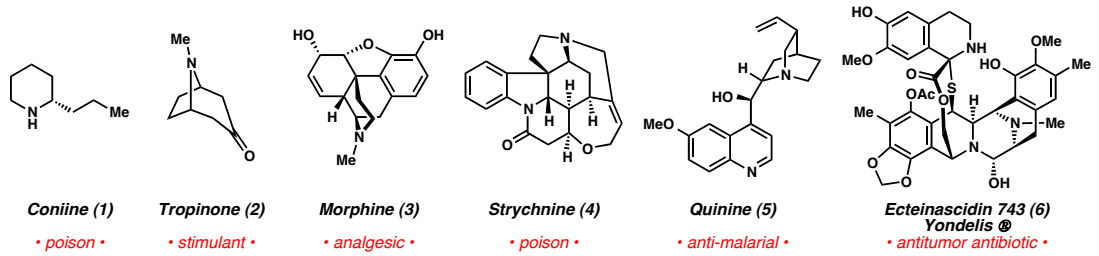
CHAPTER 1

Aryne Annulations in the Synthesis of Nitrogen Heterocycles

1.1 INTRODUCTION

As organic chemistry nears the eve of its third century, the fundamental concerns of a modern synthetic chemist remain startlingly similar to those facing Friedrich Wöhler in the 1820s.[1] Namely, planning a series of transformations in an order that imparts efficiency, selectivity, and reactivity over the course of a total synthesis. Countless innovations in instrumentation and methodology have helped the synthetic community better address those criteria through improved understanding of specific transformations. Application of these developments to chemical synthesis has created both tactical breakthroughs[2] and incremental improvements[3] on existing methodologies[4] to construct all manner of structural motifs. With new target molecules reported every day, the developmental challenges confronting the community are not diminishing; they are being brought into sharper focus.[5,6] Historically, perhaps no class of molecules has inspired synthetic creativity or a sense of its futility as deeply as the alkaloids (Figure 1.1).[7]

Figure 1.1. *Alkaloids of classical and contemporary significance*



This nitrogen-containing family of more than 12,000 natural products includes molecules of a breathtaking expanse of structural diversity.[8] Moreover, their exceptionally broad range of biological activity has woven them so tightly with humanity that this group includes compounds that have been used for the breadth of human history. Their impact on the synthetic community has been enormous. From the first total synthesis of the poison coniine (**1**) by Ladenburg[9] in 1886 to the current clinical trials for ecteinascidin-743 (**6**) as a potent anticancer agent,[10] chemists have conceived of persistently inventive ways to synthesize these target molecules to maximize efficiency, enhance selectivity, and moderate reactivity. In the following chapter, we will briefly overview some of these strategies before detailing the synthesis of heterocycles using aryne intermediates. Because the synthetic efforts in pursuit of various members of this family have been extensively detailed elsewhere, our focus will be on benzannulated, polycyclic nitrogen-containing heterocycles.[7]

1.2 ALKALOIDS AND THE SYNTHESIS OF NITROGEN HETEROCYCLES

The only defining structural feature of any alkaloid is a nitrogen atom set in a particular carbon framework. Many of the alkaloids contain complex polycyclic core structures that are in large part responsible for their potent and highly specific biological

activity. Consequently, any approach to these molecules will inevitably encounter the challenge of nitrogen heterocycle synthesis. Despite of the structural diversity of alkaloids, the fundamental structural components found in these molecules are limited in variety. These motifs can be broadly divided into monocyclic *N*-heterocycles (Figure 1.2) and benzannulated bicyclic systems (Figure 1.3).

Figure 1.2. *Simple, monocyclic nitrogen-containing heterocyclic structures*

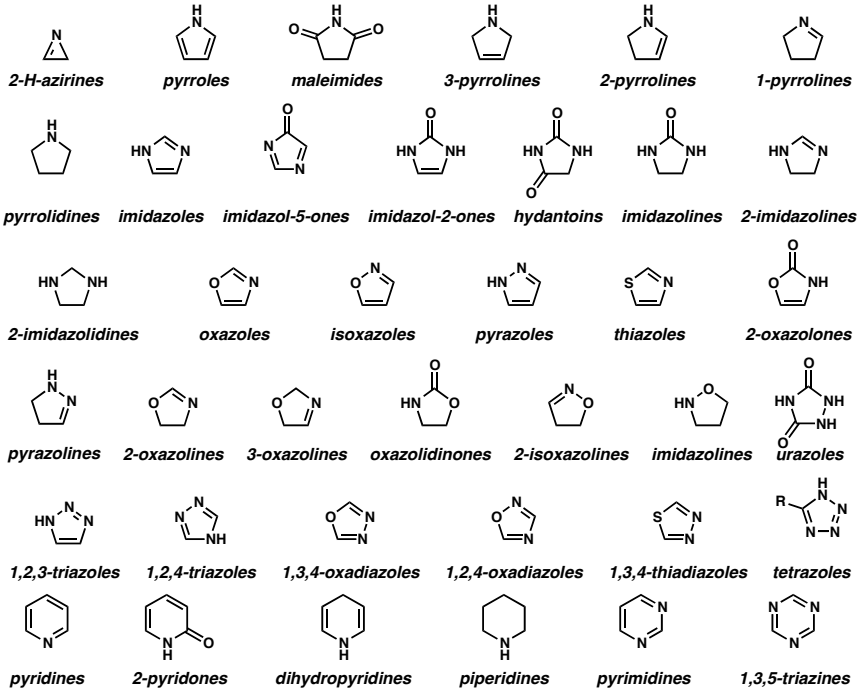
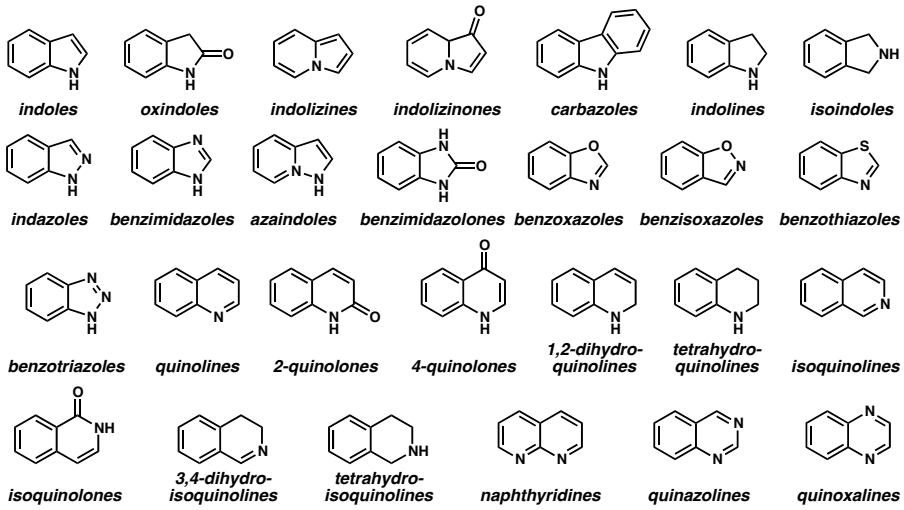


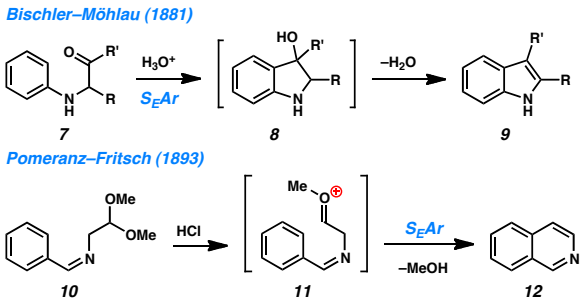
Figure 1.3. *Fundamental benzannulated nitrogen-containing heterocycles*



The presence of an arene in an aromatic, bicyclic heterocycle severely limits the synthetic approaches available to these molecules. While methods do exist to construct an aryl ring directly from non-aromatic precursors on a heterocycle,[11,12] the most direct and efficient approaches to these structures rely upon formation of the nitrogen-bearing ring at a late stage. Thus, these benzannulated heterocycles require a detailed understanding of reactivity to properly activate aromatic systems for bond formation.

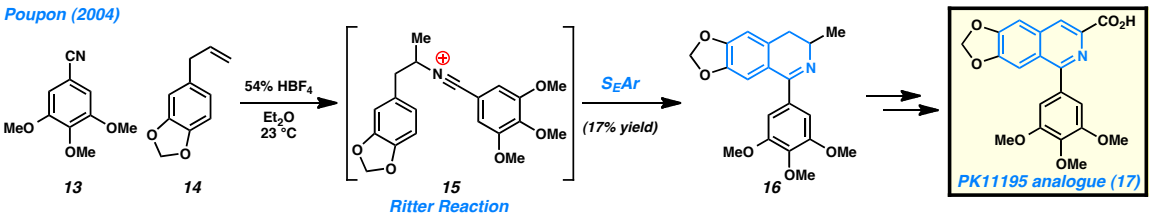
The most effective way to generate reactivity from an unactivated aryl ring is to promote the formation of a Lewis acidic intermediate capable of undergoing electrophilic aromatic substitution. Many approaches, including the classic Bischler–Möhlau[13] and Pictet–Spengler[14] reactions, have been developed to synthesize indoles and isoquinolines, respectively, through this reaction pathway (Scheme 1.1). In chapter 2, we present a detailed analysis of classical synthetic approaches to indoles and isoquinolines, so the summary that follows will include lesser-known approaches.

Scheme 1.1. *Benzannulated heterocycles by electrophilic aromatic substitution*



There are numerous variations upon this general theme, as used in Poupon's synthesis of PK11195 analogue **17** (Scheme 1.2).[15] The approach uses an interesting Ritter reaction where allyl arene **14** and aryl nitrile **13** are coupled to form an intermediate nitrilium species (**15**). The nitrilum is attacked by the arene, and cyclizes to furnish 3,4-dihydroisoquinoline **16**, which is subsequently advanced to the target molecule. The low yield of this process shows that even electron-rich aromatic systems do not provide predictable reactivity in such transformations.

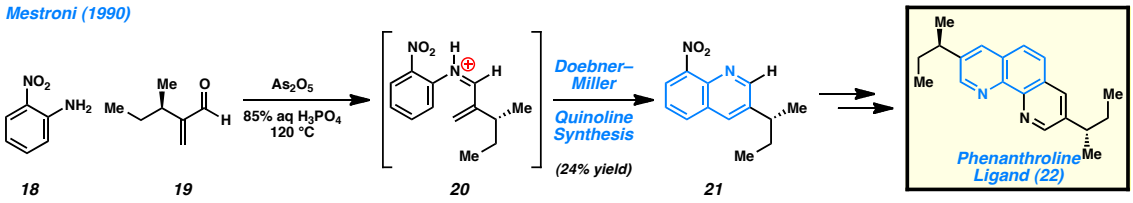
Scheme 1.2. *Ritter reaction in Poupon's synthesis of isoquinoline* ***17***



Mestroni was able to use a similar electrophilic aromatic substitution approach to generate phenanthroline ligands (**22**, Scheme 1.3).[16] By using a Doebner–Miller quinoline synthesis,[17] enal **19** and nitroaniline **18** are condensed to form α,β-unsaturated

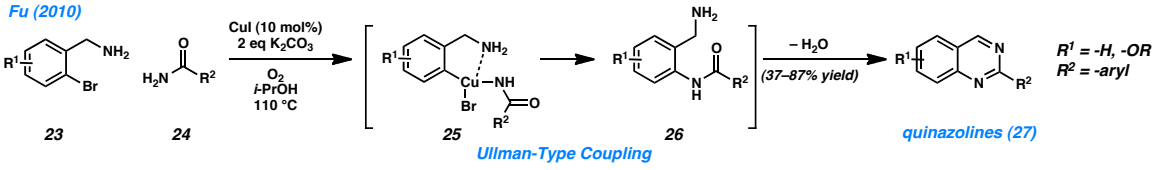
iminium **20**. Cyclization of this intermediate generates the quinoline (**21**), which is advanced to the chiral ligand (**22**).

Scheme 1.3. *Chiral phenanthroline ligands (**22**) through Doebner–Miller quinoline synthesis*



Not all approaches to heterocycle synthesis use electrophilic aromatic substitution to create bonds. More recently, there have been several reports that use transition metal catalysis to regioselectively form substituted heterocycles.[18] By taking advantage of this characteristic, Fu has been able to develop an efficient synthesis of substituted quinazolines (**27**) through an Ullman-type coupling of *ortho*-bromo benzylamine **23** and amide **24** (Scheme 1.4).[19]

Scheme 1.4. *Ullman-type couplings to generate quinazolines (**27**)*



Benzannulated nitrogen heterocycle synthesis can proceed through other mechanisms, but the above general strategies dominate heterocycle synthesis. Prefunctionalization of the aromatic ring with electron-rich (e.g., Pictet–Spengler), halogen (e.g., Ullman couplings), or nitrogen (e.g., Doebner–Miller) substituents is a

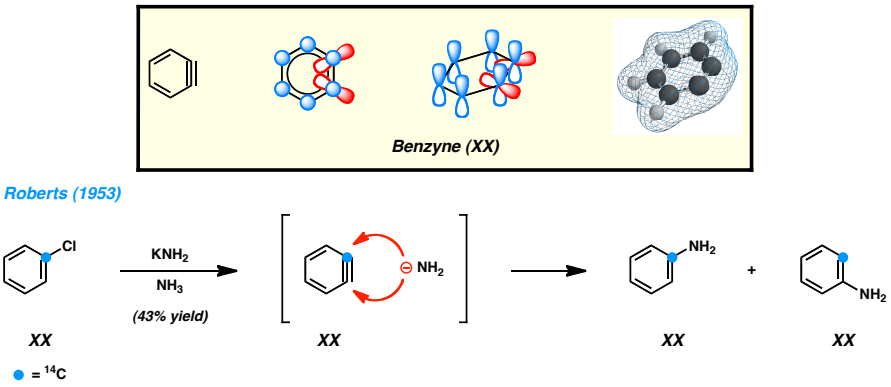
prerequisite for these cyclization methodologies to proceed. As a consequence, there are limitations to how efficient these processes are, and to the variety of known and unknown benzannulated heterocyclic motifs that are accessible by these pathways. To address these potential pitfalls, an alternative strategy using highly reactive aryne intermediates has been developed to complement these more common approaches.

1.3 ARYNE ANNULATIONS IN THE SYNTHESIS OF NITROGEN HETEROCYCLES

1.3.1 A Brief Introduction to Arynes

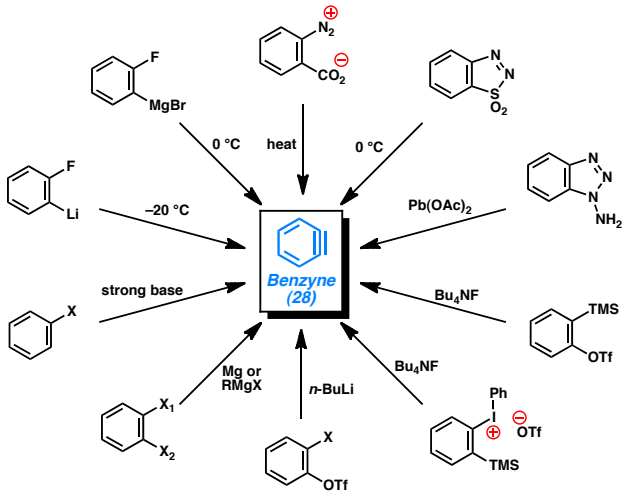
Benzyne (**28**), or 1,2-dehydrobenzene, is a six-membered aromatic ring containing a highly strained alkyne (Scheme 1.5). Due to the ring strain imparted on the alkyne, benzyne is a highly reactive species and often acts as an electrophile in chemical transformations. Aromatic molecules containing this strained triple bond are more generally known as arynes, and bear similar reactivity to the prototypical benzyne. Historically, the specific structural notion of an aryne reactive intermediate—and the term "benzyne" itself—come from seminal work by Roberts, wherein an amination reaction using isotopically labeled unsubstituted chlorobenzene-1-^{14}C (**29**), proceeded to give a mixture of labeled isomers, of aniline-1-^{14}C (**31**) and aniline-2-^{14}C (**32**) in 43% yield.[20] This mixture suggested the existence of a symmetrical intermediate into which the amide could add to form the observed product mixture.[21]

Scheme 1.5. *Benzyne (**28**), and Roberts' seminal structural proof*

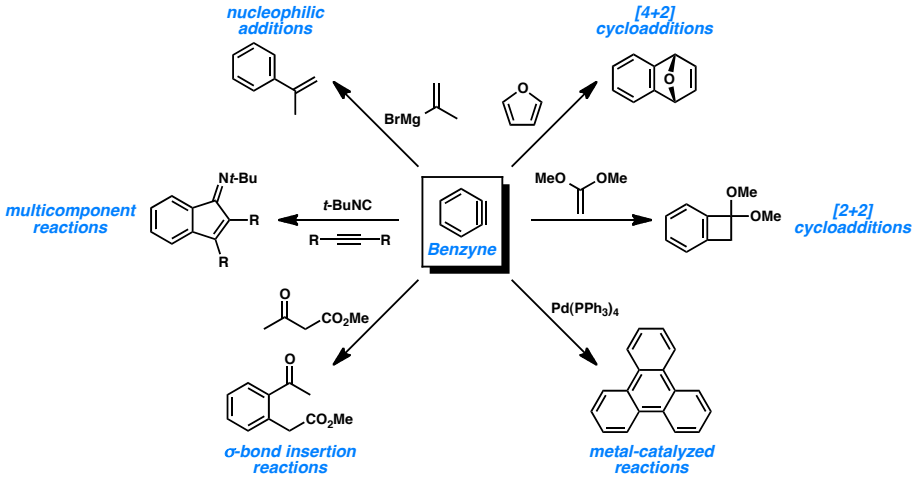


Since Roberts used the deprotonative method for benzyne generation, many more ways have been developed to form the strained aryne triple bond. More recently, mild methods for aryne generation have led an expansion in the application of this intermediate to synthetic organic efforts (Scheme 1.6). As a result more than 75 reported natural product syntheses have utilized aryne reactive intermediates,[22] with countless more reports of synthetic methodologies complementing the growing body of literature on the subject (Scheme 1.7).[23] In the survey that follows, we elected to focus exclusively on arynes that are used to form benzannulated *N*-heterocyclic molecules. For ease of organization, we have categorized these methodologies into intra- and intermolecular reactions, and subdivided both groups based upon the bonds formed with the aryne itself. When applicable, we have placed these reactions in the context of broader synthetic efforts, but we will not discuss that work in any greater detail.

Scheme 1.6. *The many roads to benzyne*[24]



Scheme 1.7. *Some representative reactions using benzyne*



1.3.2 Heterocycle Synthesis via Intramolecular Aryne Annulation

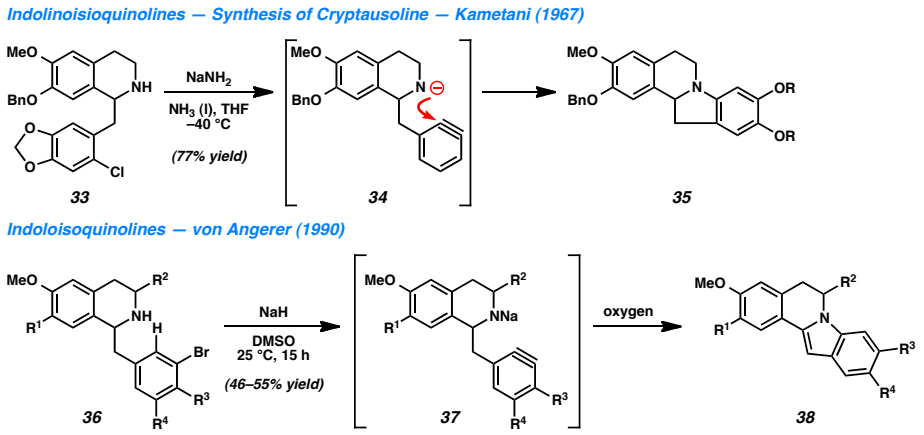
1.3.2.1 Carbon–Nitrogen Bond-Forming Reactions

The application of arynes to any synthetic effort must exploit the highly reactive intermediate under controlled circumstances. Strategies using intramolecular amide attack upon arynes to form heterocyclic structures are appealing because they combine an understood nucleophile (the amide) and a potent, internal electrophile (the aryne).

Interestingly, many of the initial reports of these reactions occur exclusively in the context of natural product total synthesis. Over time, as more mild conditions were developed to generate arynes, these reactive intermediates began to see more application in broader synthetic methodologies.

The first application of an aryne annulation strategy occurred en route to Kametani's 1967 total synthesis of cryptausoline, wherein tetrahydroisoquinoline **33** is deprotonated and undergoes addition to the aryne (**34**) generated from the pendant aryl chloride (Scheme 1.8).[25] Subsequent protonation of the resultant aryl anion affords the indolinoisoquinoline ring system. Von Angerer used a very similar 5-exo cyclization to construct several different indoloisoquinolines (**38**) from 1-benzyl tetrahydroisoquinolines (**36**) two decades later for the use in artificial, biologically active structures.[26]

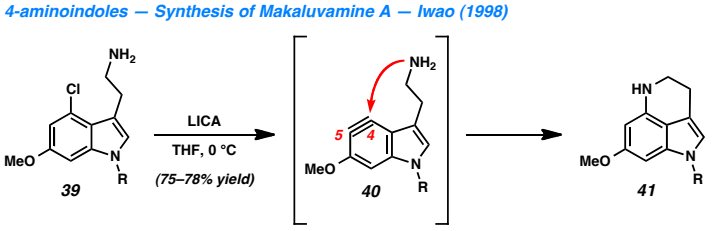
Scheme 1.8. *Indoloisoquinolines by aryne annulation*



Iwao used an aminocyclization in a different manner, by generating 4,5-indolyne (**40**) from a chlorinated tryptamine derivative (**39**) to ultimately build a tricyclic

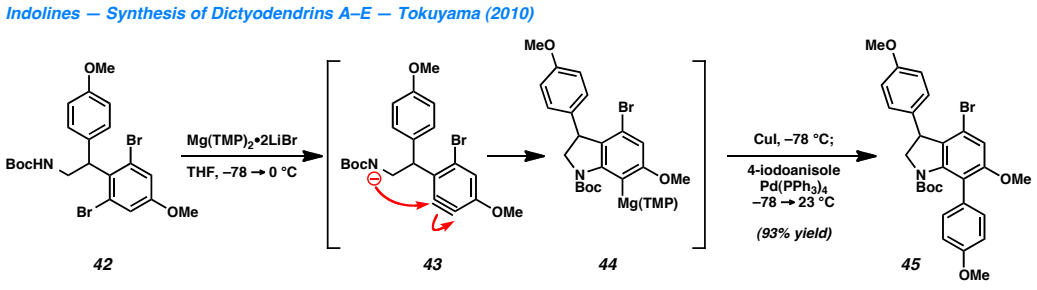
intermediate (**41**) that he subsequently advanced to several makaluvamines (Scheme 1.9).[27]

Scheme 1.9. *Iwao aminocyclization with indolyne (**40**)*



Tokuyama was able to obtain similar reactivity by using magnesium to generate the aryne from an aryl bromide (**42**, Scheme 1.10).[28] By this method, the Boc-protected amine was successfully cyclized onto the aryne (**43**), yielding an arylmagnesium intermediate (**44**). Next, cupric iodide and a palladium catalyst were added with iodoanisole, which, upon warming, was cross-coupled with the organomagnesium intermediate (**44**) to provide an advanced indoline intermediate **45** for the synthesis of dictyodendrin A.

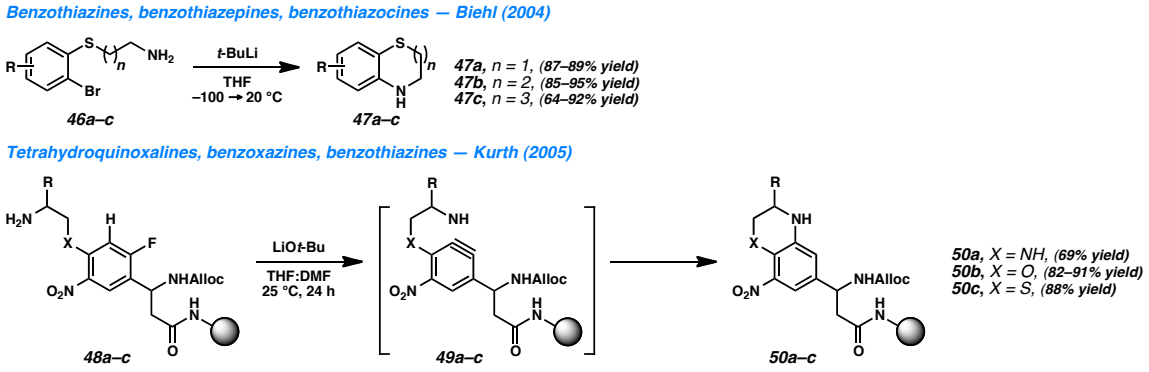
Scheme 1.10. *Indoline formation with tandem cross-coupling*



Biehl has recently been able to adopt a new direction in these intramolecular aryne aminocyclization methods (Scheme 1.11).[29] By using the low-temperature

conditions with *tert*-butyllithium, alkylated 2-bromo thiophenol derivatives (**46**) bearing pendant amines can undergo a ring closure to generate thiazyl heterocylces (**47**) in a variety of sizes. In a more limited case, Kurth has developed a solid-suppoted synthesis of similar benzannulated heterocycles (**50**) by using bulky alkoxide bases to form arynes (**49**) from nitroarenes (**48**).[30]

Scheme 1.11. *Sulfur and oxygen containing nitrogen heterocycles by internal aryne annulation*



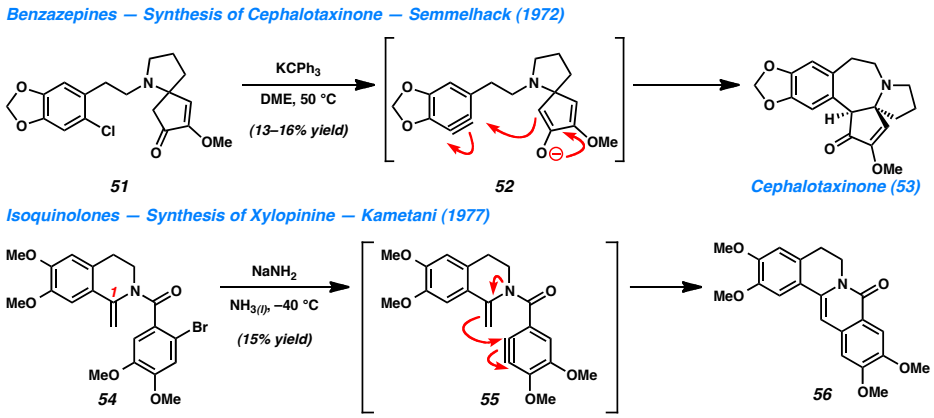
1.3.2.2 Carbon–Carbon Bond-Forming Reactions

Typically, C–N bond formations through intramolecular addition to arynes led to very similar products and possessed similar reactivity. Conversely, closing heterocyclic structures by forming a new carbon-carbon bond can proceed through a nucleophilic addition or, as an alternative strategy, a cycloaddition pathway.

In one of the earliest reports of heterocycle formation, the C–C bond was created by nucleophilic addition to the aryne. Semmelhack was able to complete his synthesis of the cephalotaxus alkaloids (**53**) by trapping an aryne intermediate (**52**) generated from aryl chloride (**51**) with a pendant enolate to close the benzazepine and form a new C–C bond (Scheme 1.12).[31] Kametani was similarly able to exploit a 3,4-dihydroisoquinoline

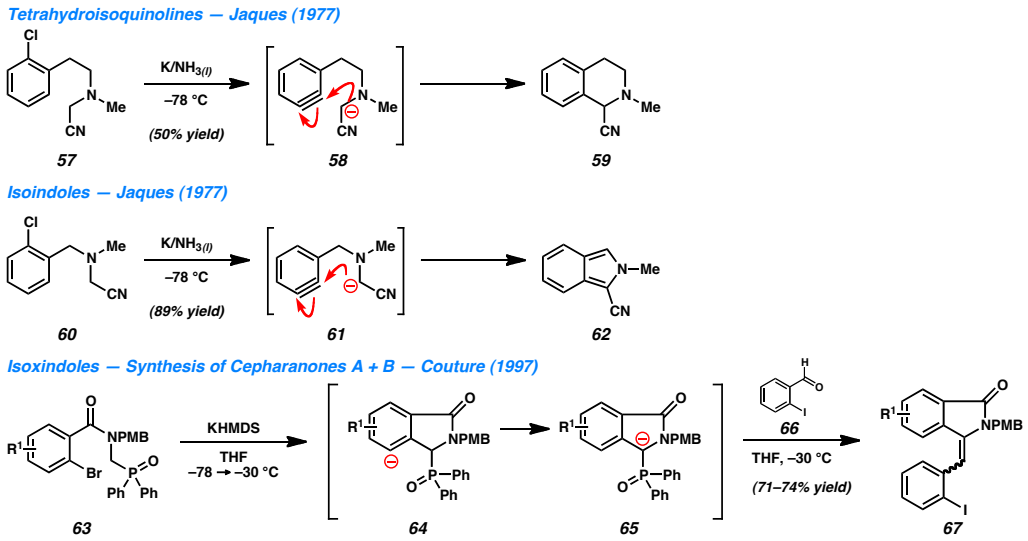
bearing a C(1)-*exo*-methylene substituent (**54**).[32] Following aryne generation, intermediate **55** was cyclized by intramolecular nucleophilic addition to the triple bond, forming the isoquinolone component of the xylopinine core (**56**).

Scheme 1.12. *Cyclization by intramolecular enamine and enolate attack*



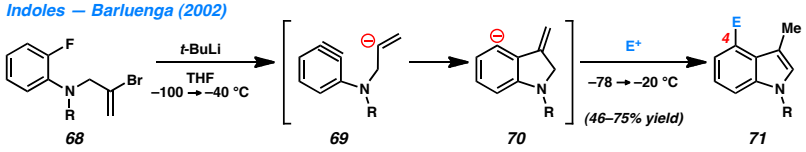
Following these initial reports, there were efforts to use stabilized anions to perform similar reactions. Jaques had limited success in developing a synthesis of both tetrahydroisoquinolines (**59**) and isoindoles (**62**) from aryl chlorides **57** and **60**, respectively through a general intramolecular addition of stabilized carbanions (**58** and **61**) to arynes (Scheme 1.13).[33] In 1997, Couture reported a synthesis of cepharanones A and B, wherein the aryne generated from aryl bromide **63** can undergo 5-exo cyclization (**64**) through addition of the phosphine oxide-stabilized anion.[34] Interestingly, a second deprotonation adjacent to the phosphine oxide (**65**) is followed by addition of a benzaldehyde derivative (**66**) to form the benzylidene isoxindole product (**67**) by a tandem aryne annulation/olefination sequence.

Scheme 1.13. *Ring closure by intramolecular stabilized enolate attack of arynes*



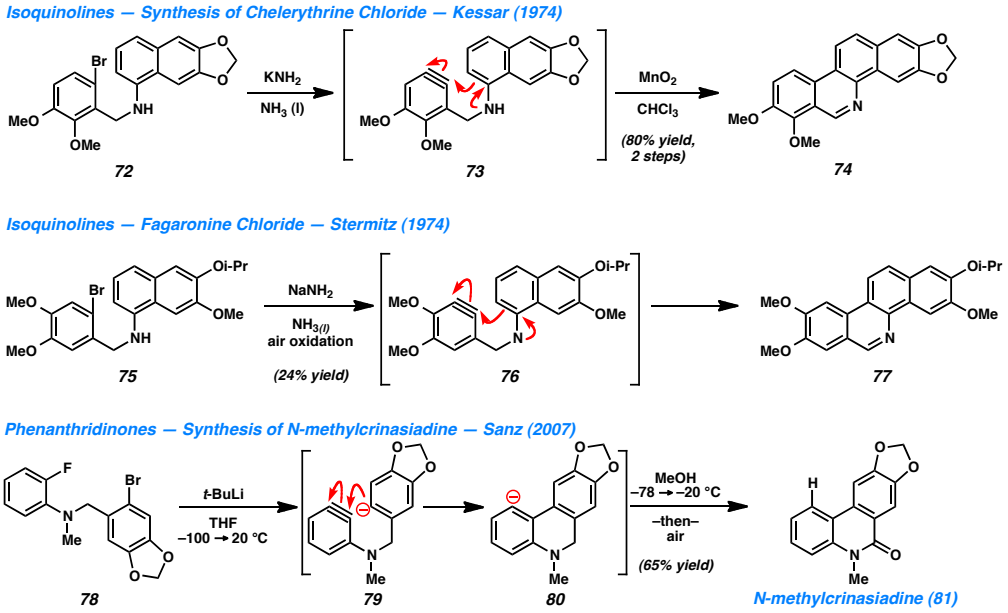
A more direct approach to the intramolecular anionic C–C bond formation using arynes was reported by Barluenga, who was able to develop an approach to 3,4-disubstituted indoles (**71**) by low-temperature lithiation (Scheme 1.14).[35] In his examples, *ortho*-fluoro anilines with pendant 2-bromo-allyl fragments (e.g., **68**) generate aryne intermediates (**69**) upon treatment with *tert*-butyllithium that close to form indole-3-methylidenes (**70**) with a C(4) anion, which, upon warming, are quenched with various electrophiles to form the products (**71**). Notably, the reaction proceeds selectively, generating the aryne by elimination of the aryl fluoride while simultaneously performing a lithium-halogen exchange to form the vinyl anion (**69**).

Scheme 1.14. *Barluenga indole synthesis by lithiation/annulation*



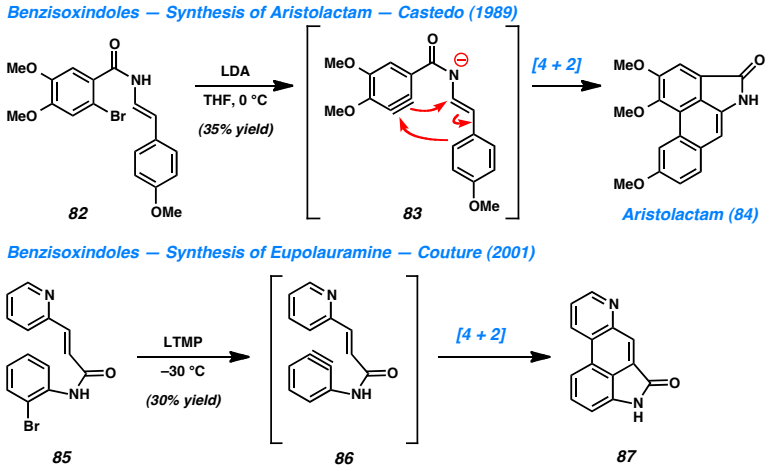
A common, but much less obvious nucleophile for these intramolecular cyclizations is another aryl ring, acting through an electrophilic aromatic substitution reaction (Scheme 1.15). Kessar first reported such a reaction in the conversion of aryl bromide **72** to fused isoquinoline intermediate **74** in his total synthesis of chelerythrine chloride.[36] The proposed mechanism for the ring closure involves amine-assisted intramolecular addition to the aryne (**73**) by the aminonaphthyl functional group. Oxidation in the next step furnishes the observed isoquinoline product. At the same time, Stermitz reported a nearly identical approach to the naphthoisoquinoline core (**77**) of fagaronine chloride through an aryne intermediate (**76**) generated from aryl bromide **75**.[37] Sanz was recently able to extend a variation of Barluenga's indole synthesis (vide supra) to complete the total synthesis of *N*-methylcrinasiadine (**81**). In this work, aryne generation and lithiation of the aryl bromide (**78**) are followed by cyclization of the aryl anion onto the reactive triple bond (**79→80**) and proton quench of the resulting intermediate with an equivalent of methanol.[38]

Scheme 1.15. *Forming biaryl linkages by arene addition to aryne intermediates*



Groups targeting more complex polycyclic structures with heterocycles at their core have also exploited the impressive reactivity of arynes to build complexity through multiple C–C bond formations in a single step. In particular, Castedo pioneered a method for benzisoxindole (**82**) synthesis by a [4 + 2] cycloaddition approach in his synthesis of aristolactam (**84**, Scheme 1.16).[39] The aryne (**83**), in this case, reacts by a formal cycloaddition process through enamine-assisted dearomatization of the pendant aryl ring, which forms the natural product (**84**). More than a decade later, en route to eupolauramine, Couture used a related reaction (**85**→**86**) to form a benzisoxindoles bearing a fused pyridyl ring (**87**).[40]

Scheme 1.16. *Intramolecular [4 + 2] cycloadditions*



1.3.3 Heterocycle Synthesis via Intermolecular Aryne Annulation

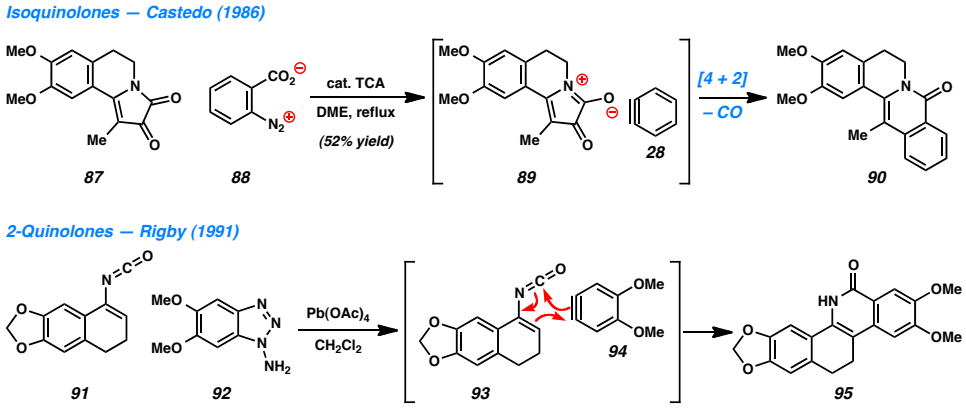
1.3.3.1 Carbon–Carbon Bond-Forming Reactions

Synthesizing heterocycles by intermolecular aryne annulation allows a different approach than the intramolecular variants. The majority of the reported efforts in this reaction manifold involve formal cycloadditions, which offers a convergent alternative to

the largely nucleophile/electrophile strategies that we have reviewed thus far. Accordingly, chemists have designed reactions that allow the functionalization of both carbon atoms of a benzyne intermediate with a single reaction partner. Intermolecular methods for aryne annulation, however, must act on both ends of the aryne bond, as they are not tethered to the arene in the first place. Such methods underscore the benefits of a convergent approach to heterocycle synthesis, where multiple, substituted components can be united, forming multiple new bonds in a single operation.

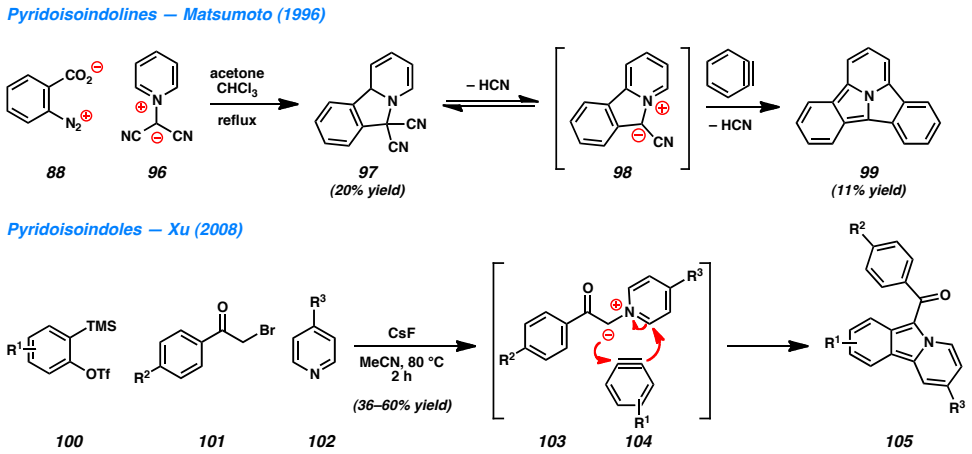
Castedo reported the first method for intermolecular nitrogen heterocycle synthesis with aryne reactive intermediates in 1986 (Scheme 1.17).[41] In this development, pyrroloisoquinolines (**87**) were coupled with benzyne (**28**) generated from diazonium carboxylate aryne precursor **88** through the imidate tautomer (**89**). A cycloaddition reaction between these intermediates and a subsequent chelotropic extrusion of carbon monoxide furnishes the isoquinolone product (**90**). Later, Rigby reported a synthesis of 2-quinolones (**95**) by the [4 + 2] cycloaddition of cyclohexenyl isocyanate **91** with the substituted aryne (**94**) produced from the lead-mediated decomposition of 1-aminobenzotriazole derivative **92**.[42]

Scheme 1.17. *Quinolones and isoquinolones through early intermolecular aryne annulations*



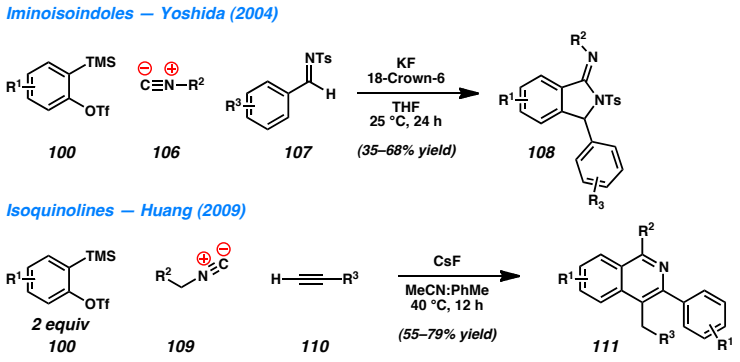
Not all approaches to heterocycles by aryne annulation use neutral intermediates for cycloadditions. Work with multicomponent synthesis has yielded an excellent general reaction partner for use with arynes, the 1,3-dipole. In the context of heterocycle synthesis, that dipole is often an activated pyridinium salt resulting from pyridine addition to an electrophile (Scheme 1.18). Matsumoto reported the first example of such a reaction with benzyne, wherein a pyridinium malononitrile (**96**) reacts with benzyne formed from phenyl diazonium carboxylate (**88**), to form pyridoisoindoline **97** in modest yields.[43] Interestingly, the product can form a second dipole (**98**) and react with another equivalent of benzyne to form the unique pentacyclic aromatic compound **99**. In 2008, Xu disclosed a three-component reaction with bromoacetophenone derivatives (**101**), pyridines (**102**) and arynes generated in situ from *ortho*-silyl aryl triflate **100**.[44] Again, a dipolar pyridinium intermediate is formed (**101**) that reacts with the aryne to create substituted pyridoisoindoles (**105**).

Scheme 1.18. *Approaches to pyridoisoindoles through a pyridinium dipolar addition (**96** and **103**)*



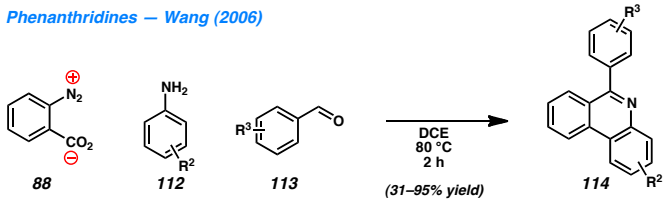
Yoshida has explored three-component processes with different reaction partners to obtain similar structures to the pyridoisoindoles (Scheme 1.19).[45] By combining arynes arising from silyl aryl triflates (**100**) with isocyanides (**106**) and aryl tosyl aldimines (**107**), an iminoisoindole product is formed (**108**). This combination of arynes and isocyanides has become very fruitful for heterocycle synthesis via aryne annulation, as demonstrated by Huang in 2009, when arynes, alkynes (**110**), and alkyl isocyanides (**109**) participated in a four-component coupling that furnished highly substituted isoquinoline products (**111**).[46]

Scheme 1.19. *Approaches to heterocycles through an isocyanide multi-component reactions*



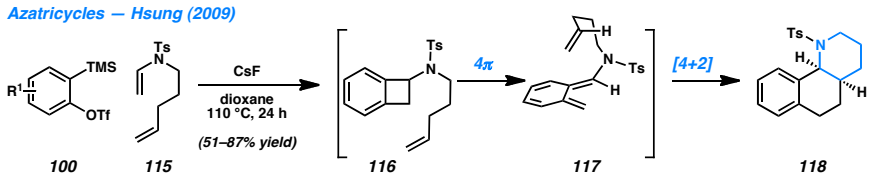
In further multicomponent reactions, Wang reported the synthesis of phenanthridines (**114**) by the union of arynes, anilines (**112**) and aryl aldehydes (**113**, Scheme 1.20).[47] Masked within the larger phenanthridine cores are substituted isoquinoline products.

Scheme 1.20. *Phenanthridines by aryne three-component reactions*



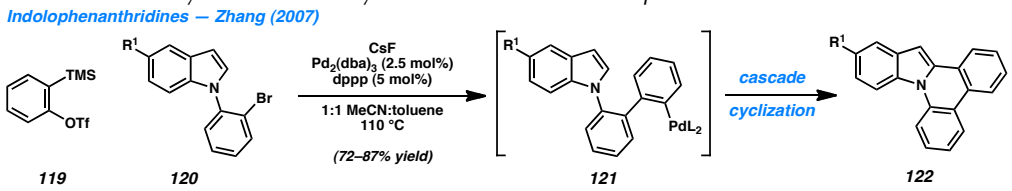
In addition to the strategies of multicomponent synthesis, dipolar addition, and cycloaddition, some new approaches to structures of higher complexity have been reported. For instance, Hsung has published a method to construct tricyclic piperidyl ring systems (**118**) through an aryne intermediate (Scheme 1.21).[48] In this example, a formal [2 + 2] cycloaddition reaction between vinyl enamine **115** and the aryne formed from silyl aryl triflate **100** produces benzocyclobutenyl intermediate **116**. This rapidly undergoes a 4π electrocyclic ring opening to reveal the *ortho*-quinone dimethide **117**, that reacts with the pendant olefin through a [4 + 2] cycloaddition, forming the core of the product (**118**). While not technically a benzannulated bicycle, the piperidine formed within tricycle **118** could not be formed without the direct participation of the aryne intermediate during the course of the reaction cascade.

Scheme 1.21. *Formal [2 + 2]/retro-4π/[4 + 2] cascade*



While palladium participation aryne annulation reactions is relatively rare, Zhang reported an intramolecular, palladium-mediated method to form indolophenanthridines (Scheme 1.22).[49] The palladium-phosphine catalyst performs an oxidative addition into the aryl bromide (**120**), and adds across an aryne equivalent to generate aryl palladium intermediate **121**. Ring closure results from carbopalladation of the palladium to forge the C–C bond between the arene and the indole, yielding the product (**122**).

Scheme 1.22. *Pd-catalyzed cascade cyclization to form indolophenanthridines*

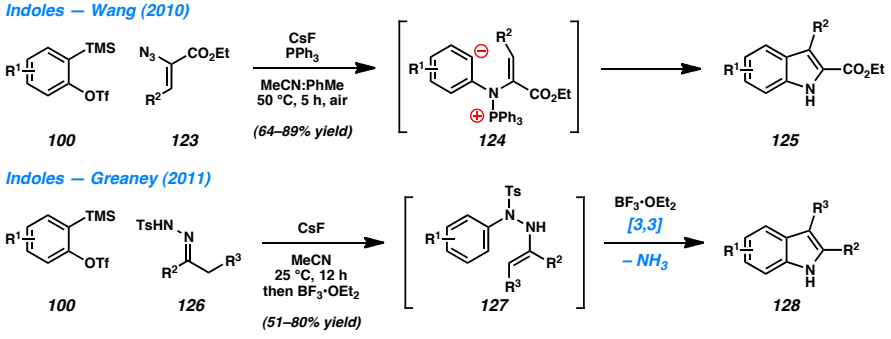


1.3.3.2 Carbon–Nitrogen Bond-Forming Reactions

In the intramolecular aryne annulation reactions, carbon–nitrogen bond formation was effectively limited to nucleophilic attack of the aryne by an amine. In the intermolecular reactions, however, the cyclizations reactions are much more diverse in their mechanisms. These various pathways are borne out in the numerous ways to generate substituted indole substructures.

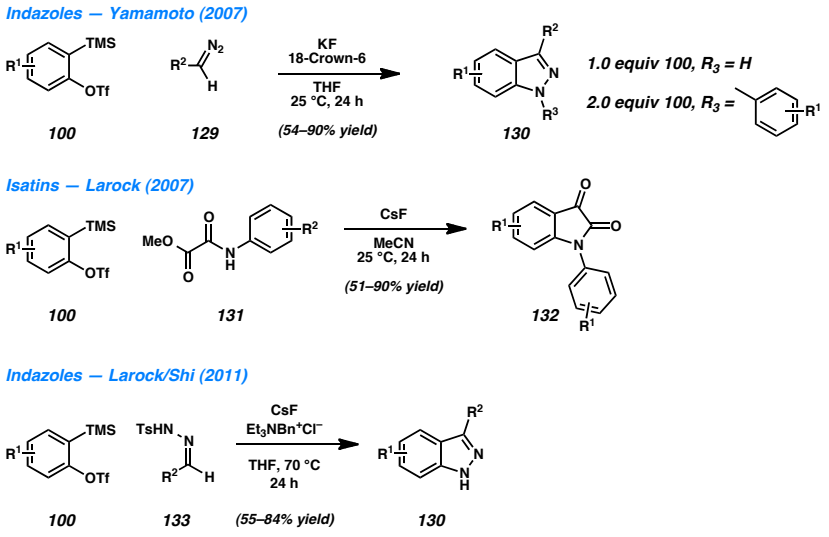
In 2010, Wang reported a direct synthesis of 2-carboxyl indoles (**125**) from the reaction between benzyne and azidoacrylates (**123**, Scheme 1.23).[50] Interestingly, this reaction requires triphenylphosphine to proceed, suggesting that a Staudinger-like reduction of the azide precedes coupling of the aminoacrylate and the aryne through azaphosphonium zwitterion **124**. This past year, Greaney examined the reaction of tosyl hydrazones (**126**) and arynes, and found that indole products result (**128**).[51] This transformation presumably proceeds through aryl hydrazide **127** via the Fischer mechanism for indole formation, mediated by the boron trifluoride Lewis acid additive.

Scheme 1.23. *Direct indole synthesis by aryne annulation*



A number of approaches have been reported for the construction of indole derivatives (Scheme 1.24). In 2007, Yamamoto showed that diazo compounds (**129**) undergo a 1,3-dipolar cycloaddition with arynes to generate indazoles (**130**).[52] Interestingly, the reaction is highly dependent upon aryne stoichiometry; additional equivalents produce the *N*-arylated indazole. That same year, Larock developed a synthesis of isatins (**132**) by condensation of arynes with *N*-aryl methyl oxamide (**131**).[53] In a separate effort, Larock coupled tosyl hydrazones (**133**) and arynes to find that, when heated, these proceed smoothly to the desired diaza product (**130**). Interestingly, this reaction does not stop at the putative aryl hydrazide (**127**) invoked by Greaney in the aforementioned indole synthesis (**126→128**).[54]

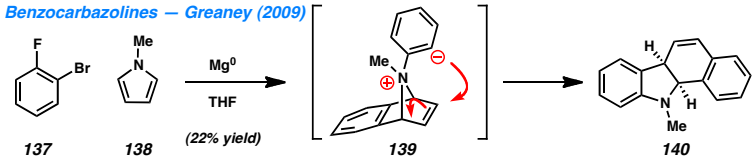
Scheme 1.24. *Indole derivative synthesis through heterocyclization with arynes*



Larock's interest in indole synthesis[55] was later extended to carbazole (**136**) formation through a two-step, one-pot, palladium-mediated aryne annulation (Scheme 1.25).[56] This reaction begins with 2-iodoaniline (**139**) addition to the aryne (from **100**) to

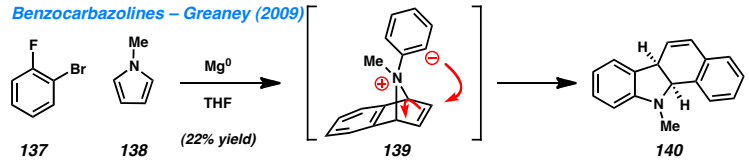
form diarylamine **135**. Palladium catalyst insertion into the aryl iodide precedes C–H functionalization and closes the 5-membered ring, yielding the carbazole (**136**).

Scheme 1.25. *Two-step, one-pot Pd-catalyzed carbazole synthesis*



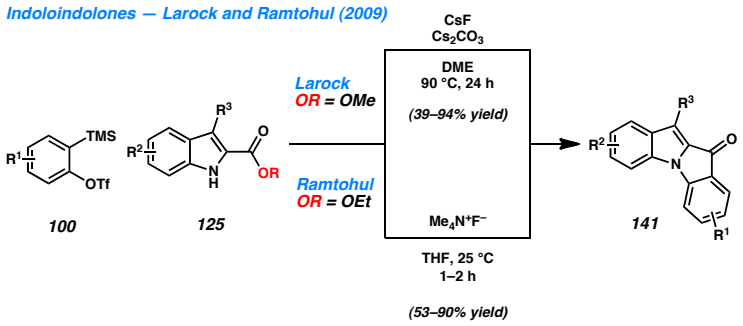
Greaney conceived of an approach to benzocarbazolines (**140**) by reaction of *N*-methyl pyrrole (**138**) with two equivalents of the aryne generated from *ortho*-fluoro bromobenzene (**137**, Scheme 1.26).[57] In this transformation, initial [4 + 2] cycloaddition of benzyne with **138** is followed by a second *N*-arylation reaction to generate the ammonium tricyclic intermediate **139**. Next, a *[3, 3]*-sigmatropic shift occurs, forming the indoline ring system of the observed benzocarbazoline (**140**).

Scheme 1.26. *Pyrrole and aryne coupling + rearrangement to form benzocarbazolines*



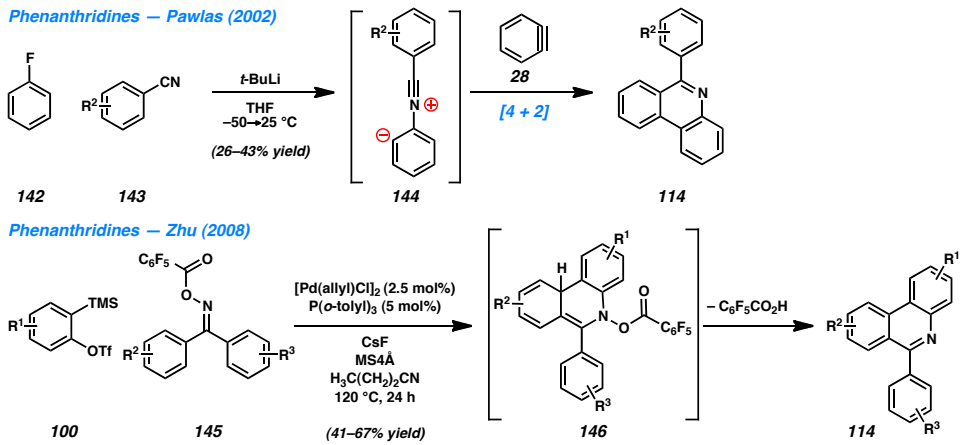
Larock[58] and Ramtohul[59] concomitantly reported very similar reactions in 2009, wherein 1-*H*-indole-2-carboxylates (**125**) react with arynes to form indoloindolones (**141**, Scheme 1.27). This condensation reaction is effective across a wide substrate scope.

Scheme 1.27. *Aryne reaction with indoles to form indoloindolones*



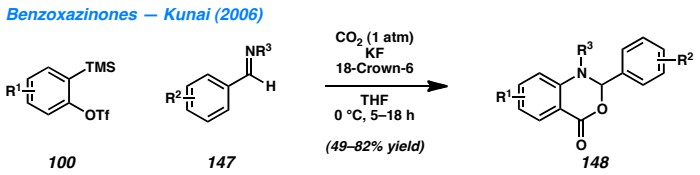
Intermolecular aryne annulations have focused on a broader range of substrates than indoles and indole derivatives. In 2002, Pawlas designed a synthesis of phenanthridines (**114**) from the reaction aryl nitriles (**143**) and two equivalents the reactant aryne through the activated nitrilium zwitterions **144** (Scheme 1.28).[60] Zhu was able to use an aryne annulation to complete the same molecules while maintaining an alternative approach from functionalized oximes (**145**).[61] The role of palladium in the reaction is not clear, but it might assist in N–O bond cleavage after the hetero Diels–Alder reaction to form the core of the product (**114**).

Scheme 1.28. *Phenanthridines by direct arylation*



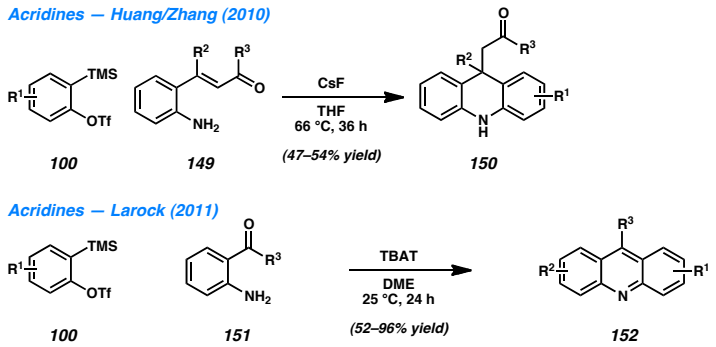
In an exceptional display of aryne reactivity, Kunai was able to form benzoxazinones (**148**) by reaction of aryl aldimines (**147**) with arynes and gaseous carbon dioxide (Scheme 1.29).[62]

Scheme 1.29. *CO_2 incorporation to form benzoxazinones*



Interestingly, *ortho*-acyl- (**149**)[63] and *ortho*-acrolyl anilines (**150**)[64] effectively react with arynes generated from *ortho*-silyl aryl triflates (**100**), yielding variously substituted acridines (**150** and **152**) as products (Scheme 1.30). Huang and Larock have independently demonstrated this reactivity.

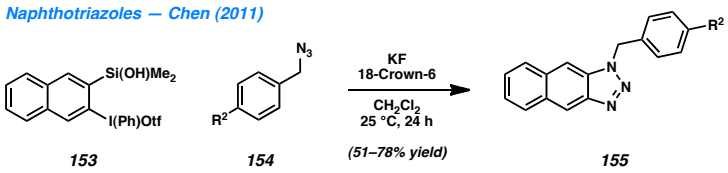
Scheme 1.30. *Acridines by aryne annulation of ortho-substituted anilines*



The widespread application of azide-alkyne cycloaddition chemistry, has led to the use of arynes as activated partners for this reaction, as demonstrated by Chen

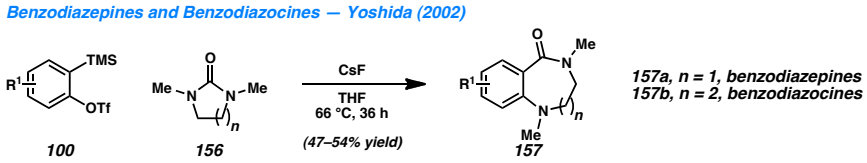
(Scheme 1.31).[65,66] In this account, naphthylyne is generated from silyl iodonium triflate **153**, and forms the triazole analog (**155**) through a standard 1,3-dipolar cycloaddition with benzyl azide **154**.

Scheme 1.31. *Naphthotriazoles through aryne-azide coupling*



Interestingly, Yoshida reported different kind of reactivity than what is often seen in these heterocyclization reactions, in his account of benzodiazopine (**157**) synthesis (Scheme 1.32).[67] In this case, the heterocyclic products were formed by an aryne C–N bond insertion reaction between the urea carbonyl and one of its nitrogen subsitutents (**156**). While aryne C–N bond insertion is known,[68] this marks its only application in heterocycle formation to date.

Scheme 1.32. *Yoshida's C–N insertion for benzodiazepine synthesis*

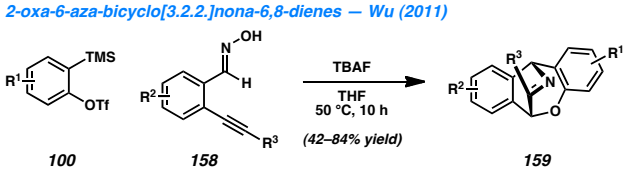


1.3.3.3 Carbon–X Bond-Forming Reactions

One of the relatively uninvestigated aspects of aryne annulation chemistry is the ability to form entirely novel heterocyclic ring systems that include second heteroatom partners. A few leading efforts have reported truly unique heterocycles using arynes.

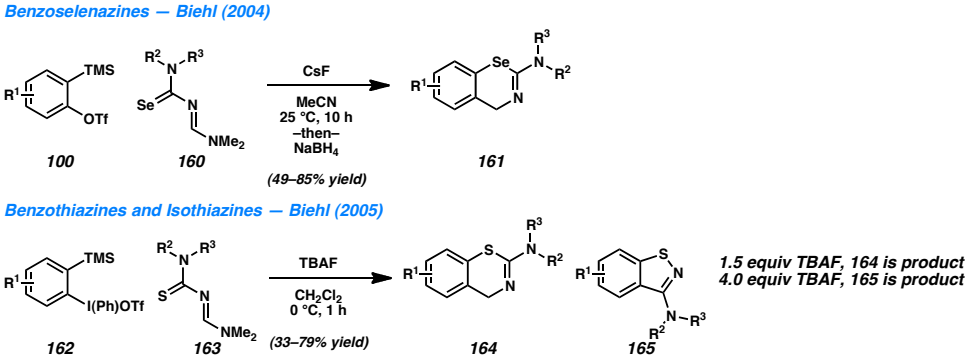
The interesting bridged tetracyclic product (**159**) of *ortho*-alkynyl aryl oxime (**158**) reaction with an equivalent of aryne reported by Wu touches upon potentially new structures available for investigation by aryne annulation reactions (Scheme 1.33).[69]

Scheme 1.33. *Aryne C–O bond formation to form bridged tetracycle* ***159***



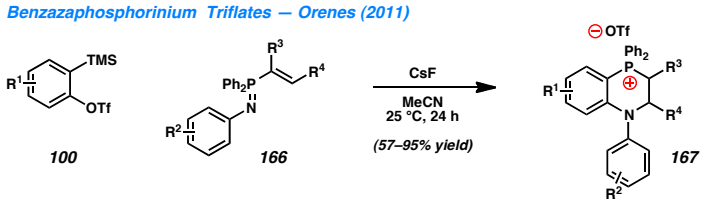
Biehl has used derivatives of seleno- (**260**)[70] and thiourea (**163**)[71] starting materials to form unprecedented structures with completely unknown properties (Scheme 1.34). Interestingly, formation of the benzothiazines (**164**) produced by cyclization of benzyne with the thiourea derivatives (**163**) can be controlled by fluoride stoichiometry to such an extent that isothiazine (**165**) products can actually be favored.

Scheme 1.34. *Biehl's syntheses of benzoselenazines, benzothiazines, and isothiazines*



Finally, Orenes very recently suggested that phosphorus might be a competent agent to incorporate into aryne annulation pathways (Scheme 1.35).[72] When vinyl phosphazenes (**166**) are reacted with arynes, interesting benzazaphosphorinium triflate salts (**167**) result.

Scheme 1.35. *P–N heterocycles by aryne annulation of phosphazenes*



These completely novel products of aryne annulation suggest that, as chemistry continues to evolve into targeted synthesis more carefully designed molecules, aryne annulations will continue to have a place in pushing innovation in the field.

1.4 CONCLUDING REMARKS

The prevalence of nitrogen-containing heterocyclic systems in natural products has led to a number of inventive methods to generate highly complex structures. Reactions using arynes as intermediates for the synthesis of benzannulated heterocycles are appealing alternatives to the prevalent strategies that rely on transition metal catalysis and electophilic aromatic substitution. Because of their highly reactive nature, aryne annulation is a complementary strategy to these known approaches, allowing chemists to access challenging heterocyclic motifs through intra- and intermolecular C–C and C–N bond formations. Reactions with arynes allow the functionalization of two adjacent

positions on an aromatic ring, a property that makes them exceedingly amenable to convergent synthetic procedures. Moreover, the propensity of benzyne to participate in multicomponent reactions, and transformations with generally inert, unique reaction intermediates combine to make these appealing agents for the synthesis of novel heterocyclic structures.

1.5 REFERENCES AND NOTES

(1) Wöhler, F. *Ann. Phys. Chem.* **1828**, *2*, 253–256.

(2) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc.* **1954**, *76*, 4749–4760.

(3) Belanger, E.; Cantin, K.; Messe, O.; Tremblay, M.; Pacquin, J.-F. *J. Am. Chem. Soc.* **2007**, *129*, 1034–1035.

(4) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927.

(5) Li, J. W.-H.; Vederas, J. C. *Science* **2009**, *325*, 161–165.

(6) Wilson, R. M.; Danishefsky, S. J. *J. Org. Chem.* **2006**, *71*, 8329–8351.

(7) (a) Bentley, K. W. In *The Isoquinoline Alkaloids*; Ravindranath, B., Ed.; Harwood Academic Publishers: Amsterdam, 1998; pp 107–122. (b) Bentley, K. W. *Nat. Prod. Rep.* **2005**, *22*, 249–268.

(8) Begley, T. P. Natural Products in Plants: Chemical Diversity. In *Wiley Encyclopedia of Chemical Biology*, Wiley: New York, **2008**, p. 213.

(9) Ladenburg, A. *Ber. Dtsch. Chem. Ges.* **1886**, *24*, 1628–1633.

(10) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202–9203.

(11) For a Bergman cyclization with pyrimidines, see: Choy, N.; Blanco, B.; Wen, J.; Krishan, A.; Russell, K. C. *Org. Lett.* **2000**, *2*, 3761–3764.

(12) For the Nenitzescu indole synthesis: Nenitzescu, C. D. *Bull. Soc. Chim. Romania* **1929**, *11*, 37.

(13) (a) Mohlau, R. *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 171. (b) Bischler, A.; Fireman, P. *Ber. Dtsch. Chem. Ges.* **1883**, *26*, 1346.

(14) (a) Pomeranz, C. *Montash.* **1893**, *14*, 116. (b) Fritsch, P. *Dtsch. Chem. Ges.*, **1893**, *26*, 419. (c) Schlittler, E.; Muller, J. *Helv. Chim. Acta.* **1948**, *31*, 914.

(15) Janin, Y. L.; Decaudin, D.; Monneret, C.; Poupon, M.-F. *Tetrahedron* **2004**, *60*, 5481–5485.

(16) Gladelli, S.; Pinna, L.; Delogu, G.; De Martin, S.; Zassinovich, G.; Mestroni, G. *Tetrahedron: Asymm.* **1990**, *60*, 635–648.

(17) Doebner, O.; Miller, W. *Ber.* **1881**, *14*, 2812–2815.

(18) (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198. (b) D'Souza, D. M.; Mueller, T. J. J. *J. Chem. Soc. Rev.* **2007**, *36*, 1095–1108.

(19) Wang, C.; Li, S.; Liu, H.; Jiang, Y.; Fu, H. *J. Org. Chem.* **2010**, *75*, 7936–7938.

(20) Roberts, J. D.; Simmons, H. E., Jr.; Carlsmith, L. A.; Vaughan, C. W. *J. Am. Chem. Soc.* **1953**, *75*, 3290–3291.

(21) Reaction rates for additions to ^{14}C-labeled positions have been noted to be as much as 16% less than those to ^{12}C-positions. For example, a difference in rates of 10% is calculated to produce a 47.8 : 52.4 ratio of 1-^{14}C : 2-^{14}C-labeled aniline (**36** : **37**). See: Ropp, G. A. *Nucleonics* **1952**, *10*, 22–27.

(22) Tadross, P. M.; Stoltz, B. M. *Chem. Rev.* **2012**, *Accepted for publication*.

(23) For reviews on the general reactivity of arynes, see: a) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 502–528. b) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, *59*, 701–730. c) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, pp 483–515. d) Sanz, R. *Org. Prep. Proc. Int.* **2008**, *40*, 215–291.

(24) For methods of benzyne generation, see: a) Kitamura, T.; Yamane, M. *J. Chem. Soc. Chem. Commun.* **1995**, 983–984. b) Campbell, C. D.; Rees, C. W. *J. Chem. Soc. (C)* **1969**, 742–747. c) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 6735–6736. d) Friedman, L.; Logullo, F. M. *J. Am. Chem. Soc.* **1963**, *85*, 1792–1797. e) Logullo, F. M.; Seitz, A. H.; Friedman, L. *Org. Synth.* **1968**, *48*, 12–17. f) Wittig, G.; Hoffmann, R. W. *Org. Synth.* **1967**, *47*, 4–8. g) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967.

(25) Kametani, T.; Ogasawara, K. *J. Chem. Soc. (C)* **1967**, 2208–2212.

(26) Ambros, R.; Schneider, M. R.; von Angerer, S. *J. Med. Chem.* **1990**, *33*, 153–160.

(27) Iwao, M.; Motoi, O.; Fukuda, T.; Ishibashi, F. *Tetrahedron* **1998**, *54*, 8999–9010.

(28) (a) Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5925–5929. (b) Tokuyama, H.; Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T. *Chem. Asian J.* **2011**, *6*, 560–572.

(29) Mukherjee, C.; Biehl, E. *Heterocycles*. **2004**, *63*, 2309–2318.

(30) Dixon, S.; Wang, X.; Lam, K. S.; Kurth, M. J. *Tetrahedron Lett*. **2005**, *46*, 7443–7446.

(31) (a) Semmelhack, M. F.; Chong, B. P.; Jones, L. D. *J. Am. Chem. Soc*. **1972**, *94*, 8629–8630. (b) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc*. **1975**, *97*, 2507–2516.

(32) Kametani, T.; Sugai, T.; Shoji, Y.; Honda, T.; Satoh, F.; Fukumoto, K. *J. Chem. Soc. Perkin Trans. 1* **1977**, 1151–1155.

(33) Jaques, B.; Wallace, R. G. *Tetrahedron Lett*. **1977**, *33*, 581–588.

(34) Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. *Synlett* **1997**, 1475–1477.

(35) Barluenga, J.; Fananas, F. J.; Sanz, R.; Fernandez, Y. *Chem. Eur. J.* **2002**, *8*, 2034–2046.

(36) Kessar, S. V.; Singh, M.; Balakrishnan, P. *Indian J. Chem*. **1974**, *12*, 323.

(37) Gillespie, J. P.; Amoros, L. G.; Stermitz, F. R. *J. Org. Chem.* **1974**, *39*, 3239–3241.

(38) Sanz, R.; Fernandez, Y.; Castroviejo, M. P.; Perez, A.; Fananas, F. J. *Eur. J. Org. Chem.* **2007**, 62–69.

(39) (a) Estévez, J. C.; Estévez, R. J.; Guitián, E.; Villaverde, M. C.; Castedo, L. *Tetrahedron Lett.* **1989**, *30*, 5785–5786. (b) Estévez, J. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1995**, *51*, 10801–10810.

(40) Hoarau, C.; Couture, A.; Cornet, H.; Deniau, E.; Grandclaudon, P. *J. Org. Chem.* **2001**, *66*, 8064–8069.

(41) Saá, C.; Guitián, E.; Castedo, L.; Suau, R.; Saá, J. M. *J. Org. Chem.* **1986**, *51*, 2781–2784.

(42) Rigby, J. H.; Qabar, M. N. *J. Org. Chem.* **1993**, *58*, 4473–4475.

(43) Matsumoto, K.; Katsura, H.; Uchida, T.; Aoyama, K.; Machiguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2599–2602.

(44) Xie, C.; Zhang, Y.; Xu, P. *Synlett* **2008**, 3115–3120.

(45) This reaction is discussed in detail in Chapter 4 of this thesis. Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2004**, *45*, 8659–8662.

(46) Sha, F.; Huang, X. *Angew. Chem. Int. Ed.* **2009**, *48*, 1–5.

(47) Shou, W.-G.; Yang, Y.-Y.; Wang, Y.-G. *J. Org. Chem.* **2006**, *71*, 9241–9243.

(48) Feltenberger, J. B.; Hayashi, R.; Tang, Y.; Babiash, E. S. C.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 3666–3669.

(49) Xie, C.; Zhang, Y.; Huang, Z.; Xu, P. *J. Org. Chem.* **2007**, *72*, 5431–5434.

(50) Hong, D.; Chen, Z.; Lin, X.; Wang, Y. *Org. Lett.* **2010**, *12*, 4608–4611.

(51) McAusland, D.; Seo, S.; Pintori, D.; Finlayson, J.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 3667–3669.

(52) Jin, T.; Yamamoto, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 3323–3325.

(53) Rogness, D. C.; Larock, R. C. *J. Org. Chem.* **2011**, *76*, 4980–4986.

(54) Li, P.; Zhao, J.; Wu, C.; Larock, R. C.; Shi, F. *Org. Lett.* **2011**, *13*, 3340–3343.

(55) For the first report of the eponymous Larock Indole Synthesis: Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

(56) Liu, Z.; Larock, R. C. *Tetrahedron* **2007**, *63*, 347–355.

(57) Cant, A. A.; Bertrand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 1–5.

(58) Rogness, D. C.; Larock, R. C. *Tetrahedron Lett*. **2009**, *50*, 4003–4008.

(59) Giacometti, R. D.; Ramtohul, Y. K. *Synlett* **2009**, 2010–2016.

(60) Pawlas, J.; Begtrup, M. *Org*. *Lett*. **2002**, *4*, 2687–2690.

(61) Gerfaud, T.; Neuville, L.; Zhu, J. *Angew*. *Chem*. *Int*. *Ed*. **2008**, *47*, 1–7.

(62) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J*. *Am*. *Chem*. *Soc*. **2006**, *128*, 11040–11041.

(63) Huang, X.; Zhang, T. *J*. *Org*. *Chem*. **2010**, *75*, 506–509.

(64) Rogness, D. C.; Larock, R. C. *J*. *Org*. *Chem*. **2011**, *13*, 5668–5671.

(65) Lin, Y.; Chen, Y.; Ma, X.; Xu, D.; Cao, W.; Chen, J. *Tetrahedron* **2011**, *67*, 856–859.

(66) (a) Huisgen, R.; Knorr, R. *Naturwissenschaften* **1962**, *48*, 716. (b) Reynolds, G. A. *J*. *Org*. *Chem*. **1964**, *29*, 3733–3734. (c) Huisgen, R.; Knorr, R.; Moebius, L.; Szeimies, G. *Chem*. *Ber*. **1965**, *98*, 4014–4021. (d) Mitchell, G.; Rees, C. W. *J*. *Chem*. *Soc*., *Perkin Trans*. *1* **1987**, 403–412. (e) Kitamura, T.; Fukatsu, N.; Fujiwara, Y. *J*. *Org*. *Chem*. **1998**, *63* 8579–8581. (f) Kitamura, T.; Todaka, M.; Shin-machi, I.; Fujiwara, Y. *Heterocycl*. *Commun*. **1998**, *4*, 205–208. (g) Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org*. *Lett*. **2008**, *10*, 2409–2412.

(67) Yoshida, H. Y.; Shirakawa, E.; Honda, Y.; Hiyama, T. *Angew*. *Chem*. *Int*. *Ed*. **2002**, *41*, 3247–3249.

(68) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112–13113.

(69) Ren, H.; Luo, Y.; Ye, S.; Wu, J. *Org. Lett.* **2011**, *10*, 2552–2555.

(70) Rao, U. N.; Sathunuru, R.; Biehl, E. *Heterocycles* **2004**, *64*, 1067–1075.

(71) Sathunuru, R.; Zhang, H.; Rees, C. W.; Biehl, E. *Heterocycles* **2005**, *65*, 1615–1627.

(72) Alajarin, M.; Lopez-Leonardo, C.; Raja, R.; Orenes, R.-A. *Org. Lett.* **2011**, *13*, 5668–5671.