short-lived benzyne molecule was reported in 1940 by Wittig when observing how the molecules' ionization influenced the reactivity[1] (Scheme 1). Wittig witnessed the generation of an *o*-lithiated biphenyl intermediate **5** rather than the expected biphenyl when ionizing fluorobenzene. He then provided a zwitterionic structure **4** as the rationale for the observation. This reactive species was further examined in 1953 when Roberts and coworkers aminated ^{14}C labeled chlorobenzene and observed equal amounts of amination at both the C(1) and the C(2) position.[2] This data supports a reactive symmetrical intermediate such as benzyne. Various methods have been employed to generate this valuable intermediate, notably the Hexadehydro-Diels-Alder (HDDA) reaction has become invaluable to this field.

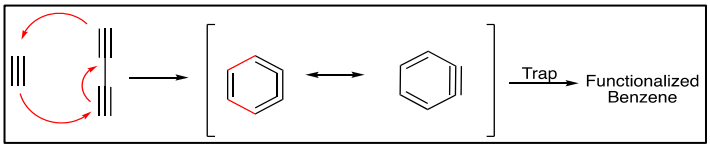
Scheme 1. First Experimental Evidence for Benzyne.



HEXADEHYDRO-DIELS-ALDER REACTION AND RECENT ADVANCEMENTS

The HDDA reaction is a cyclization between an alkyne and diyne that results in the generation of benzyne, which is then functionalized by a reagent (Scheme 2**).** The first reports of HDDA were disclosed in 1997[3-4] independently by both Ueda and Johnson. In 2012, Hoye and coworkers further advanced this field by demonstrating the compatibility of the reaction conditions with various substrates, including base-sensitive functional groups that are not suitable with other benzyne-generating methods. In recent years, many variations of this method have been developed.[5]

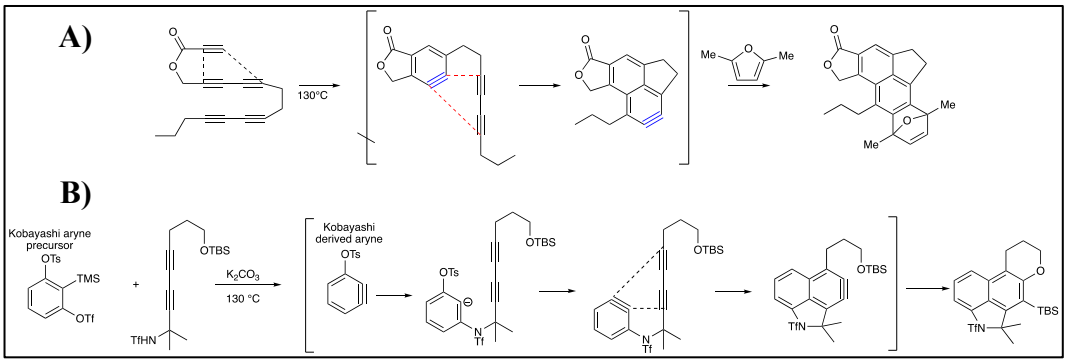
Scheme 2. Mechanism of the HDDA Reaction



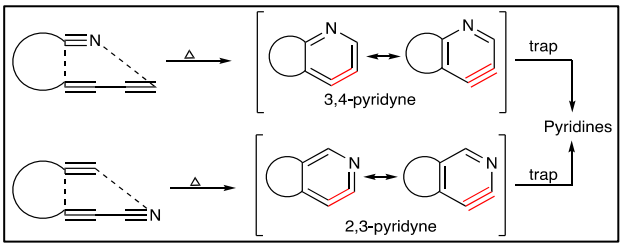
The first strategy development arose in 2017 by Hoye and coworkers as the photochemical HDDA reaction.[6] This variant involves using UV irradiation rather than heat to provide the necessary energy for the cyclization to occur. This variant allows for the cyclization to be performed at or below ambient temperature. However, the substrate scope is quite limited to only tetraynes that contain two aryl substituents on the termini of the diynes. Moreover, both electron-withdrawing and electron-donating substituents on the aryl rings are compatible with this system. Interestingly, HDDA reactions performed the on unsymmetrical tetraynes under thermal and photochemical conditions provide the same ratio of

isomers regardless of activation method. In 2018, Hoye and coworkers investigated and coined the domino HDDA reaction using a pentayne substrate[7] (Scheme 3A). This advancement involves an intramolecular cyclization. The newly formed aryne is now the diynophile for the next diyne allowing for successive cyclizations that ultimately result in structurally complex molecules. Additionally, the domino HDDA reaction can also be implemented in various settings. For example, Li and coworkers use a Kobayashi aryne precursor to generate the first benzyne intermediate.[8] This intermediate then performs an S_N2 displacement with a triflamide appended to a diyne, which allows for the subsequent HDDA reaction and trapping with a tethered TBS ether (Scheme 3B). Finally, the most recent strategy advance is the aza-HDDA reaction, developed in 2019;[9] this development replaces a terminal alkyne of the triyne substrate with a nitrile and, upon cyclization, yields a pyridyne intermediate (Scheme 4). Subsequent trapping allows for the generation of highly functionalized pyridine molecules that are valuable motifs in medicinal chemistry. However, limitations exist, such as slow reaction rate, high temperatures, and difficulties in substrate synthesis.

Scheme 3. (A) Domino-HDDA Involving a Naphthyne Intermediate (B) Combined Kobayashi and HDDA Domino Reaction



Scheme 4. Aza-HDDA General Strategy



As new strategies have been developed in recent years, the HDDA reaction has become more versatile and applicable in various settings. It is expected that this field will continue to grow as its full potential is explored.

REFERENCES

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