

RECENT DEVELOPMENTS IN ARYNE CHEMISTRY

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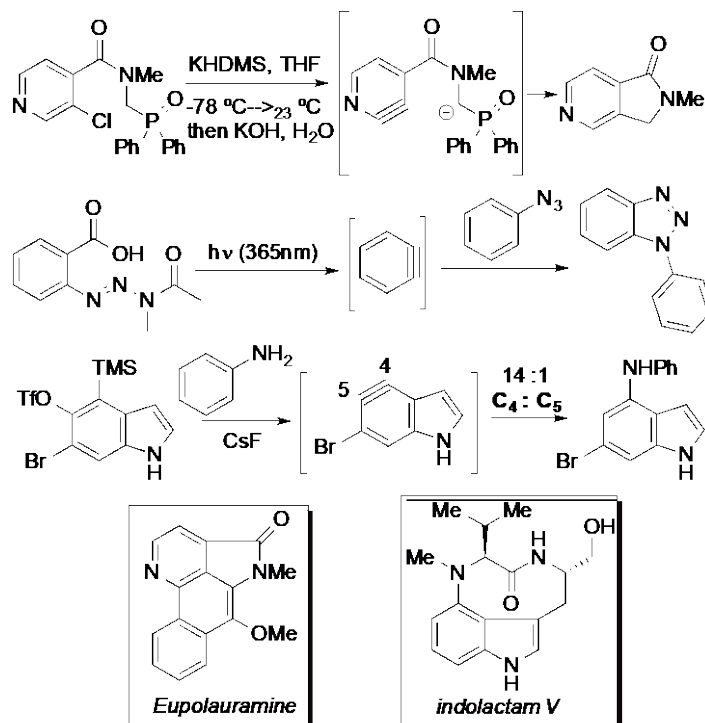
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INTRODUCTION

J. D. Roberts first introduced the term of “benzyne” in 1953¹ to explain the unexpected reaction between an aryl chloride and an alkyl metal amide. Single crystal X-ray structures of η^2 -bound-metal-benzyne complexes were obtained in the late 1970s,² providing direct proof for the proposed triple bond structure. Due to the significantly lowered LUMO energy,³ arynes --including benzyne and its heterocyclic analogues --are extremely electrophilic and reactive, which lead to applications in complex molecules synthesis. Despite the long history, new concepts and reactivity have been developed in the last decade.

ARYNES FROM ELIMINATION AND APPLICATIONS IN SYNTHESIS

Traditionally, arynes are generated *in situ* because of their high reactivity by elimination of ortho-components on a pre-formed aromatic ring. Strong bases and metals are used to generate arynes from aryl halides species.⁴ Milder conditions, such as fluoride promoted desilylation⁵ and entropy driven eliminations,⁶ are also widely applied in aryne generation (Scheme 1).

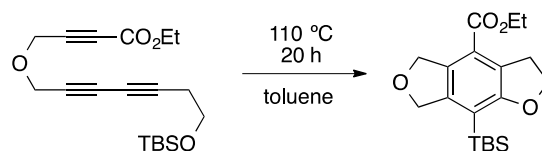


Scheme 1. Aryne from Elimination and Applications

Pericyclic reactions and nucleophilic additions are widely applied in aryne chemistry. In Couture’s total synthesis of eupolauramine,⁴ the 2,3-pyridyne intermediate is generated by basic elimination of pyridyl chloride followed by an intramolecular carbanion nucleophilic attack to give a single product. Photochemically generated symmetrical benzyne intermediates can rapidly undergo a [3+2]-cycloaddition with azides.⁶ In Garg’s total synthesis of indolactam V, the regioselectivity for intermolecular nucleophilic attack on the asymmetrical indolyne intermediate generated by fluoride-induced elimination is studied by a predictive calculation model and the calculated selectivity is confirmed experimentally (Scheme 1).⁵

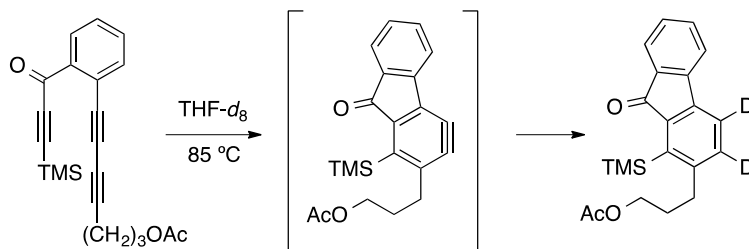
ARYNES FROM CYCLOADDITION AND TRAPPING STRATEGIES

In 2012, Hoye and coworkers reported a hexadehydro-Diels-Alder (HDDA) reaction to generate a benzyne intermediate thermally (Scheme 2).⁷ The fundamentally new way to produce a benzyne intermediate with high structural complexity is not only applicable to traditional aryne chemistry reactivities, but also provides opportunities for exploring new intrinsic reactivities due to the external reagent free and by-product free reaction conditions.



Scheme 2. Initial Report of Hexadehydro-Diels-Alder Reaction

Following the initial report, kinetic studies and DFT calculations have been done to probe the mechanism of silyl ether trapping followed by the HDDA reaction.⁸ Other than nucleophilic additions and pericyclic reactions that are prevalent in traditional aryne chemistry, new trapping modes are being explored to achieve new transformations. Alkane desaturation,⁹ aromatic ene reaction¹⁰ and silver-catalyzed alkane C—H insertion¹¹ are successful trapping modes for HDDA generated benzyne intermediates (Scheme 3). The ability to form an aromatic ring from a linear precursor and the development of new trapping strategies reveals the great potential for HDDA reactions to be applied in total synthesis.



Scheme 3. Double Hydrogen Transfer Followed by HDDA Reaction

As new reaction modes and applications are being developed in the resurgence of aryne chemistry within the last decade, it is reasonable to expect that this field will be further explored and more widely used in complex molecule synthesis.

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