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ARYNE-MEDIATED SYNTHESIS OF HETEROCYCLES

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Dedicated to Professor Ekkehardt Winterfeldt on the occasion of his 75th birthday

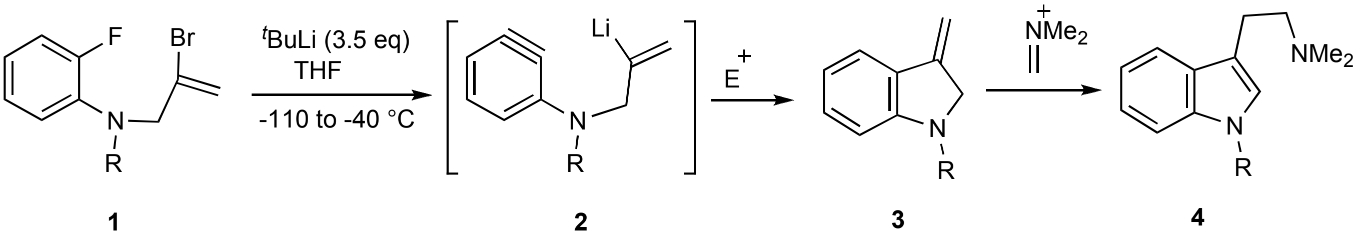
Abstract – Arynes have been used as intermediates in the synthesis of heterocycles with a variety of heteroatoms (O, N, S, Ni, Pd) and rings sizes (from 5 to 8-membered).

In 2003 a review on the use of arynes in organic synthesis was published by Santelli and Pellisier covering the literature until the beginning of this century.[1] Since then a significant number of publications dealing with optimized or new procedures for the aryne-mediated synthesis of heterocycles have appeared. The aim of this review is to highlight those that are more relevant from a conceptual point of view or more useful for synthetic purposes.

Synthesis of 5-membered rings: indoles, carbazoles, dibenzofurans and dibenzothiophenes

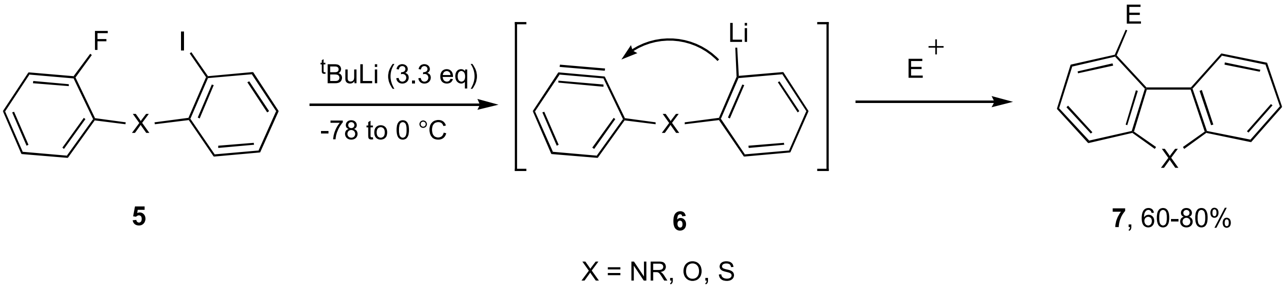
Intramolecular nucleophilic attack on an aryne continues to be the most useful procedure for the aryne-mediated synthesis of heterocycles. It is particularly advantageous if the aryne and the nucleophile can be generated at the same time, as shown in the following examples.

Treatment of **1** with 3.5 eq. of t-BuLi causes lithium-bromine exchange and HF elimination to generate aryne intermediate **2**, which undergoes an intramolecular nucleophilic attack to afford, after protonation, compound **3**. Use of other electrophiles instead of protons allows easy access to a broad range of 4-substituted indole derivatives. The reaction of **3** with Eschenmoser's salt affords tryptamine **4** (Scheme 1).[2]



Scheme 1

In a similar way, compounds **5**, undergo the cyclization to an aryl carbanion **6**, which was reacted with electrophiles to yield carbazoles, dibenzofurans and dibenzothiophenes **7** (Scheme 2).[3]

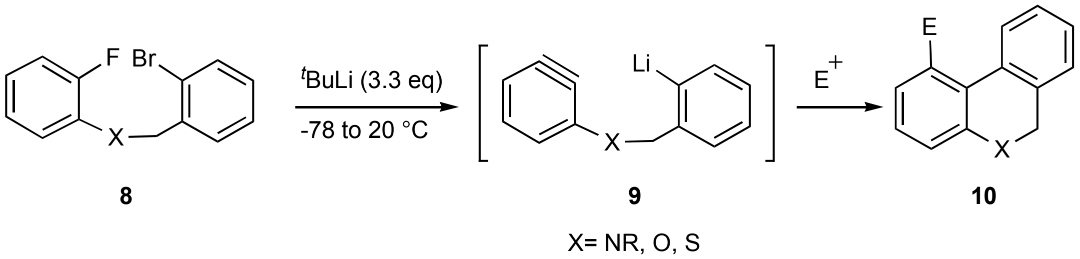


Scheme 2

Synthesis of 6 to 8-membered rings containing N, O or S atoms

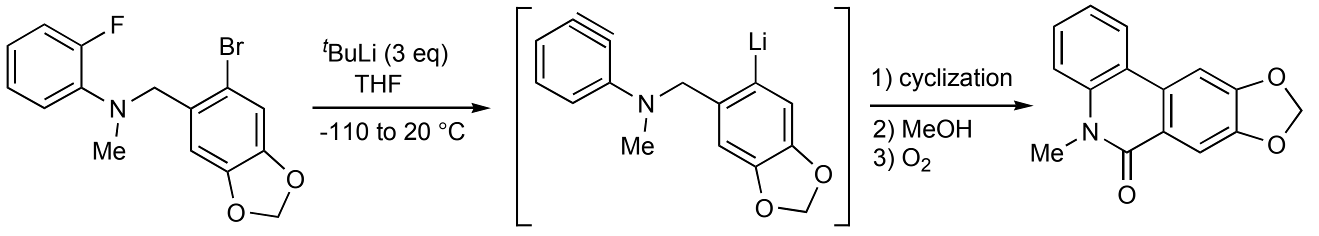
The same methodology has been used for the preparation of 6-membered heterocycles, with moderate to good yields, as shown in Schemes 3 and 4.

The use of amines, ethers or thioethers **8** as starting materials affords quinolines (or isoquinolines if the left-hand aromatic ring is considered), pyrans or thiopyrans **10**, respectively (Scheme 3).[4]



Scheme 3

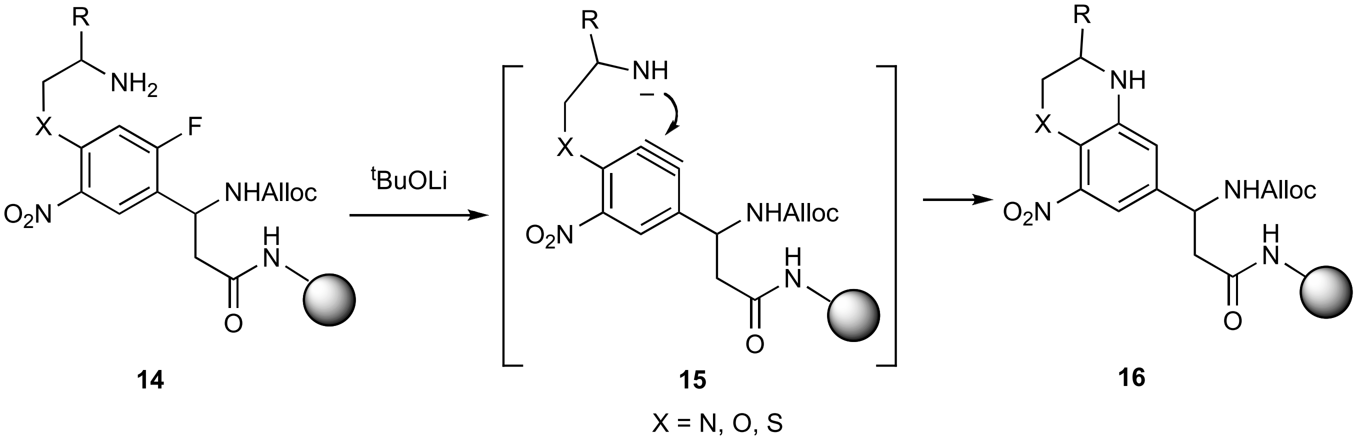
The synthesis of isoquinoline alkaloid *N*-methylcrinasiadine (**13**) from amine **11** is shown in Scheme 4. The key step, the cyclization of **12** by intramolecular nucleophilic attack of the lithium carbanion on the aryne, is followed by air oxidation to give isoquinolone **13**.[4]



11 **12** **13,** *N*-methylcrinasiadine (65%)

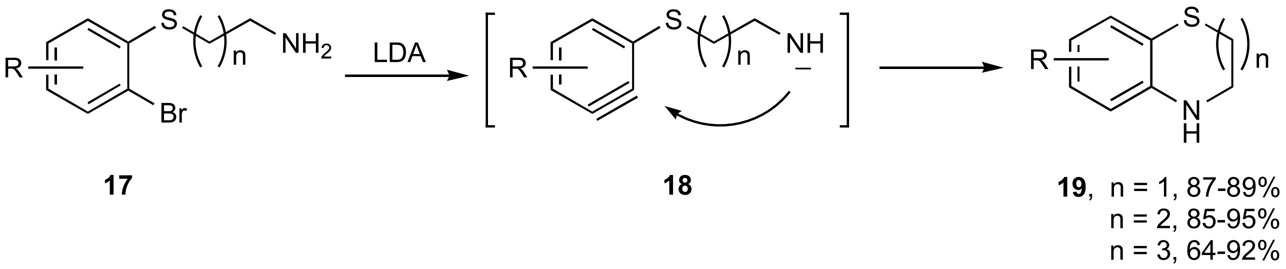
Scheme 4

A related procedure in which ^{t}BuOLi is used to generate aryne and the activation of the nucleophile from **14** has been reported. In this case a diazine, an oxazine or a thiazine **16** were obtained by the intramolecular nucleophilic attack of an amide anion on the aryne **15**. A remarkable feature of this solid-phase synthesis is its compatibility with the presence of two additional N-H groups in the molecule (Scheme 5).[5]



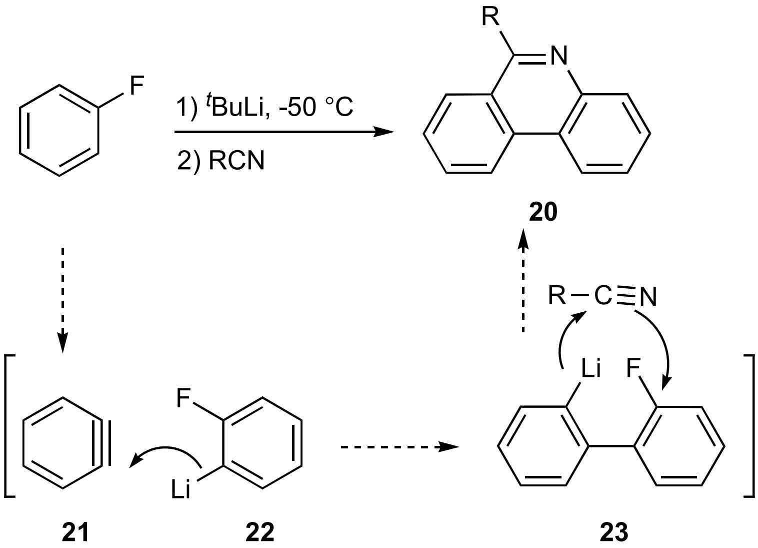
Scheme 5

Even medium-sized rings can be prepared in good yields by these nucleophillic cyclizations, as shown in Scheme 6. Treatment of **17** with LDA afforded intermediate **18**, which undergoes intramolecular nucleophilic attack to give **19**.[6]



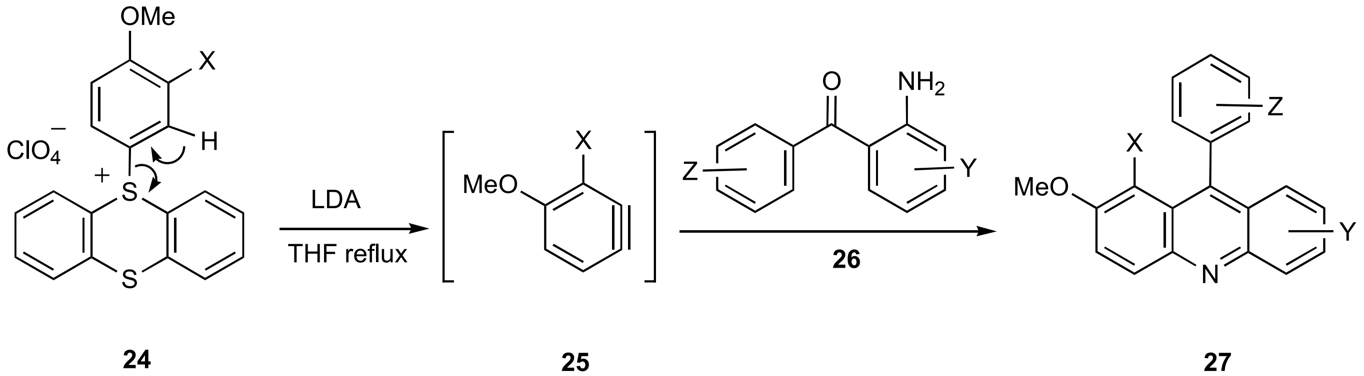
Scheme 6

A one-pot procedure for the synthesis of 6-substituted phenanthridines **20** has been reported and involves the reaction of three components- benzyne (**21**) and o-fluorophenyl lithium (**22**), both formed from the reaction of fluorobenzene with *t*-BuLi, and a nitrile. This procedure gives modest yields of phenanthridines **20** and is limited in scope (Scheme 7).[7]



Scheme 7

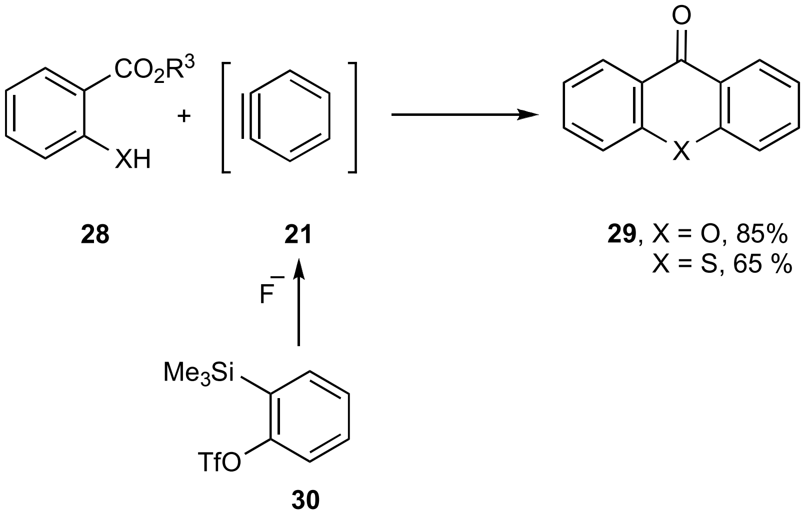
Acridines **27** have been prepared by nucleophilic additions of amine **26** to an aryne **25**, followed by intramolecular trapping of the resulting carbanion with a ketone. Aryne **25** was generated by a very unusual method involving the treatment of a thianthreniumyl perchlorate **24** with LDA (Scheme 8).[8]



Scheme 8

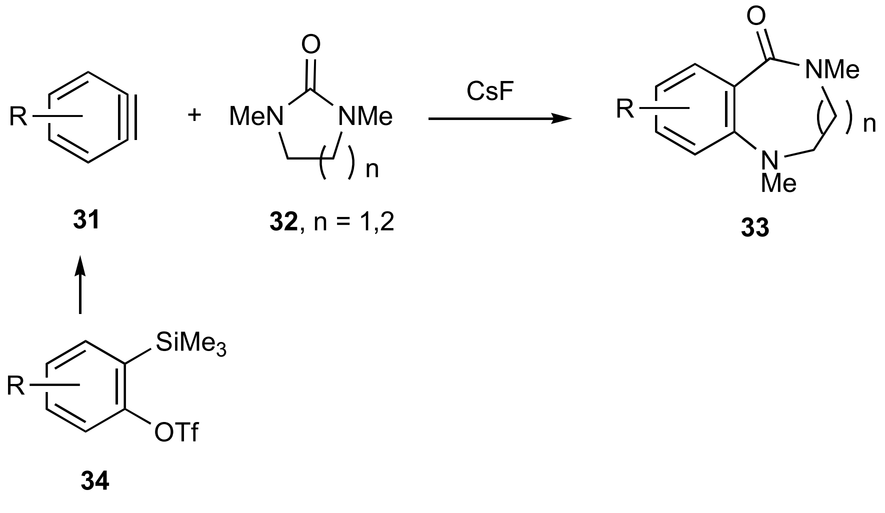
All of these synthetic methodologies have in common the use of strong bases, such as t-BuLi or LDA, which are not compatible with many common functional groups. The development of a new, mild procedure for the generation of arynes, based on the fluoride-induced decomposition of *o*-(trimethylsilyl)aryltriflates has contributed to overcoming this limitation.[9,10] Some examples of the synthesis of heterocycles using this method of aryne generation are described below.

The same strategy reported above for the synthesis of acridines has been used for the preparation of xanthones and thioxanthones **29**, but in this case benzyne (**21**) was generated from *o*-(trimethylsilyl)aryltriflate (**30**, Scheme 9).[11]



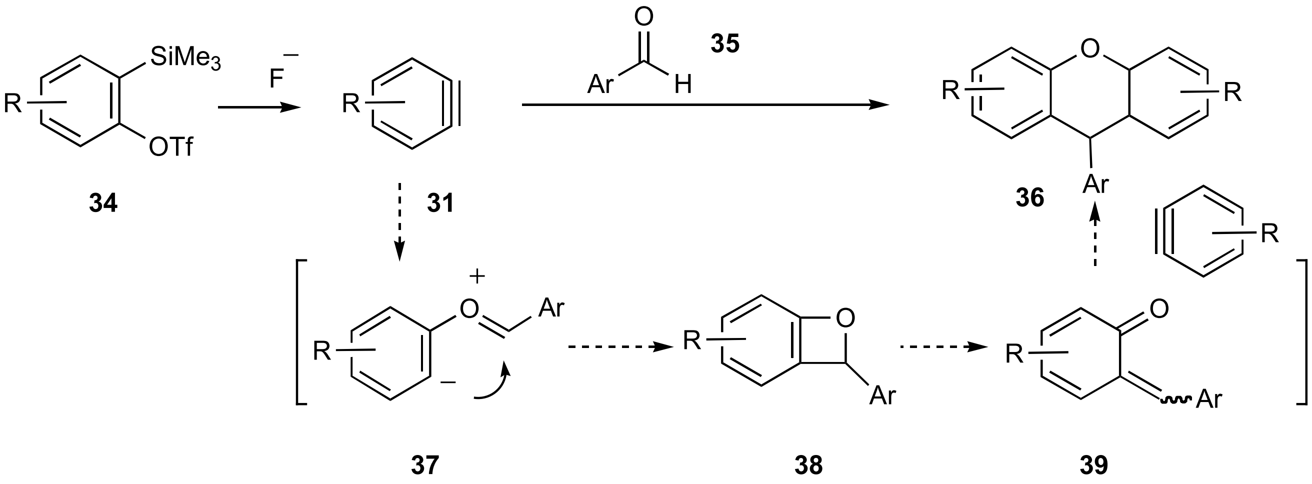
Scheme 9

Synthetic procedures based on the formal insertion of arynes into sigma bonds have been developed. For example, benzodiazepines **33** (n = 1) and benzodiazonines **33** (n = 2) have been obtained from the insertion of arynes **31** into the sigma C-N bond of a cyclic urea **32** (Scheme 10).[12]



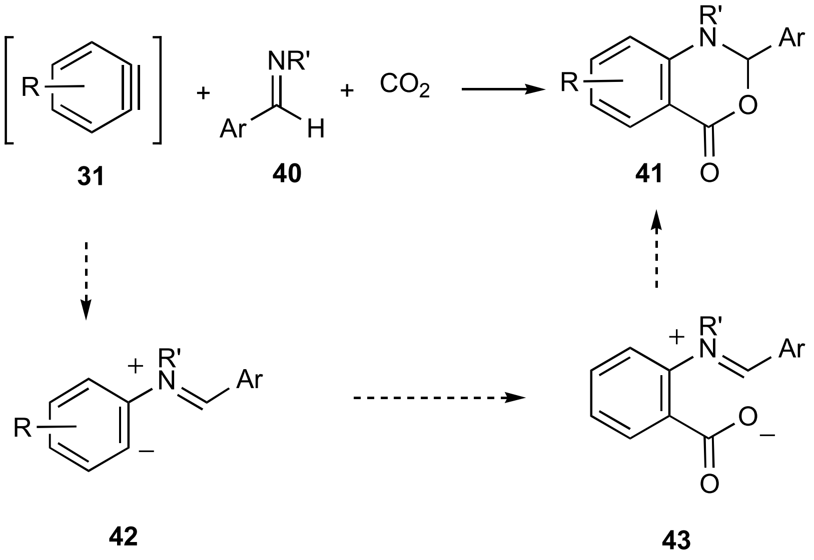
Scheme 10

A formal insertion of arynes **31** into a C=O bond of an aldehyde **35** has been used for the synthesis of pyrans **36**. The proposed mechanism involves the formation of zwitterion **37**, cyclization to oxetane **38**, electrocyclic opening to **39** and Diels-Alder reaction with aryne **31** (Scheme 11).[13]



Scheme 11

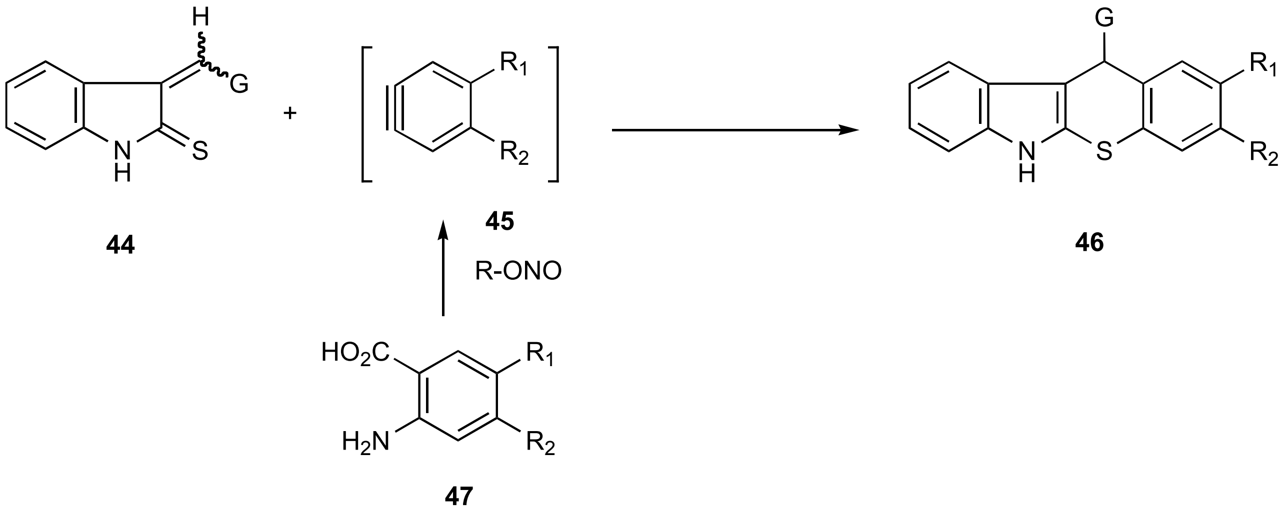
Its worth noting that replacing the aldehyde **35** by an imine **40** and adding carbon dioxide completely changes the result and affords benzoxazinone **41**. Presumably zwitterion **42** is formed, but instead of cyclization a nucleophillic addition to CO_2 takes place to form **43**, which undergoes cyclization to **41** (Scheme 12).[14]



Scheme 12

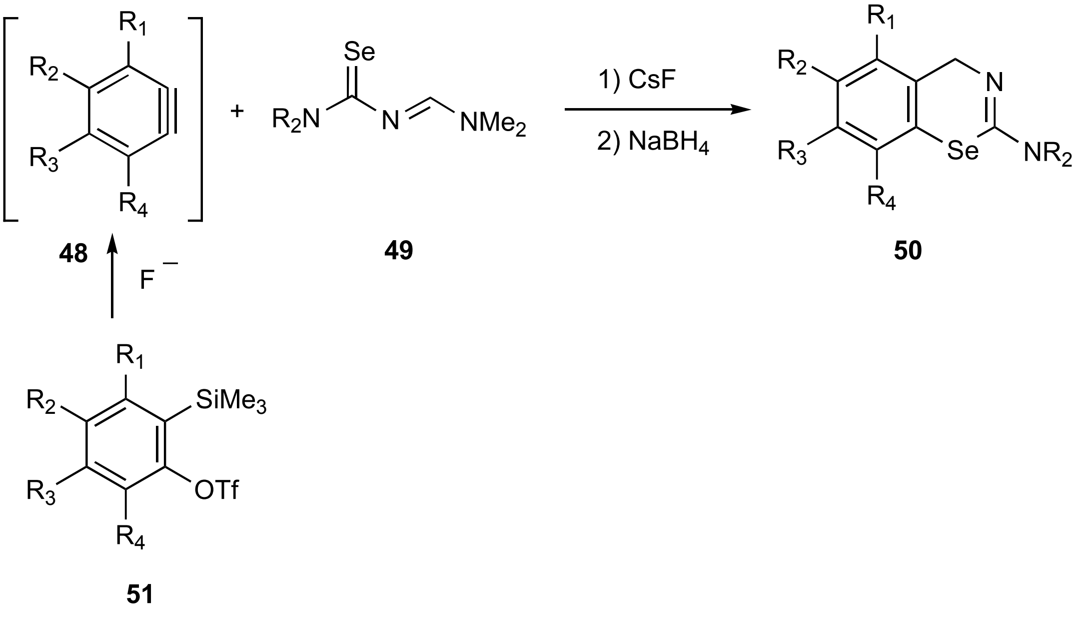
Several 6-membered heterocycles have been prepared by formal Diels-Alder reactions between arynes and suitable dienes. Classical methods of aryne generation, such as the diazotization of anthranilic acids, and those based on fluoride-induced eliminations have both been used for this purpose.

Indol derivatives **46** have been prepared by cycloaddition of dienes **44** to arynes **45**, generated from diazotization of anthranilic acids **47** (Scheme 13).[15]



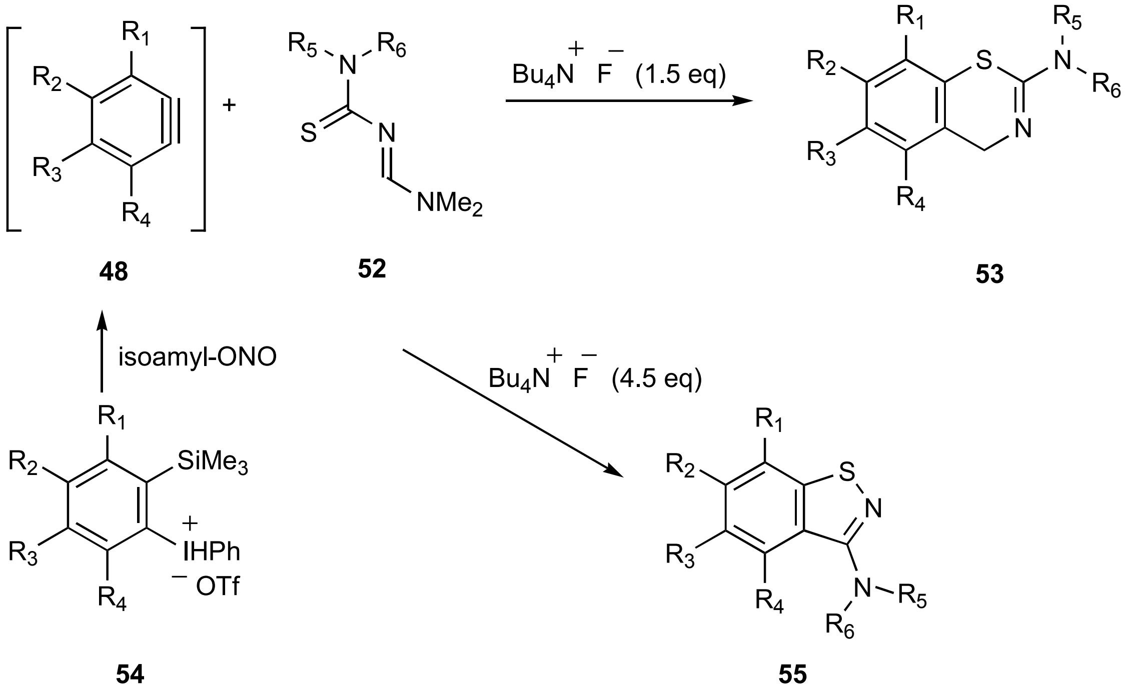
Scheme 13

A similar Diels-Alder reaction between arynes **48**, generated from **51** by Kobayashi's method, and seleno azadienes **49** afforded 4H-1,3-benzoselenazines **50** (Scheme 14).[16]



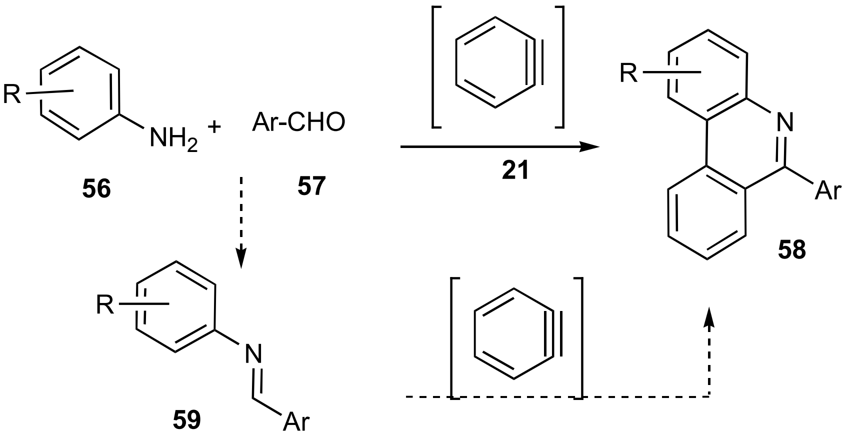
Scheme 14

The use of iodonium salt **54** as an aryne precursor led to the same results as above if 1.5 eq. of fluoride were used. Unexpectedly, the use of 4.5 eq of fluoride led to 3-substituted 1,2-benzisothiazoles (Scheme 15).[17]



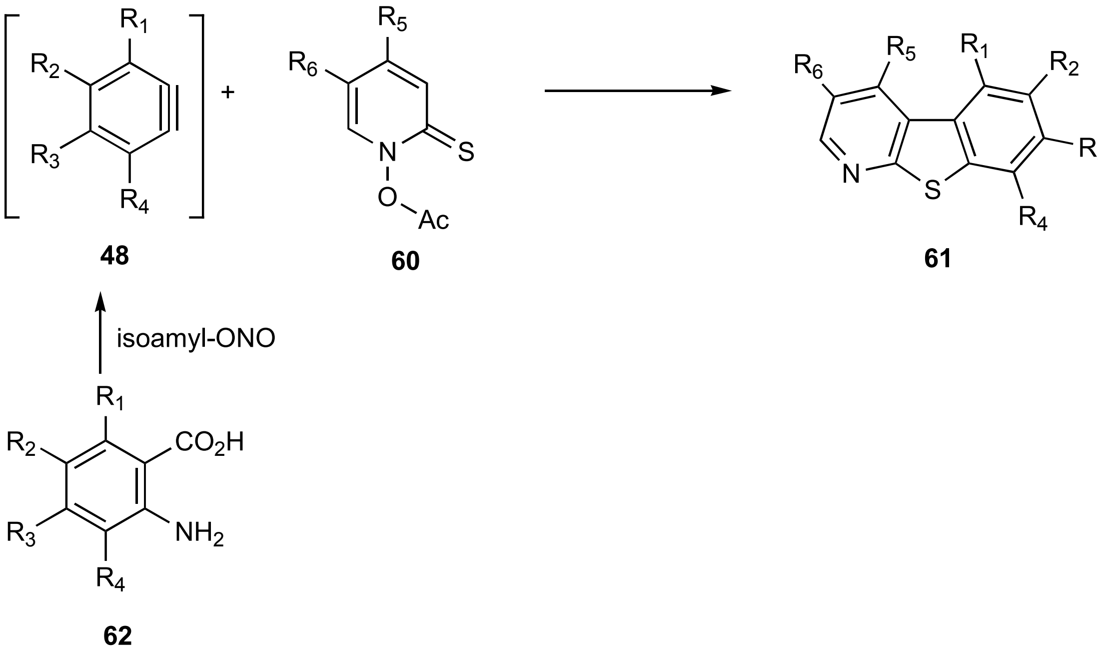
Scheme 15

Phenanthridines **58** have been obtained by Diels-Alder reaction of benzyne **21** with azadienes **59** generated in situ from anilines **56** and aldehydes **57** (Scheme 16).[18]



Scheme 16

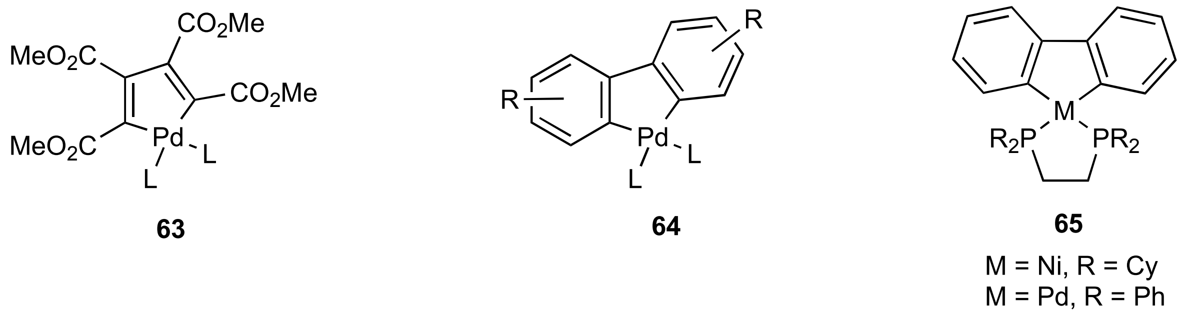
An SET mechanism has been proposed for the formation of heterocycles **61** by treatment of Barton esters **60** with arynes **48**, in this case generated by treatment of anthranilic acids **62** with isoamyl nitrite (Scheme 17).[19]



Scheme 17

Metallacycles

The discovery of the palladium-catalyzed cyclotrimerization of arynes proved that Kobayashi's method for aryne generation may be compatible with transition metal catalysis, opening new synthetic perspectives.[20-23] Metallacycles such as **63** and **64** have been proposed as intermediates in the catalytic cycle but have not been isolated.

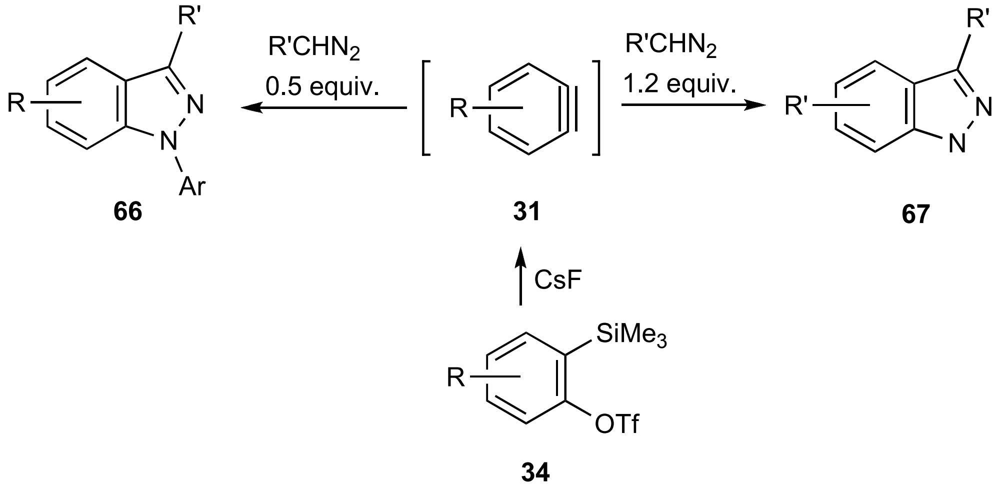


Scheme 18

However, it should be remarked that the use of bidentate ligands and controlled conditions allowed the characterization of metallacycles **65**.[24,25]

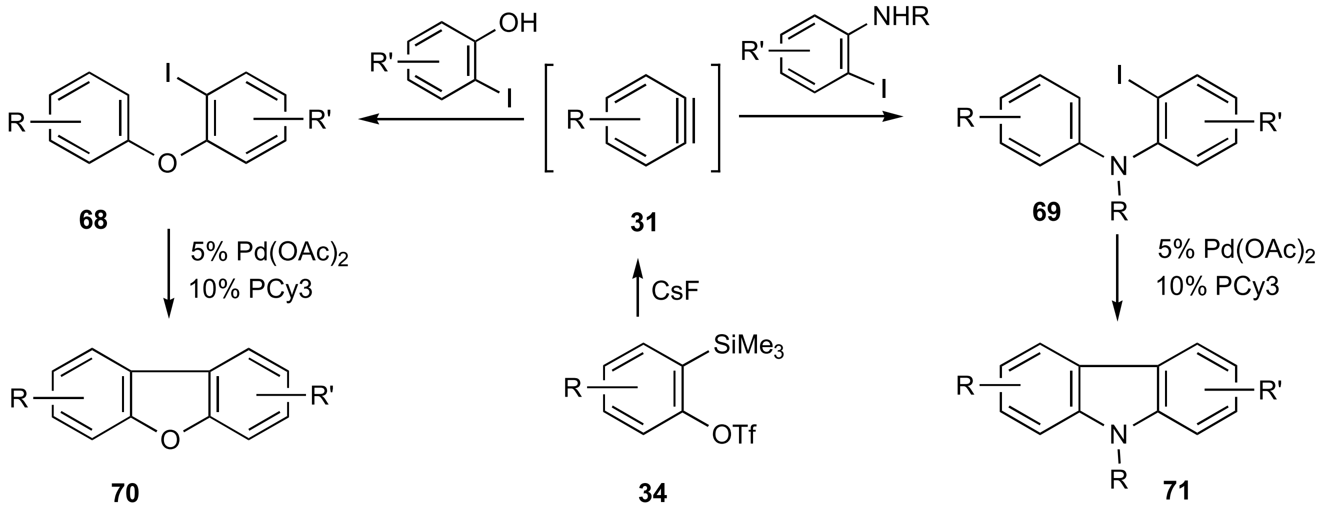
ADDENDA

During the preparation of this review new syntheses of 1*H*-Indazoles, carbazoles and dibenzofurans have been published. 1*H*-Indazoles **66** or **67** were obtained by 1,3-dipolar cycloaddition of arynes with diazomethane derivatives. (Scheme 19).[26]



Scheme 19

Dibenzofurans **70** and carbazoles **71** have been prepared by a two-step sequence involving nucleophilic addition of a *o*-iodophenol or a *o*-iodoaniline to an aryne, to gave **68** or **69**, respectively, followed by palladium-catalyzed cyclization (Scheme 20).[27]



Scheme 20

ACKNOWLEDGEMENTS

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Enrique Guitián received his PhD degree from the University of Santiago de Compostela (Spain) working in the field of natural product synthesis in the group of Prof. L. Castedo. After a postdoctoral stay in the University of Hannover (Prof. Winterfeldt) in 1982-83, he returned to Santiago where he was appointed to a lectureship in 1985. He became Professor of the same university in 1992. His research interests are the synthesis of natural product of biological interest, the chemistry of arynes, with particular emphasis on its pericyclic and transition metal-catalyzed reactions, and the synthesis of functional aromatic compounds.