CHEMICAL REVIEWS

Review

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A Comprehensive History of Arynes in Natural Product Total Synthesis

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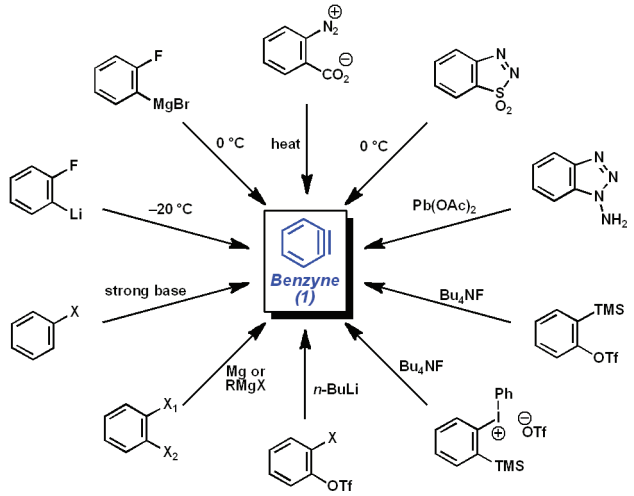
CONTENTS

1. INTRODUCTION

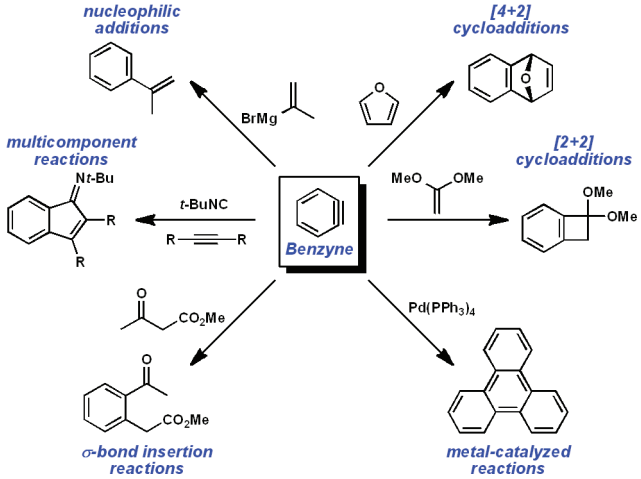
Within 14 years of the seminal experiments of J. D. Roberts leading to the first proposal of the structure of benzyne (**1**),[1] synthetic organic chemists recognized the potential to exploit this highly reactive intermediate (and its substituted variants) in the total synthesis of natural products. More specifically, it was recognized that arynes offered the strategic advantage of rapidly functionalizing an aromatic ring by forming multiple carbon−carbon or carbon−heteroatom bonds in a single operation, often in a regioselective manner. Initially, the scope of synthetic applications was somewhat limited by the harsh conditions required to produce the aryne species.[2] Many of these methods required strong bases, such as *n*-BuLi, or high temperatures (Scheme 1). However, with the development of milder methods for the generation of arynes came increased interest in employing them in the synthesis of more complex polycyclic systems. Most recently, the use of *o*-silyl aryl triflates as aryne precursors has allowed generation of the reactive intermediate under almost neutral conditions.[3]

To date, over 75 individual natural products have been prepared using arynes to generate key synthetic intermediates. Herein are recounted the reports of total syntheses that utilize arynes in ways that build complexity or introduce motifs essential to the completion of their targets. The methods by which the authors featured in this review accomplish this task reflect the versatility of arynes as reactive intermediates for synthesis (Scheme 2).[4,2g] For the purposes of organization, the syntheses are divided into subgroups on the basis of the type of aryne transformation: (i) nucleophilic additions or multicomponent reactions, (ii) σ-bond insertion reactions,

Scheme 1. Methods for the Generation of Benzyne (1)



Scheme 2. Representative Reactions of Benzyne (1)[6]



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(iii) [4 + 2]- and [2 + 2]-cycloaddition strategies, and (iv) metal-catalyzed aryne reactions.[5]

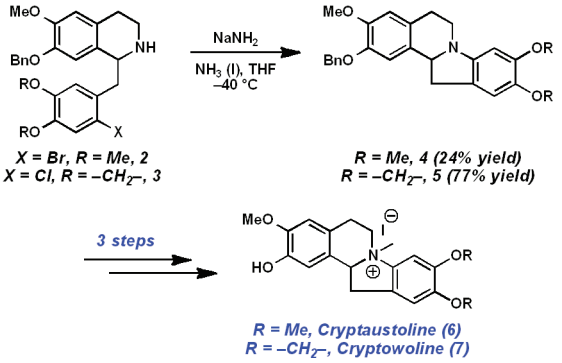
2. NUCLEOPHILIC ADDITION AND MULTICOMPONENT REACTION STRATEGIES

Strategies for the total synthesis of natural products that rely on nucleophilic additions to arynes (including multicomponent approaches) predominate in the literature over other approaches. The examples presented in this section have been divided into two groups: nucleophilic additions that form only a single new carbon−carbon or carbon−heteroatom bond to the intermediate aryne, and multicomponent reactions, in which three or more components are united in such a way that two new bonds to the aryne are formed in a single operation. Syntheses that employ nucleophilic addition strategies represent some of the oldest known applications of arynes to total synthesis, whereas multicomponent approaches to natural products have only emerged within the past decade.

2.1. Nucleophilic Additions to Arynes

The first instance in which arynes were applied to the total synthesis of natural products was reported by Kametani and co-workers at Tohoku University in 1967.[7] Kametani's synthesis of cryptaustoline (**6**) and cryptowoline (**7**) marked the beginning of a long-term research program to utilize aryne intermediates in alkaloid synthesis that would span more than 10 years. In the synthesis of cryptaustoline (**6**) and cryptowoline (**7**), substituted tetrahydroisoquinolines **2** and **3** were treated with sodamide in liquid ammonia to generate tetracycles **4** and **5**, respectively, by nucleophilic addition of the secondary amine to a pendant aryne (Scheme 3). From this point, tetracycle **4** was converted to cryptaustoline (**6**) over three steps, while tetracycle **5** afforded cryptowoline (**7**).

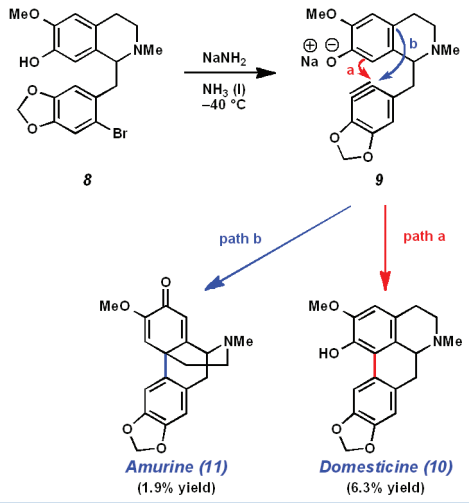
Scheme 3. Kametani's 1967 Synthesis of Cryptaustoline (6) and Cryptowoline (7)



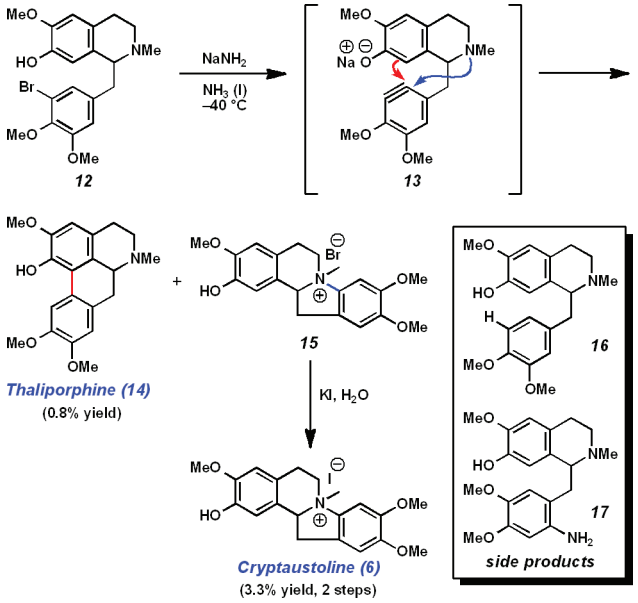
Building on this synthetic strategy, Kametani next reported the syntheses of domesticine (**10**) and amurine (**11**) (Scheme 4).[8,9] N-Methylation of tetrahydroisoquinoline intermediates such as **2** and **3** and removal of the benzyl protective group led to alternative reactivity in the key aryne cyclization, allowing access to a different class of alkaloids. Upon treatment of phenol **8** with sodamide in liquid ammonia, the authors isolated in low yields both domesticine (**10**) and amurine (**11**), resulting from attack of the phenoxide *ortho* (path a, blue bond) and *para* (path b, red bond) positions, respectively, on the aryne (**9**). Notably, the formation of amurine results in a dearomatization upon aryne cyclization.

Similarly, aryne cyclization of phenol **12** under these same conditions resulted in the formation of a mixture of compounds,

Scheme 4. Kametani's 1971 Synthesis of Domesticine (10) and Amurine (11)



Scheme 5. Kametani's 1972 Synthesis of Thaliporphine (14) and Cryptaustoline (6)



including thaliporphine (**14**) (Scheme 5).[10] Following extraction of thaliporphine (**14**) and two additional side products (**16** and **17**), concentration of the aqueous washes and treatment with potassium iodide also afforded cryptaustoline (**6**).

In their final report on this work, Kametani and co-workers extended their synthetic efforts one step further to prepare three different natural products from a single aryne precursor in one pot (Scheme 6).[11] Depending on the substitution, treatment of either tetrahydroisoquinoline **18** or **8** with sodamide in liquid ammonia yielded cryptaustoline (**6**) (following treatment with potassium iodide), thaliporphine (**14**), and *O*-methylflavinantine (**19**), or cryptowoline (**7**) (following treatment with potassium iodide), domesticine (**10**), and amurine (**11**), respectively.

It should be noted that subsequent to Kametani's publication of the syntheses featured in Scheme 6, Kessar, Gandhi, and co-workers reported an identical approach to domesticine (**10**), cryptaustoline (**6**), cryptowoline (**7**), amurine (**11**), *N*-methylcaaverine (**21**), and thalicmidine with similarly low yields.[12] Generally speaking, the consistently low yields reported in early

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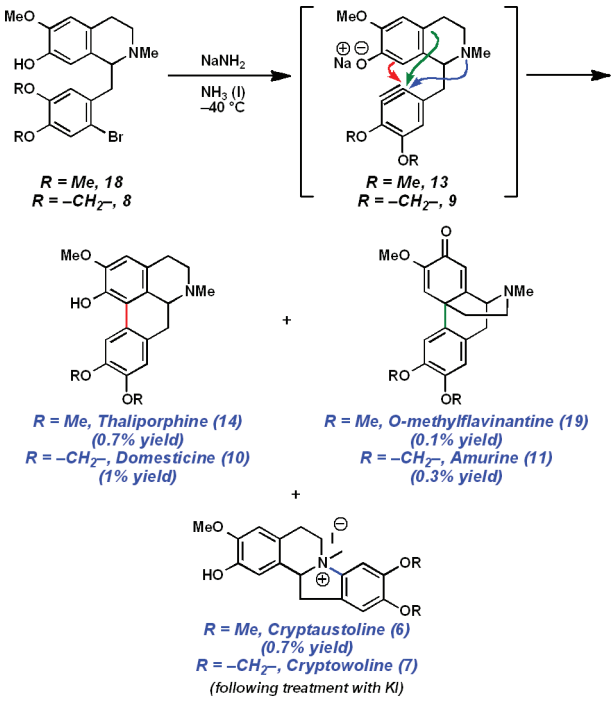
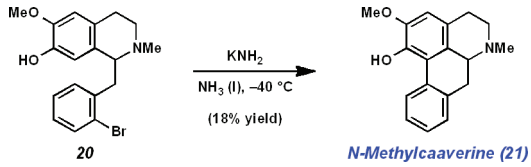
Scheme 6. Kametani's 1973 One-Pot Synthesis of Cryptaustoline (6), Thaliporphine (14), and *O*-Methylflavinantine (19) and Cryptowoline (7), Domesticine (10), and Amurine (11)



aryne-based total syntheses stem from competing reactivity pathways and reflect the infant state of such synthetic methods. Interestingly, the structure given by Kessar for thalicmidine is identical to Kametani's thaliporphine (**14**). Furthermore, the only natural product prepared by Kessar that was not targeted by Kametani was *N*-methylcaaverine (**21**), which was isolated upon aryne cyclization of tetrahydroisoquinoline **20** in 18% yield (Scheme 7).

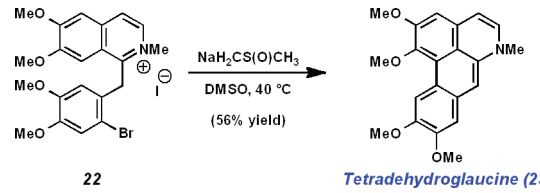
Scheme 7. Kessar's 1975 Synthesis of *N*-Methylcaaverine (21)



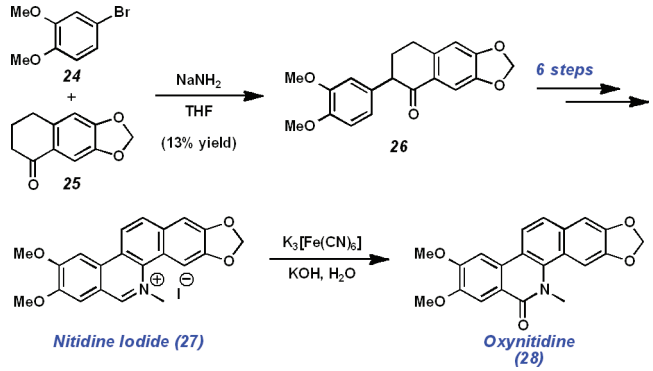
Furthermore, Castedo and co-workers extended this aryne cyclization method to include the synthesis of more oxidized relatives of natural products like thaliporphine (**14**) and domesticine (**10**). In the synthesis of tetradehydroglaucine (**23**), aryne cyclization of *N*-methyl isoquinolinium iodide **22** directly afforded the natural product upon treatment with sodium dimsylate (Scheme 8).[13]

Kametani and co-workers next turned their attention to a slightly different isoquinoline-derived alkaloid framework in their synthesis of oxynitidine (**28**) and nitidine iodide (**27**) (Scheme 9).[14] In this case, advanced intermediate **26** was prepared by arylation of α-tetralone **25** with the aryne generated in situ from aryl bromide **24**. Arylated α-tetralone **26** was converted to nitidine iodide (**27**) over six additional steps. Subsequent oxidation of nitidine iodide (**27**) provided oxynitidine (**28**).

Scheme 8. Castedo's 1987 Synthesis of Tetradehydroglaucine (23)

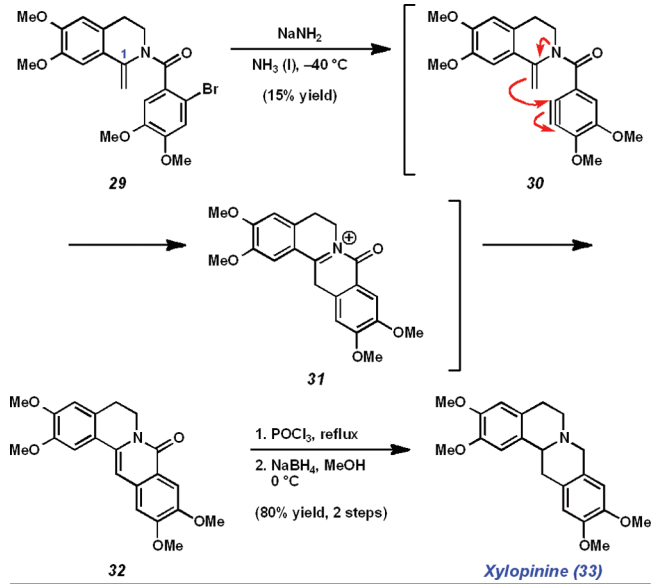


Scheme 9. Kametani's 1973 Synthesis of Nitidine Iodide (27) and Oxynitidine (28)



The final alkaloid synthesis in which Kametani and co-workers employed arynes deviates somewhat from the examples detailed above.[15] In the synthesis of xylopinine (**33**), a protoberberine alkaloid, treatment of C(1)-methylene isoquinoline derivative **29** with sodamide in liquid ammonia resulted in enamine cyclization onto the pendant aryne, furnishing tetracycle **32** upon deprotonation and further isomerization (Scheme 10). Finally, reduction of both the lactam and enamine by a two-step sequence afforded xylopinine (**33**).

Scheme 10. Kametani's 1977 Synthesis of Xylopinine (33)



Outside the realm of alkaloid synthesis, Kametani also explored how arynes could expedite the synthesis of steroid structures. In one example, treatment of nitrile **34** with sodamide in liquid ammonia resulted in formation of benzocyclobutene **36** via intermediate aryne **35** (Scheme 11).[16] Benzocyclobutenes,

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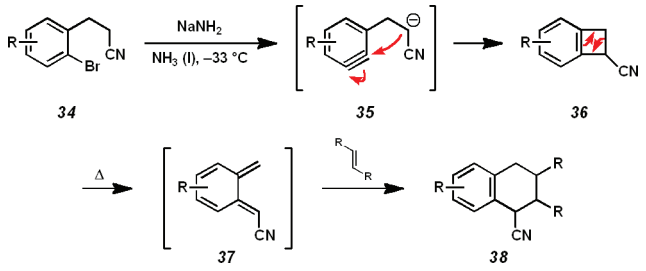
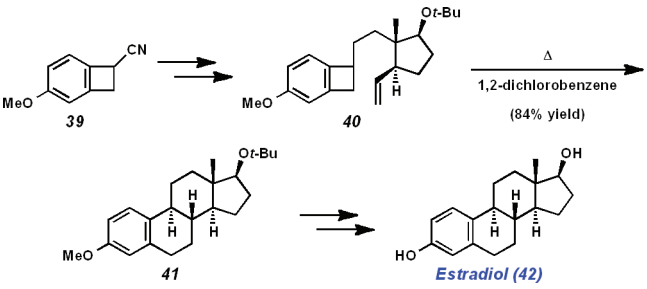
Scheme 11. Kametani's Synthesis of Benzocyclobutenes via Intramolecular Nitrile Arylation



such as **36**, have proven to be valuable intermediates for the in situ generation of *o*-quinone dimethides (**37**). Intramolecular Diels–Alder reactions of such *o*-quinone dimethides with tethered dienophiles have provided an efficient entry into tetralene synthesis. Kametani has used this method in several instances to accomplish the total and formal synthesis of naturally occurring steroids.[17]

In the synthesis of estradiol (**42**), Kametani elaborated benzocyclobutene **39** to enantioenriched cyclopentane **40**, the precursor for the key Diels–Alder cycloaddition (Scheme 12).[18]

Scheme 12. Kametani's 1978 Synthesis of Estradiol (42)

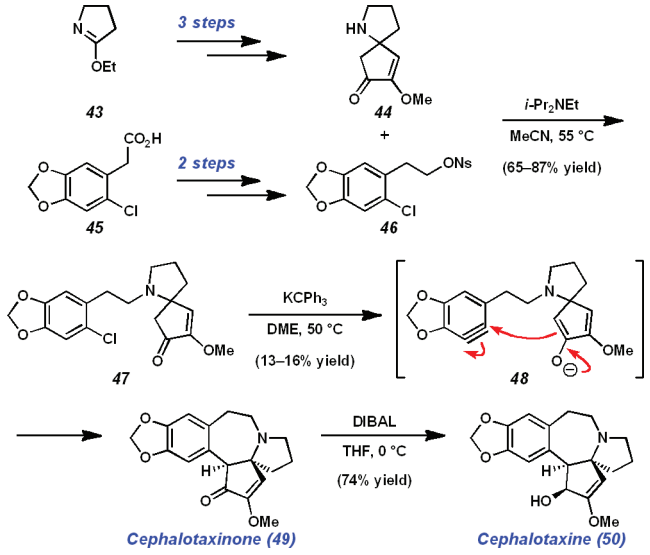


Upon heating, benzocyclobutene **40** underwent a 4π electrocyclic ring-opening and subsequent Diels–Alder reaction to afford tetracycle **41**, which was converted to estradiol (**42**) over two steps.

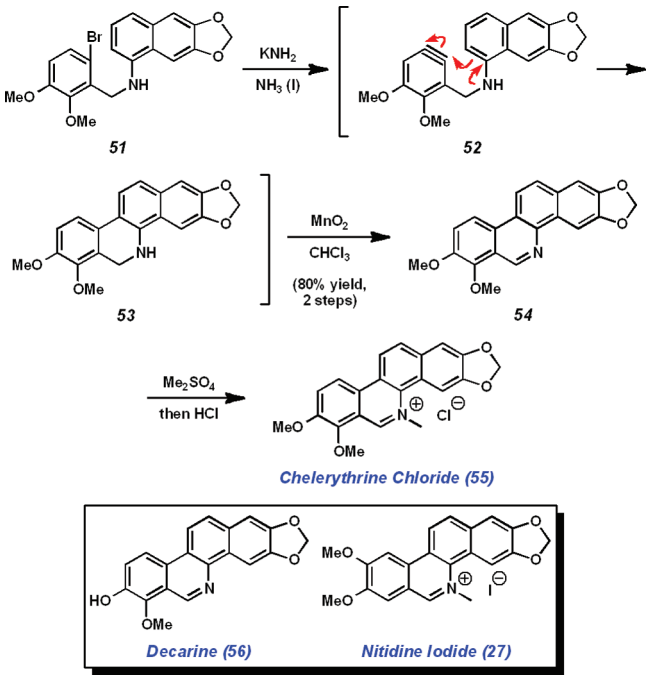
During this same time period, Semmelhack and co-workers reported a concise and convergent approach to the cephalotaxus alkaloids (**49** and **50**) based on a late-stage aryne cyclization strategy.[19] Beginning with 2-ethoxy-1-pyrroline (**43**), heterospirocycle **44** was generated in three steps, while nosylate **46** was prepared over a two-step sequence beginning with carboxylic acid **45** (Scheme 13). Following coupling of nosylate **46** with pyrrolidine **44**, treatment of tertiary amine **47** with excess potassium triphenylmethide produced cephalotaxinone (**49**) directly by enolate addition to the pendant aryne (e.g., intermediate **48**). Diastereoselective reduction of cephalotaxinone (**49**) with DIBAL then produced cephalotaxine (**50**). In total, Semmelhack and co-workers were able to achieve the synthesis of cephalotaxinone (**49**) and cephalotaxine (**50**) in only five and six steps, respectively, from 2-ethoxy-1-pyrroline (**43**).

Concurrent with Kametani's efforts toward the synthesis of isoquinoline-containing alkaloids (vide supra), Kessar and co-workers targeted other members of this class of compounds through different aryne-centered strategies. In the synthesis of chelerythrine chloride (**55**), Kessar forged a key carbon–carbon bond by treatment of aryl bromide **51** with potassium amide in liquid ammonia (Scheme 14).[20] The tetracyclic product of this aryne cyclization (**54**), which was formed in excellent yield, was

Scheme 13. Semmelhack's 1972 Synthesis of Cephalotaxinone (49) and Cephalotaxine (50)



Scheme 14. Kessar's Synthesis of Chelerythrine Chloride (55) (1974), Decarine (56) (1984), and Nitidine Iodide (27) (1988)



then methylated to afford the natural product (**55**). This same strategy was employed again by Kessar in the subsequent syntheses of decarine (**56**)[21] and nitidine iodide (**27**).[22]

Just months after Kessar's synthesis of chelerythrine chloride (**55**), Stermitz and co-workers employed an identical strategy in their synthesis of the alkaloid fagaronine chloride (**59**) (Scheme 15).[23] Aryne cyclization of aryl bromide **57** produced tetracycle **58**, which was converted to fagaronine chloride (**59**) over three steps.

Whereas the previously described synthetic efforts all focused on the formation of new carbon–carbon and carbon–nitrogen bonds, Castedo and co-workers' synthesis of oxocularine (**68**) and oxocompostelline (**69**) sought to forge carbon–oxygen

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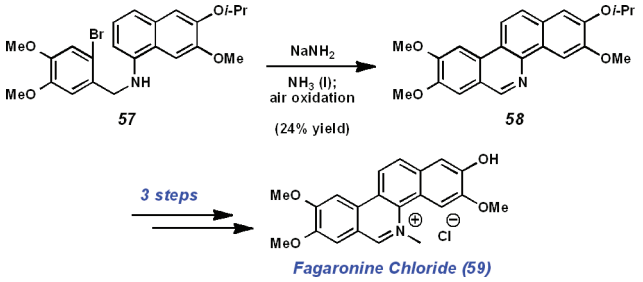
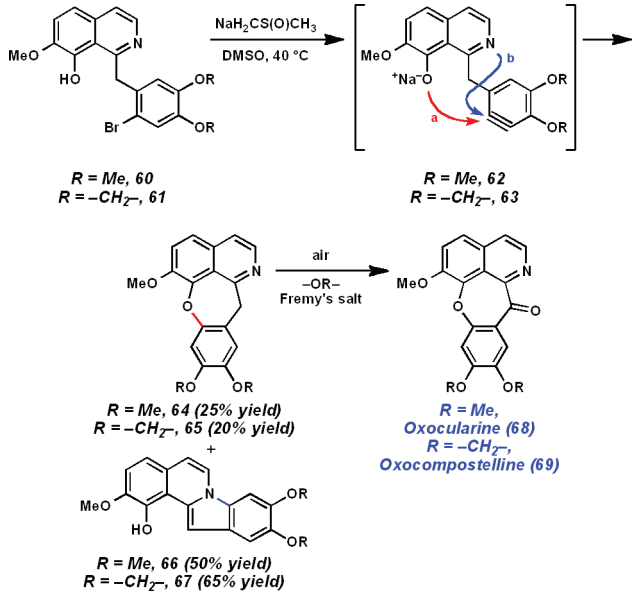
Scheme 15. Stermitz's 1974 Synthesis of Fagaronine Chloride (59)



bonds between an intermediate aryne and a pendant phenolate.[24] In the key aryne cyclization, treatment of isoquinoline **60** or **61** with sodium dimsylate led to the isolation of two new products each (**64** and **66**, or **65** and **67**, respectively) resulting from competing addition of nitrogen or oxygen to the aryne (path a or b) (Scheme 16). Though isolated as the minor products of

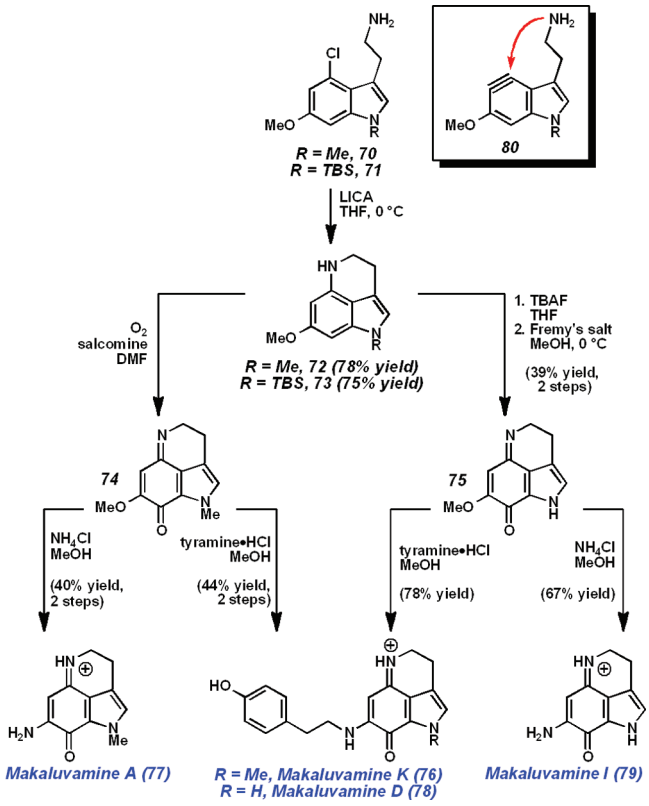
Scheme 16. Castedo's 1983 Synthesis of Oxocularine (68) and Oxocompostelline (69)



aryne cyclization, cyclic ethers **65** and **64** were readily oxidized either in air or through the use of Fremy's salt to afford oxocularine (**68**) and oxocompostelline (**69**).

To this point, all natural product syntheses employing a nucleophilic addition strategy relied on simple monocyclic arynes as the electrophilic reaction parter. In 1998, Iwao and co-workers turned to a 4,5-indolyne intermediate in their synthesis of makaluvamines A (**77**), D (**78**), I (**79**), and K (**76**) (Scheme 17).[25] Beginning with tryptamine intermediates **70** and **71**, and differing only in the indole nitrogen functionality, treatment with lithum isopropylcyclohexylamide (LICA) resulted in cyclization of the pendant amine onto the transient 4,5-indolyne (**80**), affording tricycles **72** and **73**, respectively, in very good yields. From here two paths diverge: for R = Me, oxidation of tricycle **72** with oxygen and salcomine yielded the iminoquinone (**74**). Alternatively, for R = TBS (**73**), desilylation of the indole nitrogen was followed by oxidation to iminoquinone **75**. Makaluvamines A (**77**) and I (**79**) were completed by treatment of iminoquinones **74** and **75**,

Scheme 17. Iwao's 1998 Synthesis of Makaluvamines A (77), D (78), I (79), and K (76)



respectively, with ammonium chloride in methanol. Alternatively, iminoquinones **74** and **75** were converted to makaluvamines K (**76**) and D (**78**), respectively, upon addition of tyramine hydrochloride.

Beginning in the late 1990s, Couture and co-workers embarked on a research program aimed at the synthesis of the aristolactam alkaloids by a general route involving a tandem aryne cyclization/olefination and radical cyclization. Their initial report focused on the synthesis of cepharanones A (**91**) and B (**90**)[26] and was soon followed by the synthesis of three more members of this alkaloid class, velutinam (**103**), taliscanine (**101**), and enterocarpam II (**102**).[27] In the synthesis of cepharanones A (**91**) and B (**90**), amides **81** and **82** were treated with excess KHMDS to effect simultaneous aryne generation and formation of phosphonate anion **83** (Scheme 18).[26] Following the initial cyclization of the pendant carbanion onto the aryne, isomerization of the resulting aryl anion (**84**) to the α-amino carbanion (**85**) preceded addition of *o*-iodobenzaldehyde and subsequent olefinination. The products of this tandem sequence, isoindolinones **86** and **87** (as a mixture of *E* and *Z* isomers), underwent smooth radical cyclization upon treatment with Bu_3SnH and AIBN to yield tetracycles **88** and **89**, respectively. Finally, cleavage of the *N*-protective groups furnished cepharanone A (**91**) and B (**90**).

This strategy was subsequently applied by the same group to the syntheses of additional aristolactam natural products **101**–**103**.[27] Amides **92** and **93** were converted to the respective isoindolinones (**95**–**97**) by the tandem aryne cyclization/olefination and radical cyclization sequence (Scheme 19). Finally, cleavage of the protective groups yielded velutinam (**103**), taliscanine (**101**), and enterocarpam II (**102**).

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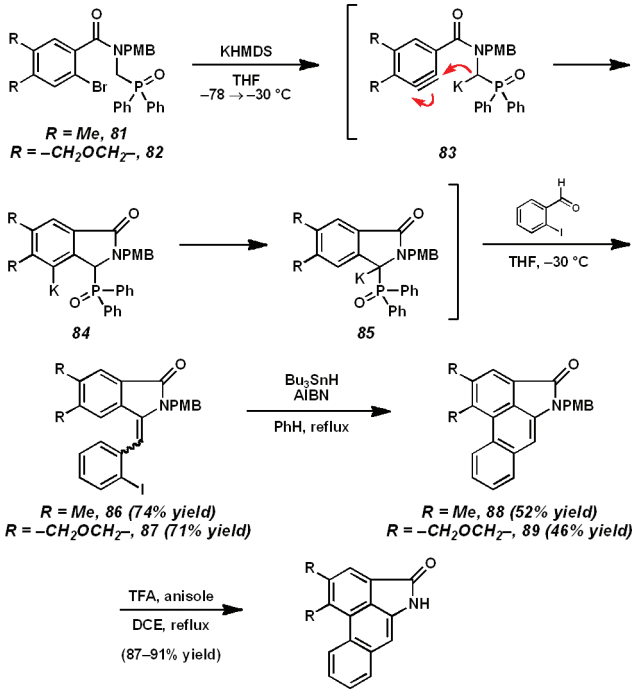
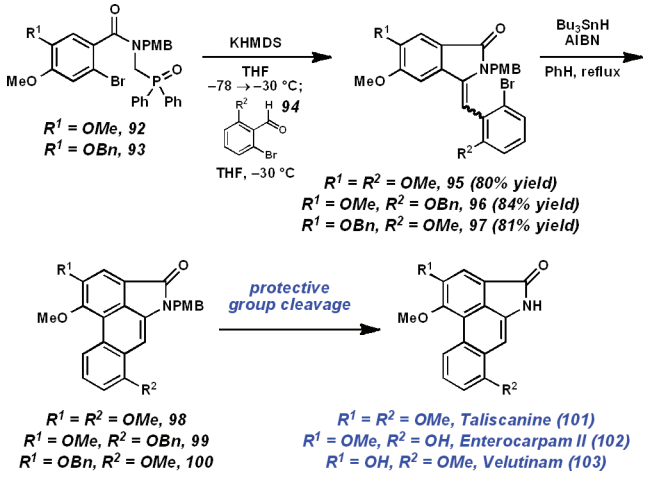
Scheme 18. Couture's 1997 Synthesis of Cepharanone A (91) and B (90)

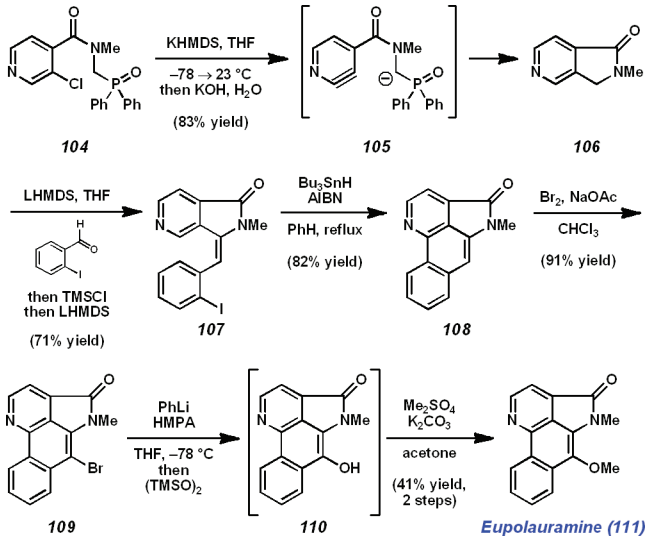


Scheme 19. Couture's 1998 Synthesis of Velutinam (103), Taliscanine (101), and Enterocarpam II (102)



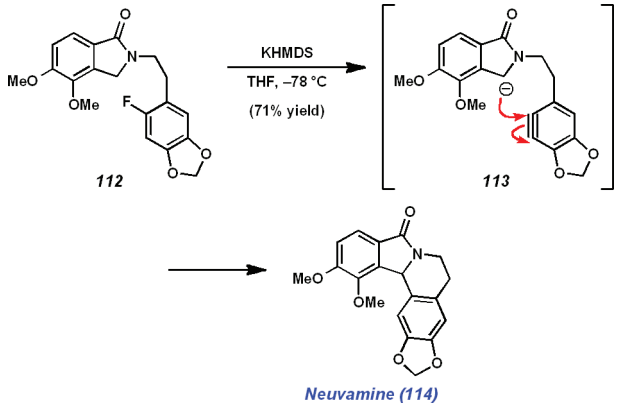
A final natural product synthesis reported by Couture and co-workers utilizing the aryne cyclization/olefination/radical cyclization sequence was that of eupolauramine (**111**) (Scheme 20).[28] This work is distinguished by the intermediacy of a 2,3-pyridyne (**105**) in place of the standard aryne employed above; the synthesis of eupolauramine (**111**) is one of only three syntheses to date to feature a pyridyne intermediate. Pyridyne cyclization of amide **104** produced azaisoindolinone **106** in good yield upon cleavage of the phosphoryl group. By performing the olefination in a stepwise fashion on azaisoindolinone **106**, excellent selectivity for the desired *E* isomer was achieved. Radical cyclization of iodide **107** yielded tetracycle **108**, which was advanced to eupolauramine (**111**) over three steps.

Scheme 20. Couture's 2001 Synthesis of Eupolauramine (111)



In a departure from the examples shown in Schemes 18–20, Couture and co-workers targeted the isooxindoloisoquinoline natural product neuvamine (**114**) by a simpler aryne nucleophilic addition.[29] Elimination of fluoroarene **112** with KHMDS and simultaneous deprotonation of the pendant isooxindole resulted in formation of the pentacyclic natural product neuvamine (**114**) (Scheme 21).

Scheme 21. Couture's 2004 Synthesis of Neuvamine (114)



To this point, all instances of nucleophilic additions to arynes in natural product synthesis have employed solely carbon, nitrogen, or oxygen nucleophiles. In 2005, Fairhurst and co-workers reported the synthesis of the thiazolone natural product S1319 (**120**), which relies upon an intramolecular nucleophilic addition of a sulfur atom to an aryne to form an intermediate benzothiazole and append the amino alcohol side-chain in a single operation (Scheme 22).[30] More specifically, treatment of thiocarbamate **115** with *t*-BuLi generated the aryne with concomitant lithiation of the thiocarbamate moiety (**116**). Following cyclization, the intermediate aryl anion species (**117**) was trapped by addition of aldehyde **118**, furnishing benzothiazole **119**. Finally, treatment of benzothiazole **119** with acid effected a global protective group cleavage, thereby completing the synthesis.

A unique approach to a pair of *Amaryllidaceae* alkaloids, trisphaeridine (**128**) and *N*-methylcrinasiadine (**127**), was reported in 2007 by Sanz and co-workers.[31] Their strategy relies upon the

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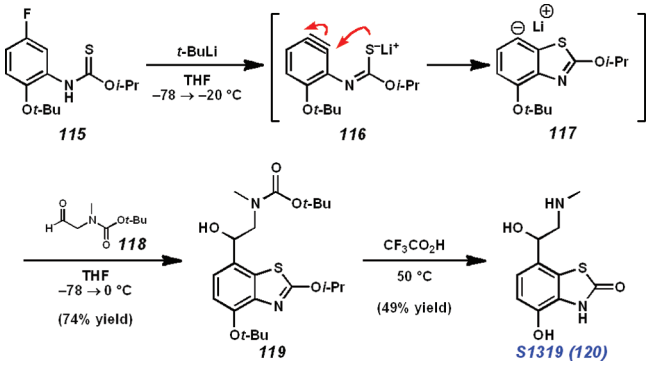
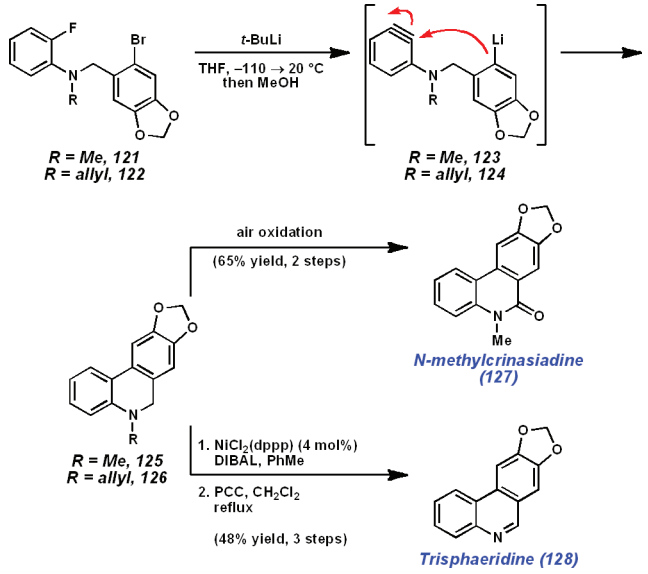
Scheme 22. Fairhurst's 2005 Synthesis of S1319 (120)



generation of an aryne through dehydrofluorination with concomitant lithium–halogen exchange of a pendant aryl bromide (Scheme 23). In this event, treatment of either *N*-methyl aniline

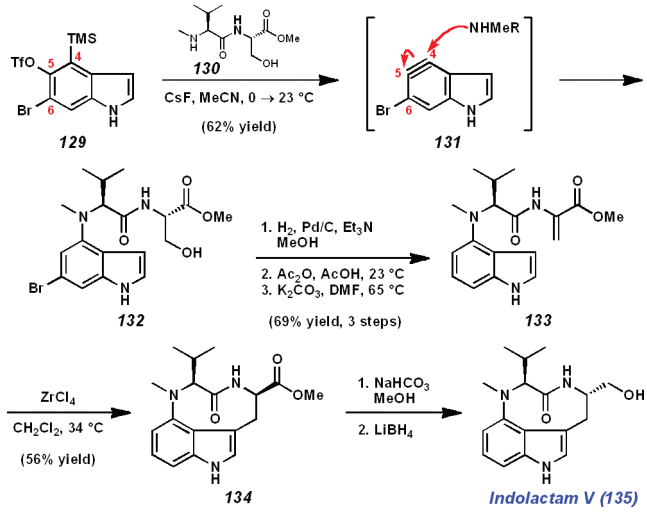
Scheme 23. Sanz's 2007 Synthesis of Trisphaeridine (128) and *N*-Methylcrinasiadine (127)



121 or *N*-allyl aniline **122** with *t*-BuLi generated the intermediate aryne tethered to the aryl lithium species (**123** and **124**), which underwent cyclization to yield tetracycles **125** and **126**, respectively. Notably, with strict temperature control, aryne formation occurs selectively on the fluoroarene, whereas lithium–halogen exchange is exclusive to the aryl bromide. Furthermore, Sanz, Barluenga, and co-workers have shown that this approach can be generalized to give access to a wide range of polycyclic aromatic structures.[32] *N*-allyl tetracycle **126** was advanced to trisphaeridine (**128**) by deallylation and oxidation, whereas the *N*-methyl variant (**125**) was converted to *N*-methylcrinasiadine (**127**) by air oxidation.

In addition to Iwao's synthesis of the makaluvamines (vide supra), Garg and co-workers recently employed a 4,5-indolyne intermediate en route to the macrocyclic lactam natural product, indolactam V (**135**) (Scheme 24).[33,34] In this case, the intermolecular nucleophilic addition of peptide **130** to 6-bromo-4,5-indolyne (**131**), generated in situ from silyl aryl triflate **129**, proceeds regioselectively to provide the 4-amino-6-bromo indole product (**132**) exclusively. Remarkably, the presence of the 6-bromo substituent reverses the native selectivity

Scheme 24. Garg's 2011 Synthesis of Indolactam V (135)



(i.e., addition to the 5-position) for nucleophilic additions to 4,5-indolyne.[34a,b] At this point, reduction of the bromide and elimination of the primary alcohol produced enamide **133**, which underwent conjugate addition with diastereoselective protonation upon treatment with $ZrCl_4$ to generate macrocycle **134**. Finally, epimerization of the newly formed C(9) stereocenter and reduction of the ester afforded indolactam V (**135**).

More recently, Garg and co-workers relied on an indolyne cyclization to complete the syntheses of several members of the welwitindolinone alkaloids, including the first total synthesis of *N*-methylwelwitindolinone C isothiocyanate (**143**) (Scheme 25).[35] Garg's strategy is centered around the intramolecular addition of an enolate into an indolyne (**138**) upon treatment of 5-bromo indole derivative **137** with sodamide. A 2.5:1 ratio of *C*- and *O*-arylation products **139** and **140**, respectively, was formed in a combined 46% yield. Importantly, the desired arylation product, **139**, contains the full tetracyclic framework of the welwitindolinone natural products and was accessible in gram quantites in only four steps from known carvone derivative **136**. Over the next 12 steps, tetracycle **139** was advanced to α-amino ketone **141**, which represents the point of divergence for each of the four natural products accessible by this route. Treatment of aminoketone **141** with thiocarbonate **142** directly furnished *N*-methylwelwitindolinone C isothiocyanate (**143**), while a two-step formylation/dehydration afforded *N*-methylwelwitindolinone C isonitrile (**144**). Finally, each of these natural products was subsequently converted to their corresponding C(3)-hydroxylated welwitindolinones (**145** and **146**) upon enolization and air oxidation.

The final example of nucleophilic addition to arynes in total synthesis was reported by Stoltz and co-workers in their synthesis of the tetracyclic meroterpenoid (+)-liphagal (**154**) (Scheme 26).[36] More specifically, an aryne cyclization was used to close the final ring of the natural product. Toward this end, secondary alcohol **148**, which was constructed over 10 steps from enantioenriched enone **147**, was successfully converted to dihydrobenzofuran **150** through the intermediacy of aryne **149**. Notably, a number of alternative methods to form this key carbon–oxygen bond, including palladium-catalyzed etherifications, failed to yield the desired product. Furthermore, reduction of the trisubstituted olefin of dihydrobenzofuran **150** to generate the trans-fused [6,7] ring system of tetracycle **151** could only be accomplished following the aryne cyclization.

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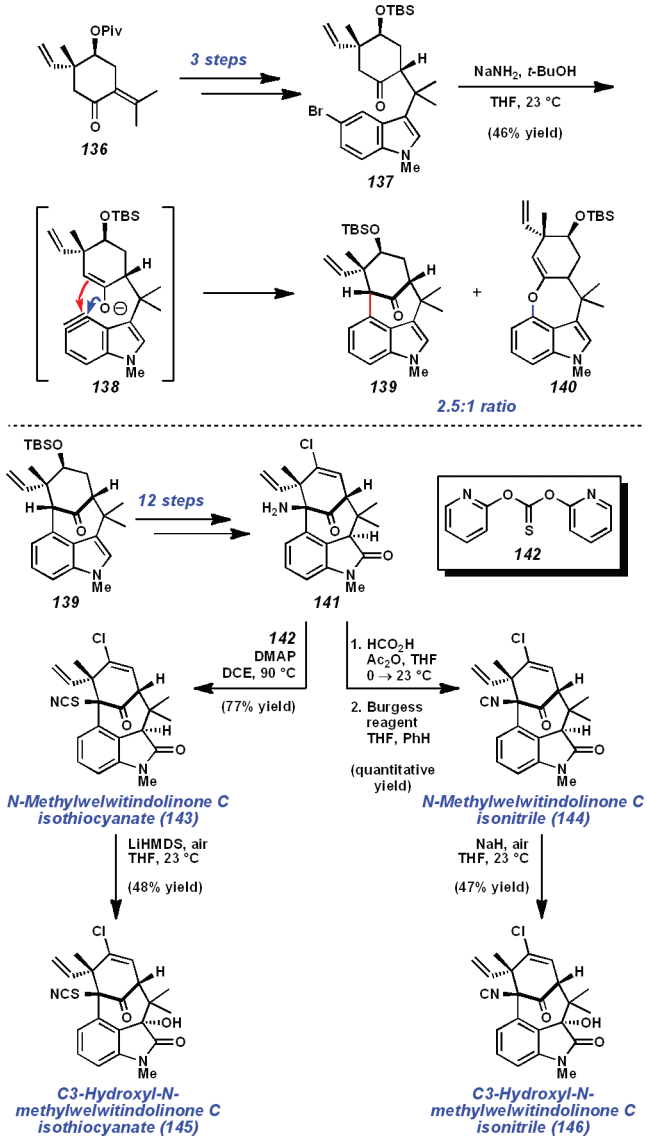
Scheme 25. Garg's 2011 Synthesis of the Welwitindolinone Alkaloids (143–146)



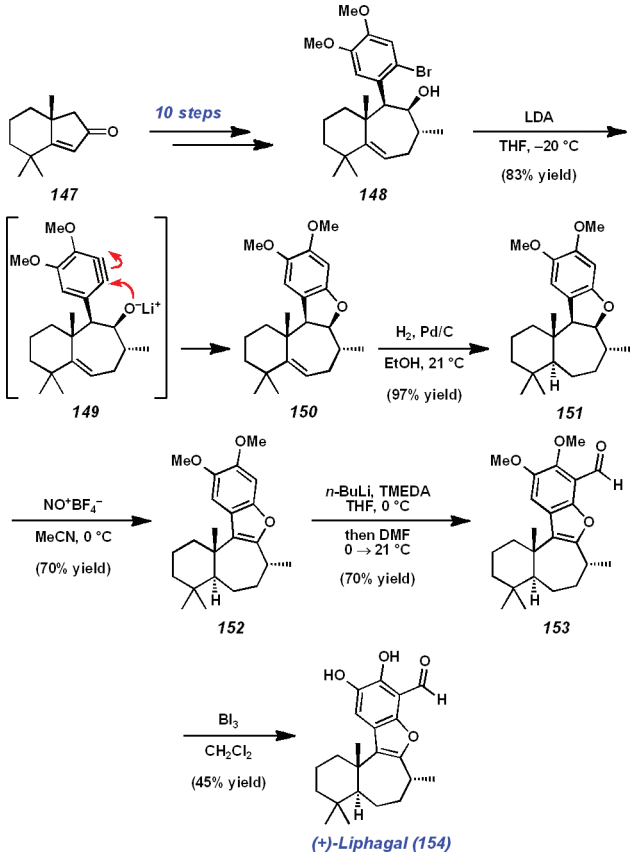
From this point, the synthesis of (+)-liphagal (**154**) was completed by oxidation of the dihydrobenzofuran (**151**), formylation, and demethylation.

2.2. Multicomponent Reactions of Arynes

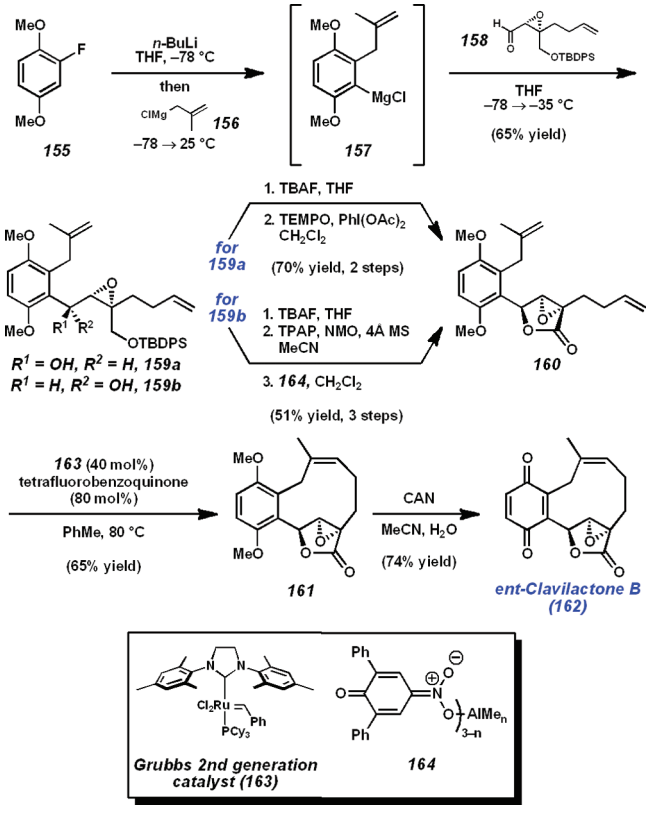
In general, arynes are well-suited to function as a relay species for multicomponent reactions. For over 70 years,[37] research groups have sought to develop three- and four-component methods for the rapid preparation of 1,2-disubstituted arenes.[38,6b] Despite the efficiency of such methodologies, only three approaches to natural products in the literature to date have employed multicomponent aryne strategies.

The first was Barrett and co-workers' synthesis of *ent*-clavilactone B (**162**) by a three-component coupling involving an aryne, an organomagnesium reagent, and an aldehyde (Scheme 27).[39] More specifically, treatment of fluoroarene **155** with *n*-BuLi resulted in the formation of an aryne to which methallylmagnesium chloride **156** was added. Next, the newly formed intermediate arylmagnesium species (**157**) underwent addition to the third component, aldehyde **158**, yielding benzylic alcohol **159** as a 2:1 mixture of diastereomers. The separable

Scheme 26. Stoltz's 2011 Synthesis of (+)-Liphagal (154)



Scheme 27. Barrett's 2006 Synthesis of *ent*-Clavilactone B (162)



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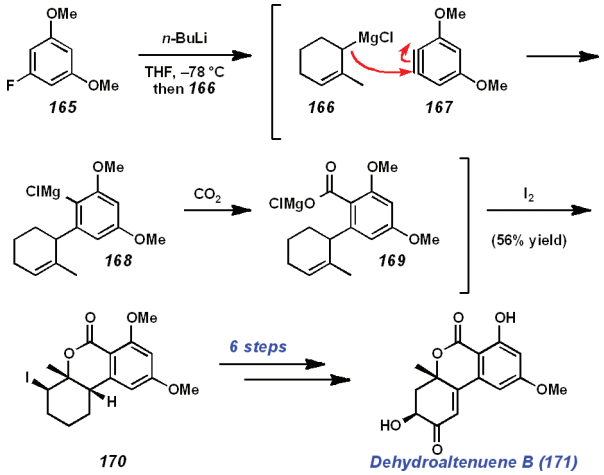
diastereomers **159a** and **159b** were individually converted to lactone **160** over two and three steps, respectively. Finally, ring-closing metathesis using a Grubbs second-generation catalyst (**163**) and oxidation afforded *ent*-clavilactone B (**162**).

More recently, in their synthesis of dehydroaltenuene B (**171**), Barrett and co-workers made excellent use of a four-component aryne coupling reaction to build the tricyclic core of the natural product (Scheme 28).[40] Beginning with elimination

Scheme 28. Barrett's 2008 Synthesis of Dehydroaltenuene B (171)



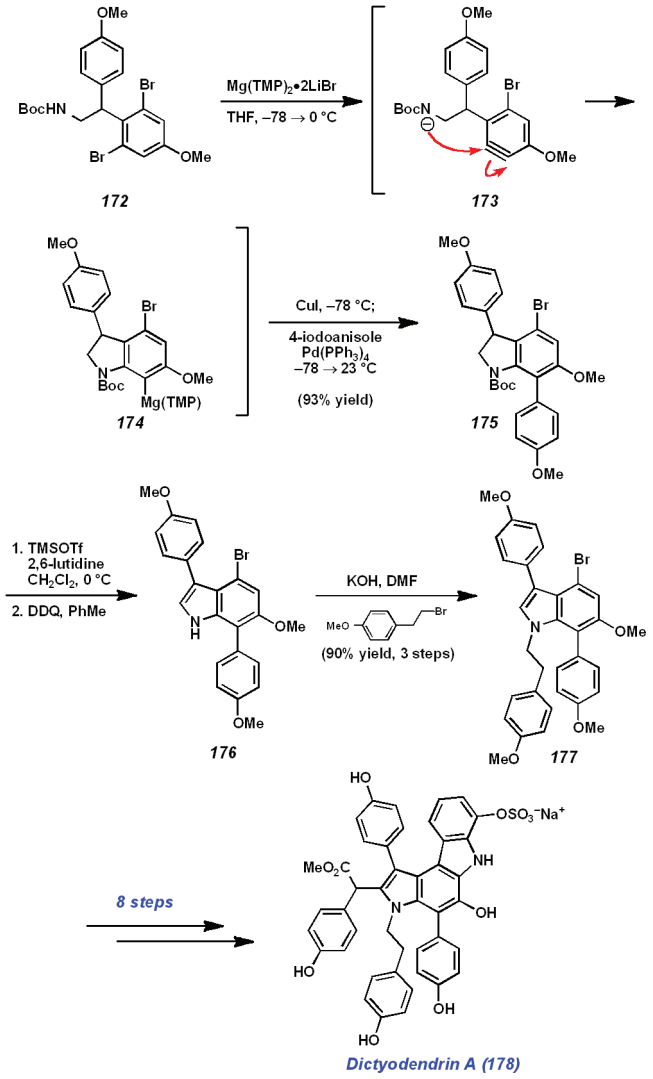
of fluoroarene **165** to generate aryne **167**, sequential addition of cyclohexenylmagnesium chloride **166**, carbon dioxide, and iodine generated iodolactone **170**. The authors propose that the reaction proceeds through addition of organomagnesium reagent **166** to aryne **167**, followed by carboxylation of the resulting arylmagnesium species (**168**), and finally diastereoselective iodolactonization. The multicomponent adduct (**170**) was then converted to dehydroaltenuene B (**171**) over a series of six additional steps.

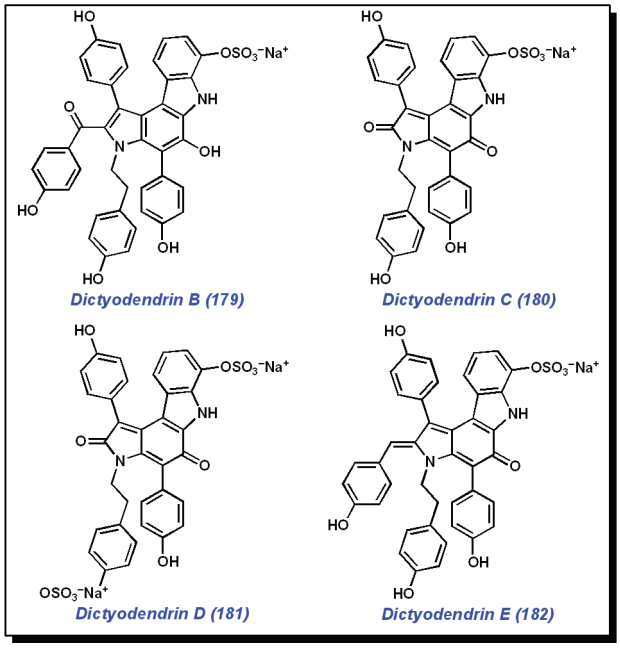
The most recent use of an aryne multicomponent coupling strategy was reported by Tokuyama and co-workers in their synthesis of dictyodendrins A–E (**178**–**182**).[41] In this case, an initial intramolecular nucleophilic addition of a nitrogen anion into a pendant aryne (**172** → **173**) was linked to a palladium-catalyzed Kumada–Tamao coupling to append *p*-iodoanisole (Scheme 29). The product of this three-component coupling (**175**) was then advanced over a three-step sequence to indole **177**, which was subsequently converted to dictyodendrin A (**178**) over eight steps. This same strategy was also applied to the synthesis of dictyodendrins B (**179**), C (**180**), D (**181**), and E (**182**).

3. BOND-INSERTION REACTION STRATEGIES

Carbon–carbon bond-insertion reactions are some of the most recent methodologies to emerge from the aryne literature. Remarkably, their use was first reported in the context of total synthesis, whereas generalized methods were not disclosed until 2005.[6a,42,43] Since these initial reports, a number of additional carbon–carbon bond-insertion methods have been disclosed.[44,38d] All of these general methods have been enabled by the development of silyl aryl triflate precursors,[3] which allow mild generation of arynes in the presence of a wide range of functional groups.

Scheme 29. Tokuyama's 2010 Synthesis of Dictyodendrins A–E (178–182)





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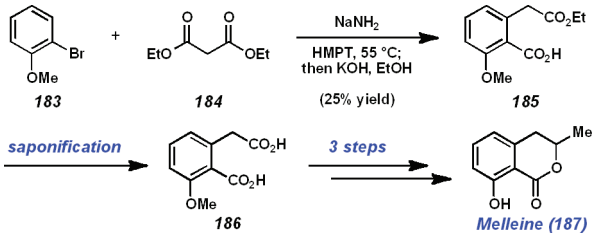
The earliest example of a total synthesis employing a σ-bond insertion reaction of an aryne in the synthesis of a natural product was completed by Guyot and Molho in 1973.[45] In this relatively simple example, a regioselective carboxyalkylation of *o*-bromoanisole (**183**) and diethyl malonate (**184**) resulted in the formation of benzoic acid **185** in 25% yield upon workup with KOH and ethanol (Scheme 30). Following saponification

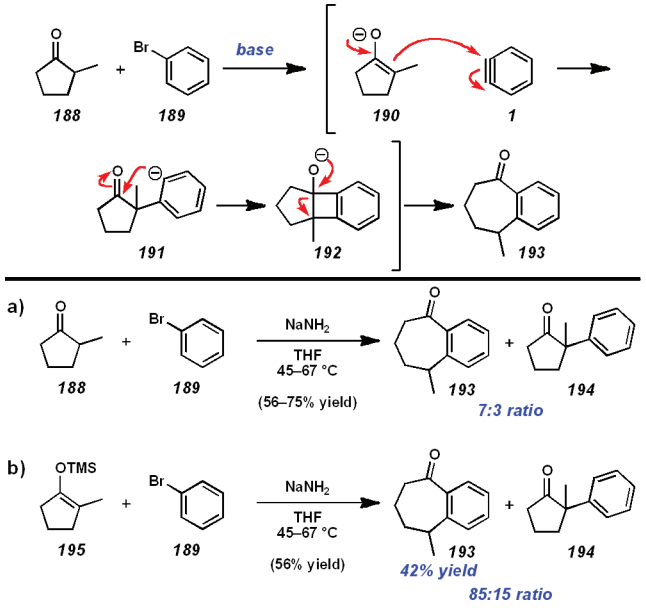
Scheme 30. Guyot's 1973 Synthesis of Melleine (187)



of the remaining ethyl ester, diacid **186** was converted to melleine (**187**) over three additional steps.

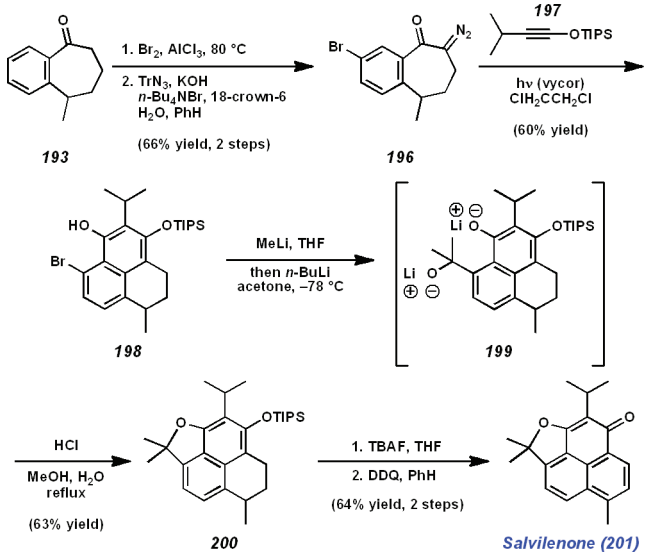
It was not until 1994 that an aryne σ-bond insertion reaction was used again in natural product synthesis. In their total synthesis of salvilenone (**201**), Danheiser and Helgason employed a ring-expansive carbon−carbon bond-insertion reaction between an aryne and a ketone enolate (Scheme 31).[46] More

Scheme 31. Danheiser's Ring-Expansive Carbon−Carbon Bond Insertion of Benzyne (1) into 2-Methylcyclopentanone (188)



specifically, ring-expansion of 2-methylcyclopentanone (**188**) with benzyne (**1**), generated in situ from bromobenzene (**189**) under basic conditions, produced benzannulated cycloheptanone **193** in addition to α-arylation product **194** in a 7:3 ratio (Scheme 31a). Importantly, this ratio could be improved to 85:15 by employing the silyl enol ether of 2-methylcyclopentanone (**195**), ultimately providing benzannulated cycloheptanone **193** in 42% isolated yield (Scheme 31b). Regioselective bromination of the arene ring followed by α-diazotization provided α-diazoketone **196** (Scheme 32). In the key transformation, irradiation of α-diazoketone **196** in the presence of

Scheme 32. Danheiser's 1994 Synthesis of Salvilenone (201)



alkyne **197** resulted in a cascade reaction consisting of Wolff rearrangement, [2 + 2]-ketene cycloaddition, 4π electrocyclic ring-opening, and 6π electrocyclic ring-closing to furnish tricycle **198**. From this point, completion of salvilenone (**201**) was readily accomplished by annulation of the final ring, desilylation, and oxidation. In full, salvilenone (**201**) was prepared in seven steps and 9% overall yield from 2-methylcyclopentanone (**188**) and bromobenzene (**189**).

Soon after Danheiser's ring-expansive C−C bond insertion studies, the Danishefsky group employed a σ-bond insertion of dimethyl malonate (**204**) with a functionalized aryne (**208**) en route to the enediyne antibiotic dynemicin A (**202**).[47] Much like the enediynes calicheamicin[48] and esperamicin,[49] dynemicin A (**202**) has demonstrated potent antitumor activity (Scheme 33).[50] Danishefsky and co-workers focused their approach to the natural product on a late-stage convergent assembly of the hexacyclic ring system, one-half of which contained the sensitive enediyne functionality. The second fragment was readily accessed in three steps beginning with the carboxyalkylation of the aryne derived from bromoarene **203** with the lithium salt of dimethyl malonate (**204**) to yield diester **205**. Mechanistically, this carboxyalkylation reaction is believed to proceed through a stepwise [2 + 2]-addition of the lithium malonate to the aryne (**208**) followed by a retro-Dieckmann fragmentation of the resultant alkoxybenzocyclobutenyl intermediate (**210**). Although the reaction of a malonate with an aryne had been reported prior to this synthesis by Guyot, the yields were significantly lower and the desired carboxyalkylation products were accompanied by extensive side-product formation.[45] Saponification of the diester was followed by treatment with (trimethylsilyl)ethynyl ether to furnish cyclic anhydride **207**, which comprises the D and E rings of the natural product.

With a suitable DE-ring fragment in hand, cyclic anhydride **207** was joined to enediyne-containing ABC-ring fragment **211** (Scheme 34). Deprotonation of cyclic anhydride **207** and addition to quinone imine **211** resulted in a formal [4 + 2]-cycloaddition and loss of CO_2 to yield a putative anthrone (**212**), which was immediately oxidized to the anthracenol (**213**). Further oxidation to the corresponding anthraquinone (**214**)

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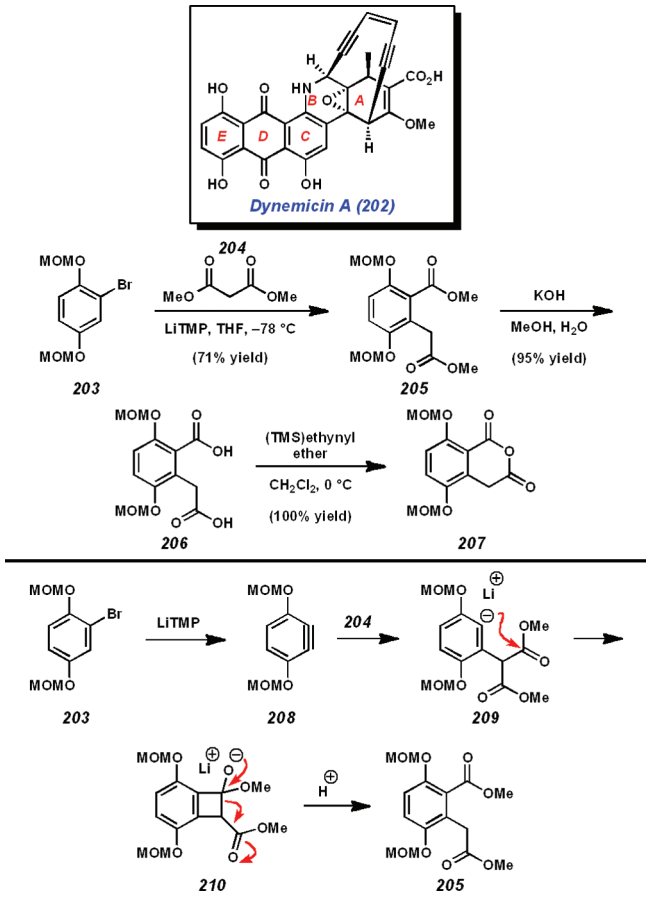
Scheme 33. Dynemicin A (202) and the Synthesis of Cyclic Anhydride 207 by Carboxyalkylation of Arynes (1995)

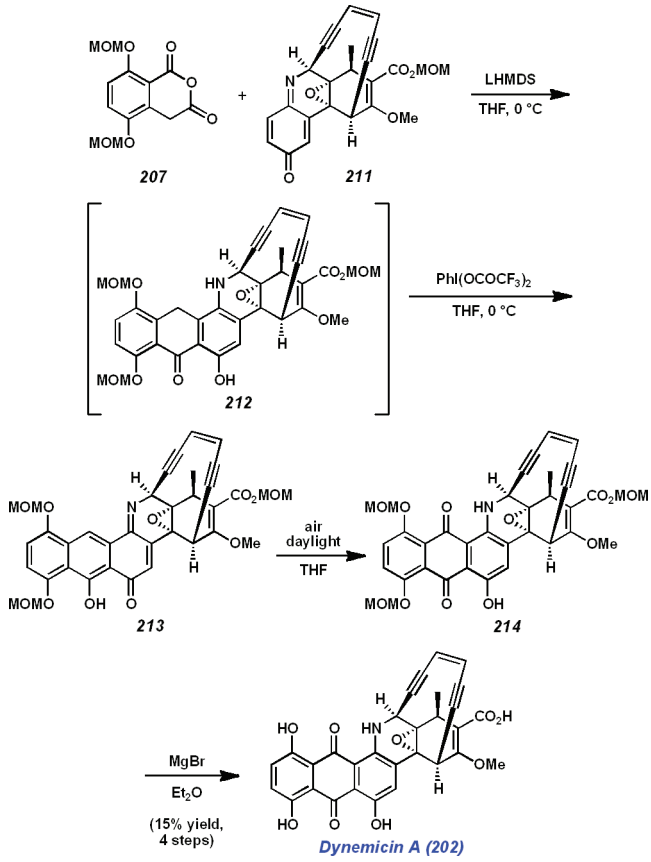


followed by global deprotection yielded dynemicin A (**202**) in 15% yield over the final four steps.

As in the Danishefsky synthesis of dynemicin A, Kita and co-workers employed a carboxyalkylation with dimethyl malonate (**204**) en route to fredericamycin A (**231**).[51] However, in this case, an unsymmetrical aryne derived from trimethoxy bromoarene **215** was used (Scheme 35). As a result, the carboxyalkylation proceeded with little regioselectively to give a mixture of two separable isomeric products (**216** and **217**) in a 2:3 ratio. Following separation, diesters **216** and **217** were each converted to their respective α-methoxy cyclic anhydrides, **220** and **221**, which represent the A and B rings of the natural product.

At the time of this work, the absolute configuration of fredericamycin A (**231**) was unknown. Strategically, the authors devised a way to convert each isomeric cyclic anhydride (**220** and **221**) into each enantiomer of the natural product by coupling them to an enantioenriched CDEF-ring fragment (**227**). Mechanistically, upon treatment of **220** or **221** with base, a reactive pyrone structure was generated (**223**) capable of reacting with dienophile **222** by a formal [4 + 2]-cycloaddition (Scheme 36). Subsequent CO_2 extrusion and syn elimination then produced the fully aromatized products. In this event, cycloadducts **228** and **229** were isolated in 97% and 94% enantiomeric excess (ee), respectively (Scheme 37). Methylation of the free phenols yielded the enantiomeric ethers ((*R*)-**230** and (*S*)-**230**). Finally, over a series of five steps, each of these intermediates ((*R*)-**230** and (*S*)-**230**) was converted to each enantiomer of the natural product (**231** and ***ent*-231**).

Scheme 34. Completion of Danishefsky's Synthesis of Dynemicin A (202) (1995)



Ultimately, Kita and co-workers determined that the compound bearing the *S* absolute configuration at the single stereocenter was the naturally occurring fredericamycin.

Following their synthesis of fredericamycin A, Kita and co-workers further applied this carboxyalkylation of arynes in their preparation of γ-rubromycin (**237**) by the regioselective reaction of the aryne derived from exocyclic enol ether **232** and dimethyl malonate (**204**) (Scheme 38).[52] The resultant carboxylalkylation product (**234**) was then advanced over a number of steps to key spiroketal **236**. Finally, an additional 12 steps converted spiroketal **236** to the natural product, γ-rubromycin (**237**).

Despite the previous five examples of aryne acyl-alkylation with malonate-derived nucleophiles, a thorough examination of this specific reactivity was not undertaken until 2005 when Stoltz and co-workers reported the reaction of arynes derived from silyl aryl triflates[3] (e.g., **238**) with β-ketoesters (e.g., **239**) (Scheme 39).[42] Of particular interest is the ring-expansive variant of this transformation, employing cyclic β-ketoesters. To date, the Stoltz group has employed this method in the enantioselective syntheses of two natural products: the isopavine alkaloid amurensinine (**245**) and the benzannulated macrolatone curvularin (**250**). In each of these examples, the acyl-alkylation reaction is used to construct key C−C bonds between a functionalized aryne and a β-ketoester to convergently assemble the natural products.

In the enantioselective total synthesis of (+)-amurensinine (**245**), the tetracyclic core of the alkaloid (**243**) was targeted by an acyl-alkylation of a sesamol-derived aryne (generated in situ from silyl aryl triflate **241**) with benzannulated β-ketoester **242** (Scheme 40).[53]

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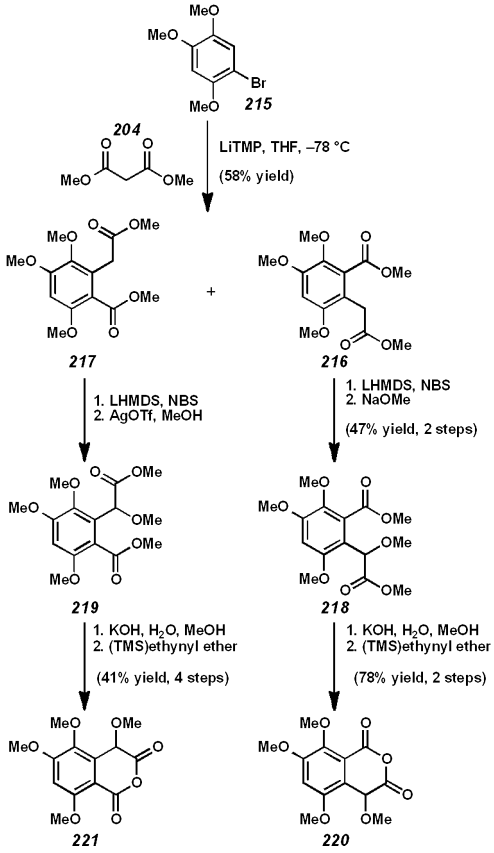
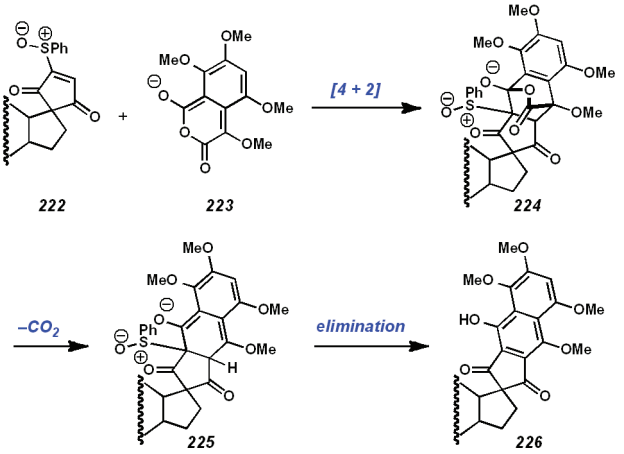
Scheme 35. Synthesis of Cyclic Anhydrides 220 and 221 by a Carboxyalkylation Route

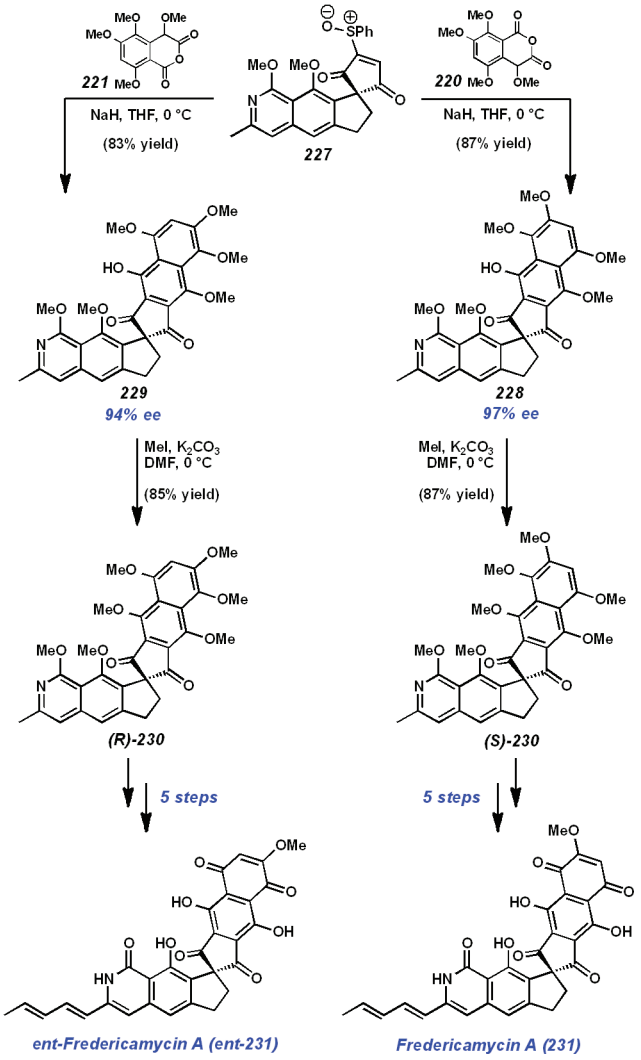


Scheme 36. Mechanism for Coupling of the AB-Ring Fragment and CDEF-Ring Fragment

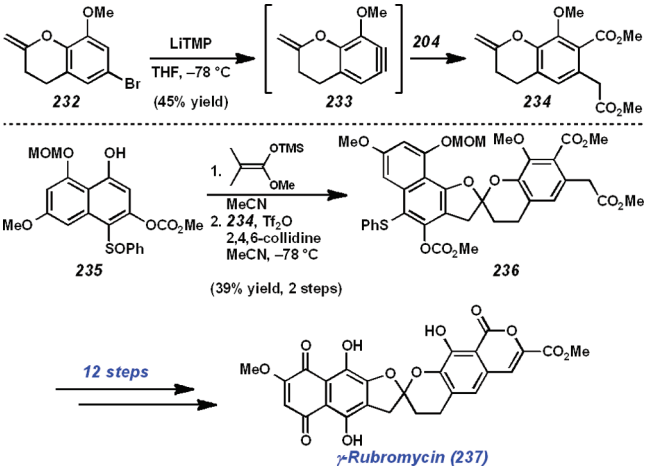


In this case, the aryne formation and the subsequent acylalkylation are triggered by a mild fluoride source, instead of the strong bases used in prior examples. The resulting tetracycle (**243**) contained all but one of carbons present in the natural product. To render the synthesis enantioselective, Stoltz and co-workers employed a palladium-catalyzed oxidative kinetic resolution of activated alcohols.[54] Following diastereoselective reduction and selective protection of the primary alcohol, oxidative kinetic resolution of secondary benzylic alcohol (±)-**244** provided enantioenriched alcohol (−)-**244** in 47% yield and >99% ee, corresponding to a selectivity factor

Scheme 37. Kita's 1999 Stereodivergent Approach to Fredericamycin (231)



Scheme 38. Kita's 2007 Synthesis of γ-Rubromycin (237)



of >47. From this point, the final ring of amurensinine was installed, completing the natural product in seven additional steps. Overall, the enantioselective synthesis of (+)-amurensinine was completed in 12 steps from silyl aryl triflate **241** and β-ketoester **242**.

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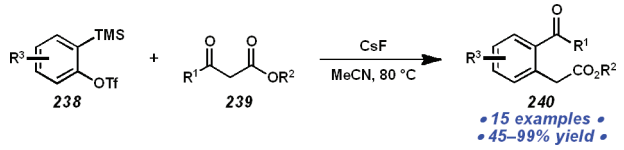
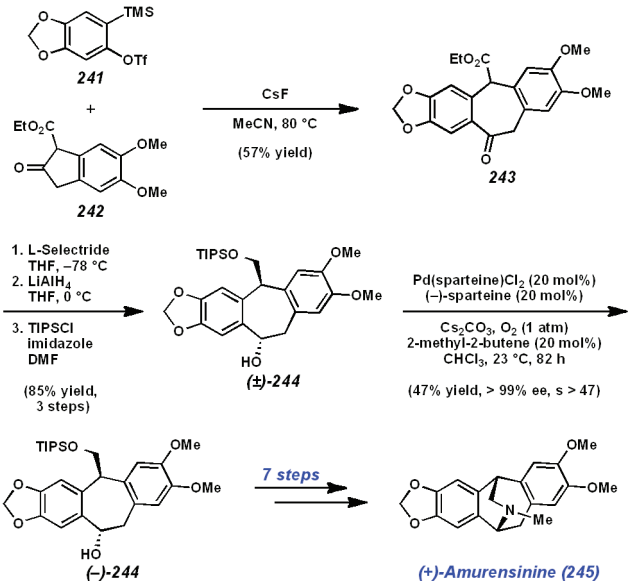
Scheme 39. Stoltz's Acyl-alkylation of Arynes with β-Ketoesters

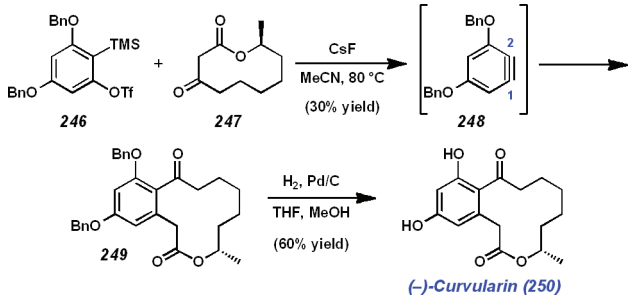


Scheme 40. Stoltz's 2006 Synthesis of (+)-Amurensinine (245)



In a second application of a ring-expansive aryne acyl-alkylation, the Stoltz lab reported the enantioselective synthesis of (−)-curvularin (**250**), a benzannulated macrolactone natural product.[55] The 12-membered lactone of the natural product was targeted by the reaction of an unsymmetrical aryne (**248**) (generated in situ from silyl aryl triflate **246**) with 10-membered β-ketolactone **247** (Scheme 41). Prior to this work,

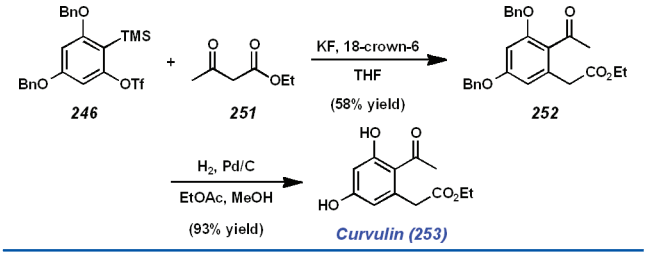
Scheme 41. Stoltz's 2010 Enantioselective Synthesis of (−)-Curvularin (250)



β-ketolactones had not been employed as substrates in the acyl-alkylation reaction. Application of the acyl-alkylation transformation in this way results in regioselective formation of the benzannulated lactone, without any formation of the undesired isomeric product derived from initial nucleophilic addition to C(2). Finally, debenzylation revealed the resorcinol core, completing (−)-curvularin (**250**) in six steps from known compounds.

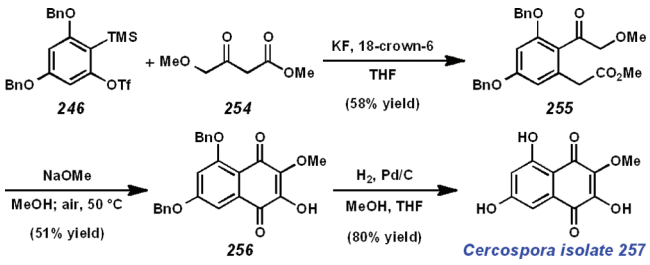
Concurrent with their report on (−)-curvularin, Stoltz and co-workers reported two additional syntheses of natural products utilizing the same protected resorcinylic silyl aryl triflate (**246**).[56] Acyl-alkylation of silyl aryl triflate **246** with ethyl acetoacetate (**251**) under modified conditions followed by debenzylation produced curvulin (**253**), an acyclic relative of curvularin often isolated from the same natural sources (Scheme 42). Alternatively, acyl-alkylation of precursor **246**

Scheme 42. Stoltz's 2010 Synthesis of Curvulin (253)



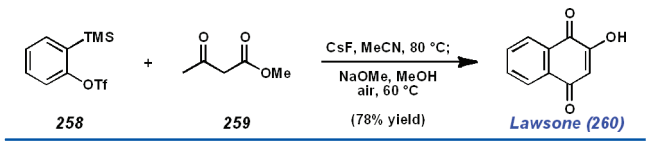
with γ-methoxy-β-ketoester **254**, followed by base-mediated cyclization and aerobic oxidation yielded hydroxynaphthoquinone **256** (Scheme 43). Debenzylation of this intermediate (**256**) provided *Cercospora* isolate **257**.

Scheme 43. Stoltz's 2010 Synthesis of *Cercospora* Isolate 257



The acyl-alkylation/condensation/air oxidation method for the formation of hydroxynaphthoquinones was further developed into a one-pot procedure by Stoltz and co-workers.[57] This streamlined method was demonstrated by the one-step synthesis of lawsone (**260**) from unsubstituted silyl aryl triflate **258** and methyl acetoacetate (**259**) by treatment of the acyl-alkylation product with sodium methoxide in situ (Scheme 44).

Scheme 44. Stoltz's 2009 Synthesis of Lawsone (260)



Shortly after publication of Stoltz's syntheses of (−)-curvularin and related natural products, Yoshida and co-workers employed a similar strategy toward cytosporone B (**267**) and phomopsin C (**264**) (Scheme 45).[58] Acyl-alkylation of ethyl 3-oxodecanoate (**261**) with unsymetrical dimethoxy aryne precursor **262** regioselectively yielded arene **263** as a single isomer in modest yield. Subsequent selective monodemethylation then afforded phomopsin C (**264**). Alternatively, acyl-alkylation of silyl aryl triflate **265** with ethyl 3-oxodecanoate (**261**) provided arene **266**, which was converted into

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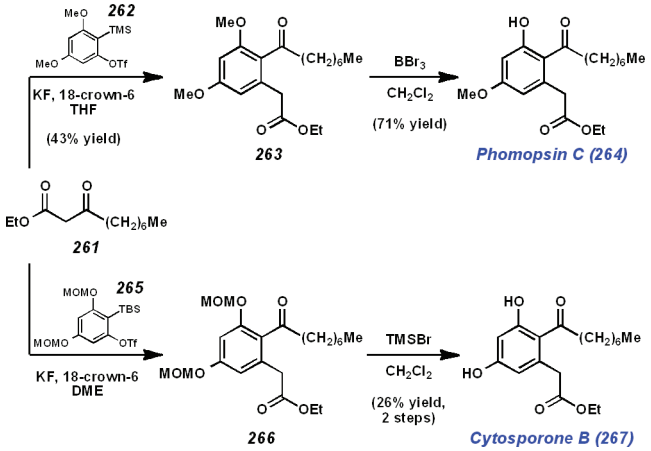
Scheme 45. Yoshida's 2010 Syntheses of Phomopsin C (264) and Cytosporone B (267)



cytosporone B (**267**) upon cleavage of the methoxymethyl ether groups.

4. [4 + 2]- AND [2 + 2]-ARYNE CYCLOADDITION STRATEGIES

4.1. [4 + 2]-Aryne Cycloaddition Strategies

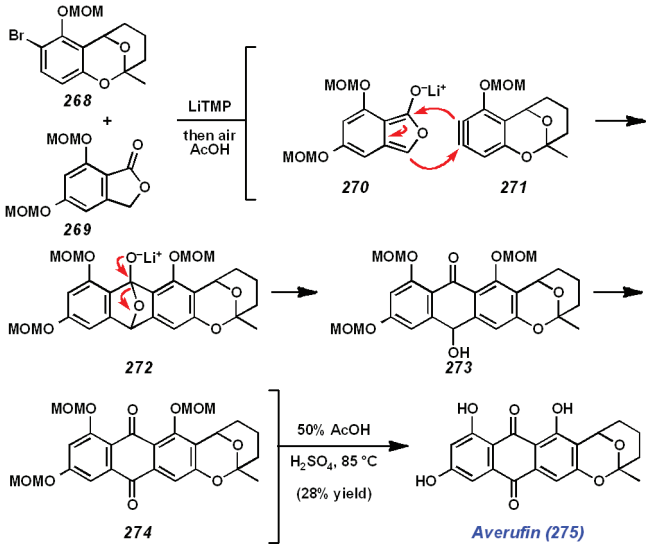
The prevalence of [4 + 2]-aryne cycloadditions as a strategy for natural product total synthesis is second in the literature only to the use of nucleophilic additions. However, despite the large volume of such approaches, there remain significant limitations to the application of aryne [4 + 2]-cycloadditions. Notably, the majority of examples described herein, with a few exceptions, require constrained dienes, most commonly furans. The use of acyclic dienes in natural product synthesis is still a considerable challenge and represents an underexplored area of aryne methodology.

Mechanistically, although some of the [4 + 2]-cycloadditions may proceed by a concerted mechanism, it is more likely that the majority of examples discussed herein occur by stepwise processes. Generally speaking, substitution on both the aryne and the diene components can heavily influence the reaction pathway to favor one mechanism over the other.

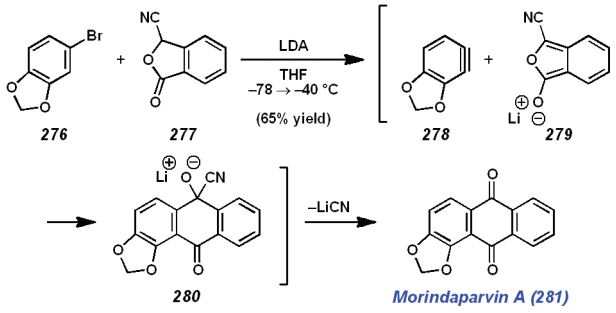
The first example of the application of an aryne [4 + 2]-cycloaddition (formal, stepwise, or concerted) in the synthesis of a natural product comes from Townsend and co-workers' preparation of averufin (**275**) in 1981 (Scheme 46).[59] Averufin (**275**) was targeted by a formal aryne [4 + 2]-cycloaddition reaction that would build the central quinone ring from a benzannulated lactone (**269**) and an aryl bromide (**268**). In the key transformation, treatment of aryl bromide **268** and lactone **269** with LiTMP resulted in enolization of the lactone (**270**) and concomitant formation of aryne **271**. Regioselective addition of enolate **270** to aryne **271** was followed by addition of the resulting aryl anion to the lactone to generate a hemiacetal (**272**). Elimination of the alkoxide from the tetrahedral intermediate furnished pentacycle **273**, which then underwent addition of acetic acid and exposure to air resulting in oxidation to the quinone (**274**). Finally, removal of the methoxy methyl ether protecting groups yielded averufin (**275**).

Following Townsend's work on averufin (**275**), Biehl and co-workers employed this same strategy to the synthesis of four different anthraquinone natural products, morindaparvin A (**281**), rubiadin 1-methyl ether (**284**), rubiadin (**285**), and damnacathol (**286**). In the first example, morindaparvin A (**281**) was accessed by reaction of 3-cyanophthalide **277** with aryl bromide **276** in the presence of LDA (Scheme 47).[60]

Scheme 46. Townsend's 1981 Synthesis of Averufin (275)



Scheme 47. Biehl's 1989 Synthesis of Morindaparvin A (281)



Notably, the use of a 3-cyanophthalide (**277**) in place of a simpler lactone removed the need for subsequent air oxidation as in the case of averufin. Instead, cycloaddition and fragmentation generated cyanohydrin **280**, which furnished the anthraquinone (**281**) directly upon ejection of cyanide.

The second of Biehl's reports applied this same method to the synthesis of rubiadin (**285**), rubiadin 1-methyl ether (**284**), and damnacathol (**286**) (Scheme 48).[61] Replacing dioxolane **276** with trisubstituted bromoarene **282** led to anthraquinone **283**, the point of divergence from which the three products were targeted. Monodemethylation with HBr in acetic acid produced rubiadin 1-methyl ether (**284**), whereas bisdemethylation with excess BBr_3 furnished rubiadin (**285**). Alternatively, benzylic oxidation of anthraquinone **283** followed by monodemethylation yielded damnacathol (**286**). Biehl and co-workers additionally completed a formal total synthesis of 4-demethoxydaunomycinone by this same method.[62] In a subsequent publication, Schmalz and co-workers employed a similar approach to an analogue of the natural product mumbaistatin.[63]

In the same year as Townsend's seminal report of an aryne [4 + 2]-cycloaddition employed in total synthesis, Best and Wege published the total synthesis of mansonone E (**294**).[64] Additional syntheses of mansonones I (**295**) and F (**296**) and biflorin (**297**) were reported the following year from a common intermediate.[65] In that work, Best and Wege reported the first intramolecular Diels–Alder reaction of an aryne by tethering an anthranilic acid-derived aryne precursor[2d,e] to a furan. Preparation of cycloaddition precursor **288** was accomplished in five steps beginning with phenol **287** (Scheme 49). Upon

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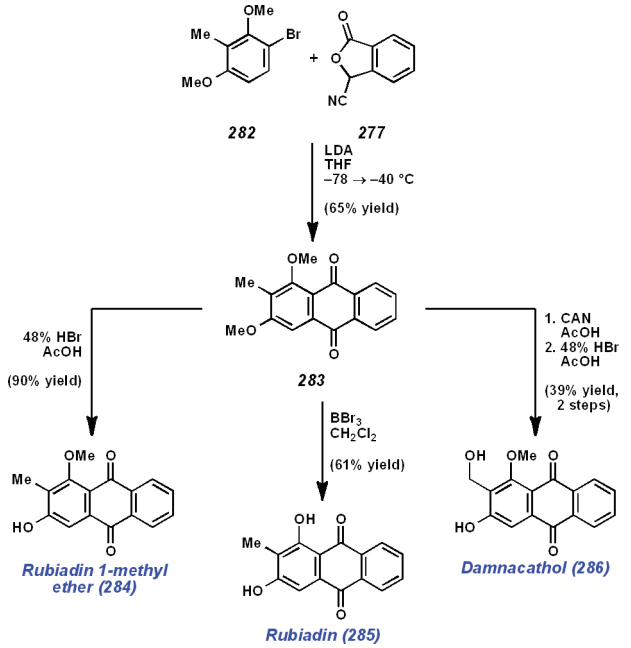
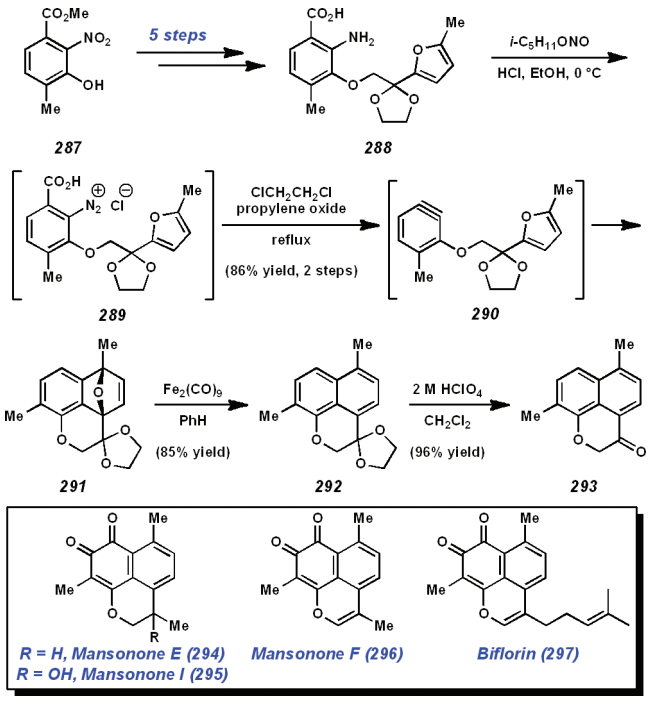
Scheme 48. Biehl's 1995 Synthesis of Rubiadin (285), Rubiadin 1-Methyl Ether (284), and Damnacathol (286)



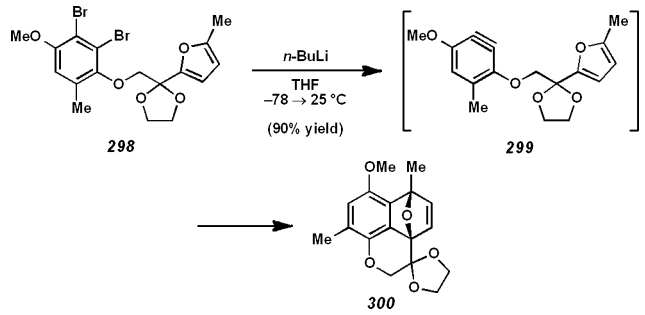
Scheme 49. Best and Wege's 1981 Synthesis of Mansonone Precursor 293



treatment of anthranilic acid **288** with i-$C_5H_{11}ONO$ in acidic ethanol, an intermediate diazonium hydrochloride (**289**) was generated that then underwent spontaneous thermal decomposition to the aryne (**290**). Cycloaddition between the aryne and the pendant furan then produced pentacyclic cycloadduct **291** in 86% yield. Subsequent deoxygenation and acetal cleavage yielded tricycle **293**, which was readily converted to mansonones E (**294**), I (**295**), and F (**296**) and biflorin (**297**).

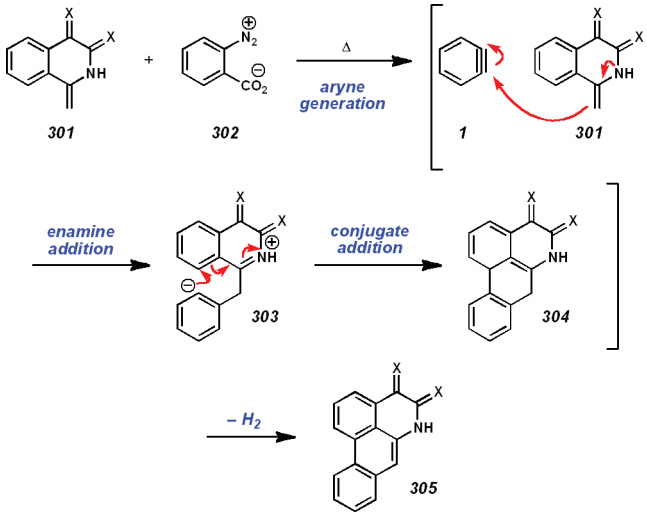
Given the potential risk of explosion associated with use of anthranilic acid-derived aryne precursors,[66] Best and Wege noted that the key intramolecular Diels–Alder cycloaddition can also be performed by elimination of the corresponding *o*-dibromide compound (**298**) with *n*-BuLi, producing cycloadduct **300** in 90% yield (Scheme 50).

Scheme 50. Alternative Aryne Generation in the Intramolecular Aryne Diels–Alder toward Mansonone E (294)



Beginning in the mid-1980s, Castedo and co-workers embarked on a program spanning more than 10 years in which they investigated the synthesis of various isoquinoline-derived alkaloids by intermolecular aryne Diels–Alder cycloadditions. One of the various general strategies they developed relied upon the [4 + 2]-cycloaddition of substituted arynes (both symmetrical and unsymmetrical) with 1-methylene-substituted isoquinoline derivatives such as **301** to generate aporphinoid alkaloids (Scheme 51).[67] Mechanistically, this annulation can be envisioned to proceed in a stepwise fashion beginning with an enamine addition of isoquinoline derivative **301** to an aryne (**1**) to generate an intermediate aryl anion (**303**). The aryl anion (**303**) can then undergo a dearomatizing conjugate addition to the pendant iminium ion to produce tetracycle **304**, which then undergoes a formal loss of hydrogen to give rise to aromatized tetracycle **305**. By varying the substitution on both the 1-methylene isoquinoline derivative (**301**) and the aryne (**1**), a variety of alkaloids were prepared, including PO-3 (**329**), norcepharadione B (**309**), cepharadione B (**311**),

Scheme 51. Castedo's General Approach to the Aporphinoid Alkaloids



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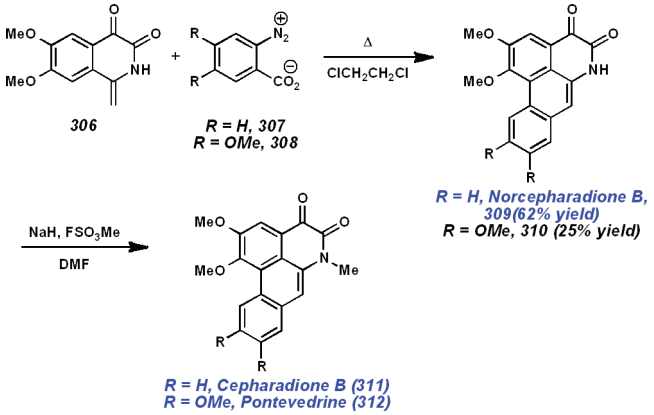
duguenaine (**322**), pontevedrine (**312**), *O*-methylatheroline (**324**), and lysicamine (**323**).[68]

In the syntheses of norcepharadione B (**309**), cepharadione B (**311**), and pontevedrine (**312**), reaction of 6,7-dimethoxy-1-methylene isoquinoline-3,4-dione (**306**) with either benzenediazonium-2-carboxylate (**307**) or its dimethoxy relative (**308**) yielded norcepharadione B (**309**) and desmethyl pontevedrine (**310**), respectively (Scheme 52).[68a] N-Methylation of each of

Scheme 52. Castedo's 1991 Syntheses of Norcepharadione B (309), Cepharadione B (311), and Pontevedrine (312)



these compounds (**309** and **310**) furnished the natural products cepharadione B (**311**) and pontevedrine (**312**).

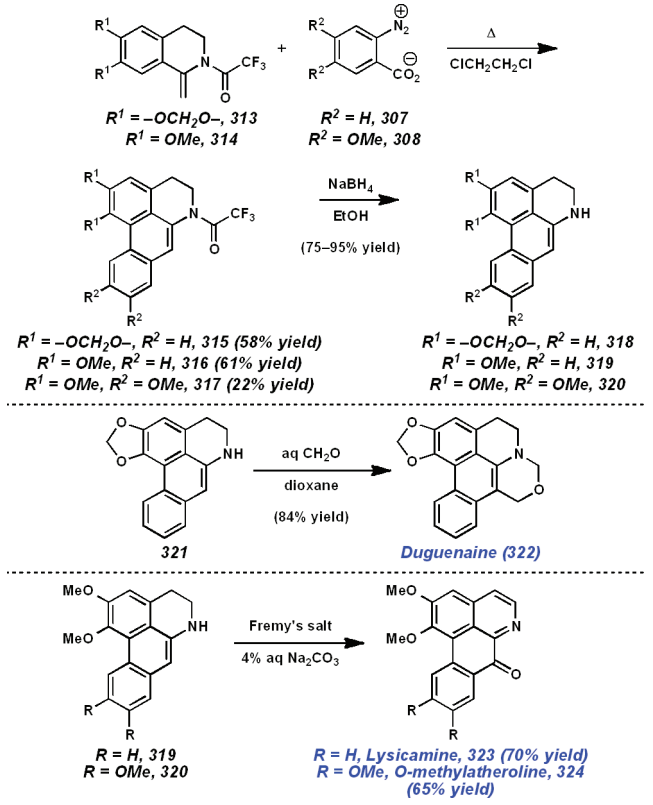
A variation on this theme produced duguenaine (**322**), lysicamine (**323**), and *O*-methylatheroline (**324**) by employing differentially substituted 1-methylene-3,4-dihydroisoquinoline cycloaddition partners (**313** and **314**) (Scheme 53).[68a] The cycloadducts of these aryne [4 + 2]-reactions (**315**–**317**) were each treated with $NaBH_4$ to remove the labile trifluoroacetamides. Condensation of pentacycle **321** with formaldehyde furnished duguenaine (**322**) in 84% yield. Alternatively, oxidation of tetracycles **319** and **320** with Fremy's salt provided the isoquinoline alkaloids lysicamine (**323**) and *O*-methylatheroline (**324**) in 70% and 65% yields, respectively.

Finally, the synthesis of the alkaloid PO-3 (**329**) highlights the excellent selectivity displayed by this particular [4 + 2]-cycloaddition when applied to unsymmetrical arynes, such as that derived from 3-methoxy benzenediazonium-2-carboxylate (**325**) (Scheme 54).[68] Following the cycloaddition, removal of the *N*-trifluoroacetyl protective group, oxidation with Fremy's salt, methylation, and thermolysis provided PO-3 (**329**).

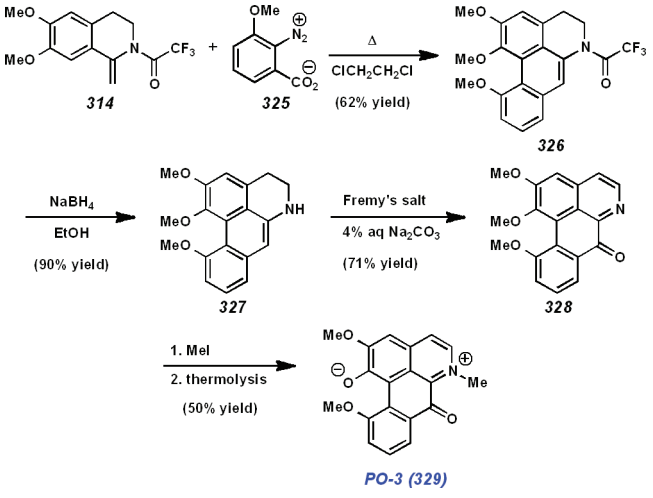
As part of their ongoing program aimed at the development of new aryne [4 + 2]-cycloadditions for alkaloid total synthesis, Castedo and co-workers targeted another class of isoquinoline-derived natural products—the protoberberines—by the cycloaddition of isoquinolinepyrrolinediones (e.g., **330**) with arynes (e.g., **1**) (Scheme 55).[69] Mechanistically, this reaction sequence begins with enamide addition to the aryne, generating intermediate aryl anion **331**. Instead of the conjugate addition observed in the synthesis of the aporphinoids (vide supra), transannular addition of the aryl anion to the amide carbonyl produces bicyclic intermediate **332**, which undergoes subsequent CO extrusion and tautomerization to furnish tetracycle **334**.

This transformation was applied to the total synthesis of the protoberberine alkaloid corydaline (**338**) beginning with cycloaddition of pyrrolinedione **336** and dimethoxy benzenediazonium carboxylate (**335**) to regioselectively provide

Scheme 53. Castedo's 1991 Syntheses of Duguenaine (322), Lysicamine (323), and *O*-Methylatheroline (324)



Scheme 54. Castedo's 1985 Synthesis of PO-3 (329)



tetracycle **337** in modest yield (Scheme 56).[69] Amide reduction followed by treatment of the resulting enamine with $NaBH_4$ furnished corydaline (**338**).

Analogous to corydaline, 8-oxypseudopalmatine (**341**) and decarbomethoxydihydrogambirtannine (**344**) were prepared by the tandem [4 + 2]-cycloaddition/CO extrusion sequence.[70] Combination of bromopyrrolinedione **339** with 4,5-dimethoxy benzenediazonium-2-carboxylate **335** under standard thermolysis conditions produced tetracycle **340** in a modest 24% yield (Scheme 57). The presence of a bromine substituent on the pyrrolinedione prevents further arylation at C(13) following the initial cycloaddition and CO extrustion. Hydrogenolysis of the bromide provided 8-oxypseudopalmatine (**341**).

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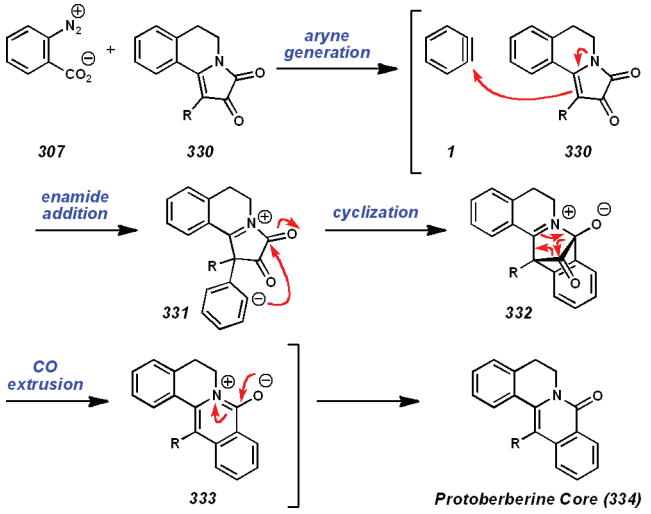
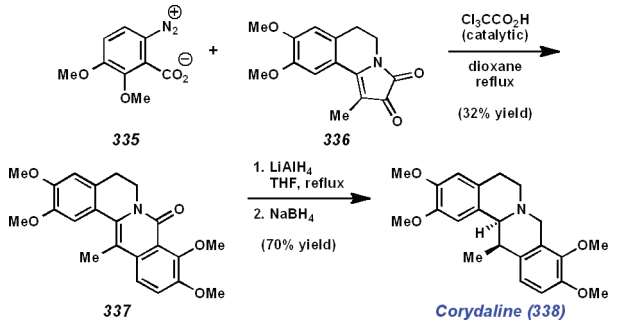
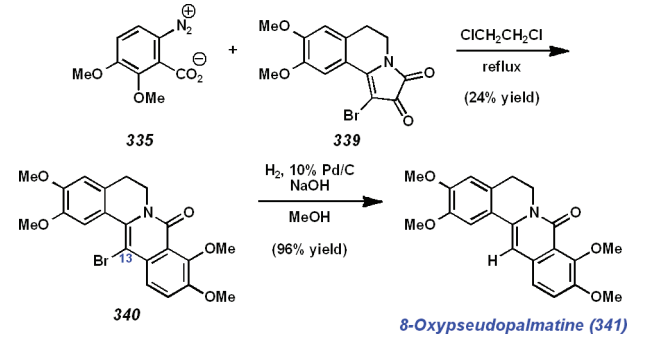
Scheme 55. Castedo's Tandem [4 + 2]-Cycloaddition/CO Extrusion Approach to the Protoberberine Alkaloids



Scheme 56. Castedo's 1986 Synthesis of Corydaline (338)



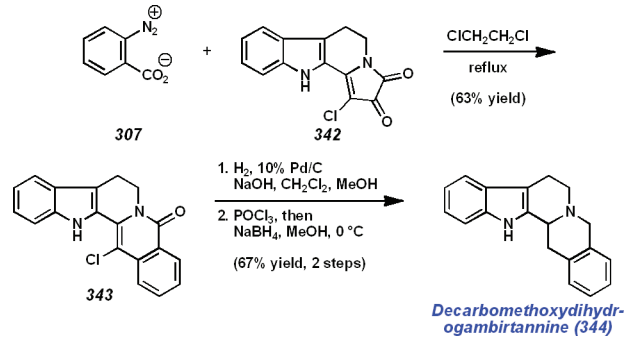
Scheme 57. Castedo's 1988 Synthesis of 8-Oxypseudopalmatine (341)



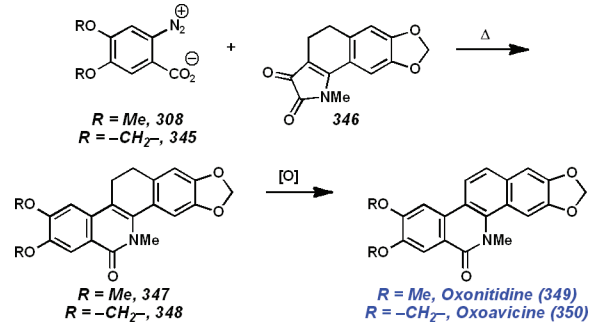
In the synthesis of decarbomethoxydihydrogambirtannine (**344**), the reaction of β-carboline-derived chloropyrrolinedione **342** and benzenediazonium-2-carboxylate (**307**) generated pentacyclic intermediate **343** in good yield (Scheme 58).[70b] Upon hydrogenolysis of the chloride and reduction of the amide, decarbomethoxydihydrogambirtannine (**344**) was obtained.

Similarly, oxoavicine (**350**) and oxonitidine (**349**) could be accessed by [4 + 2]-cycloaddition and CO extrusion with pyrrolinedione **346** and aryne precursors **345** and **308**, respectively (Scheme 59).[71] The resulting cycloadducts (**347** and **348**) were converted to oxonitidine (**349**) and oxoavicine (**350**), respectively, upon oxidation.

Scheme 58. Castedo's 1992 Synthesis of Decarbomethoxydihydrogambirtannine (344)

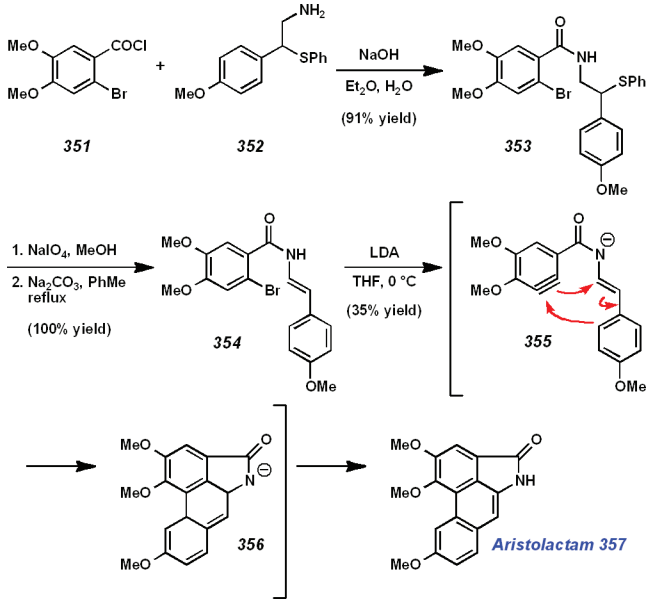


Scheme 59. Castedo's 1989 Synthesis of Oxoavicine (350) and Oxonitidine (349)



In 1989, Castedo and co-workers reported syntheses of the aristolactam and phenanthrene alkaloids featuring novel aryne [4+2]-cycloaddition strategies.[72] In these examples, the cycloaddition occurs between a tethered aryne–diene pair in an intramolecular aryne Diels–Alder reaction. In the synthesis of naturally occurring aristolactam **357**, a suitable substrate (**354**) for cycloaddition was prepared by coupling of acid chloride **351** with amine **352**, followed by oxidation and elimination (Scheme 60).[72a] Upon treatment of amide **354** with LDA at decreased temperatures, elimination of the bromide produced

Scheme 60. Castedo's 1989 Synthesis of Aristolactam 357



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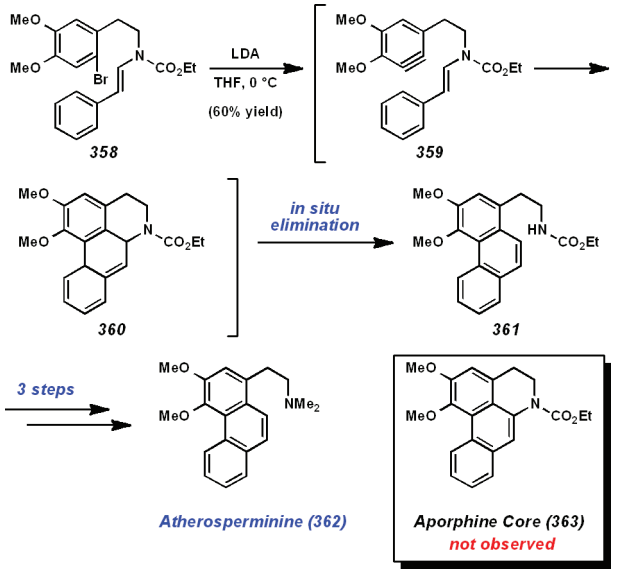
the aryne (**355**), which underwent a [4 + 2]-cycloaddition with the pendant styrene functionality. Aerobic aromatization of the newly formed 6-membered ring furnished the natural product, aristolactam **357**.

Following the synthesis of aristolactam **357**, Castedo attempted to extend this strategy to the analogous synthesis of the aporphine ring system.[72b] However, attempts to accomplish the intramolecular aryne Diels–Alder on urethane **358** with LDA at decreased temperature did not produce the expected tetracycle (**363**) (Scheme 61). Instead, phenanthrene

Scheme 61. Castedo's 1995 Synthesis of Atherosperminine (362)



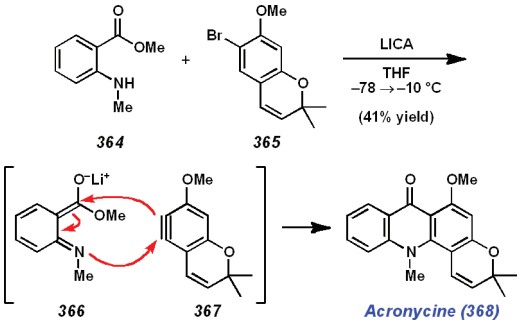
361 was isolated as the major product in 60% yield. Presumably this product arises from a pathway beginning with the desired intramolecular [4 + 2]-cycloaddition following aryne generation; however, the initial adduct (**360**) then undergoes fragmentation during aromatization to form phenanthrene **361**. Despite this surprising result, phenanthrene **361** was converted to the natural product atherosperminine (**362**) in three steps.[73] Notably, the [4 + 2]-cycloadditions employed in this example and in the synthesis of aristolactam **357** feature an acyclic diene, an uncommon occurrence in aryne Diels–Alder methodology.

In parallel with these reports, Castedo and co-workers also published reports on the synthesis of a range of alkaloid ring systems using [4 + 2]-aryne cycloaddition reactions. Some of these include syntheses of the lycorine and amaryillidaceae alkaloid ring system,[74] the ergot alkaloid framework,[75] the benzophenanthridine alkoid skeleton,[76] and the phenanthrene alkaloid ring system.[77]

The group of Watanabe and co-workers investigated the synthesis of acronycine (**368**) by a formal [4 + 2]-cycloaddition between anthranilate **364** and the unsymmetrical aryne (**367**) derived from aryl bromide **365** (Scheme 62).[78] Sequential bond formation consisting of vinylogous lithium amide (**366**) addition to the aryne (**367**) and aryl anion addition into the pendant ester resulted in direct formation of acronycine (**368**) in 41% yield.

In the mid-1980s, the groups of both Moody[79] and Gribble[80] separately reported very similar approaches to the alkaloid ellipticine (**374**) using a 3,4-pyridyne intermediate. These reports, separated by only two months, represent the first use of

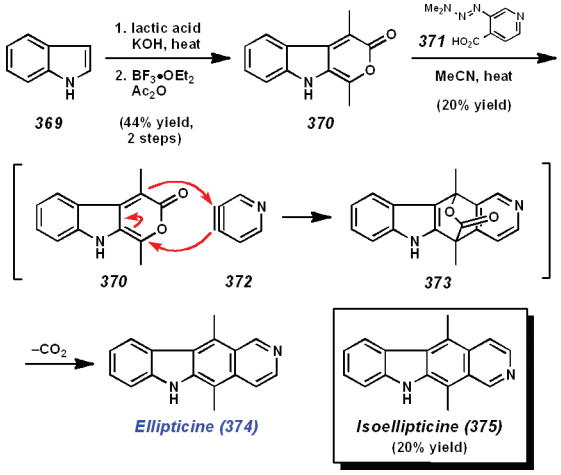
Scheme 62. Watanabe's 1984 Synthesis of Acronycine (368)



pyridyne in total synthesis. In a later publication, Mal and co-workers completed a formal total synthesis of ellipticine, also using a 3,4-pyridyne intermediate.[81]

Moody's three-step synthesis of ellipticine (**374**) begins with conversion of indole (**369**) to pyrone **370** (Scheme 63).[79]

Scheme 63. Moody's 1984 Synthesis of Ellipticine (374)



Upon thermal decomposition of triazine **371**, nonselective [4 + 2]-cycloaddition of pyrone **370** with 3,4-pyridyne (**372**) yielded a 1:1 separable mixture of ellipticine (**374**) and isoellipticine (**375**), following extrusion of CO_2.

By comparison, Gribble and co-workers relied upon a [4 + 2]-cycloaddition between furan **376** and 3,4-pyridyne (**372**) in their synthesis of ellipticine (**374**) (Scheme 64).[80] The oxabicyclic product (**378**/**379**) was formed as a mixture of inseparable isomers, which were readily converted to ellipticine (**374**) and isoellipticine (**375**) upon reaction with sodium borohydride. Subsequent to Gribble's report, Sha and Yang published a similar route to ellipticine (**374**) in 1992.[82]

Soon after the extensive work of Castedo and co-workers involving the synthesis of isoquinoline-derived alkaloids, the Rigby group reported a convergent route to the naturally occurring isoquinoline *N*-nornitidine (**387**) employing a [4 + 2]-cycloaddition between an aryne and a vinyl isocyanate (Scheme 65).[83] To this end, vinyl isocyanate **381** was prepared by a Curtius rearrangement of acid **380**. Upon decomposition of the *N*-aminobenzotriazole (**382**) to the corresponding aryne (**383**) with stoichiometric $Pb(OAc)_4$, a [4 + 2]-cycloaddition between the aryne (**383**) and the vinyl isocyanate (**381**) produced pentacyclic isoquinolone **385** following tautomerization of the initial cycloadduct (**384**). Once again, this serves as a

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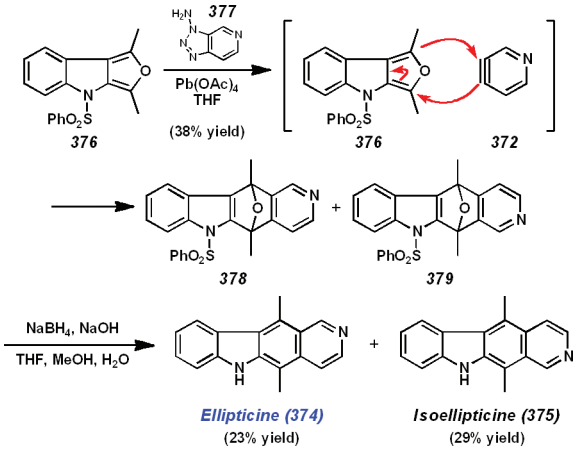
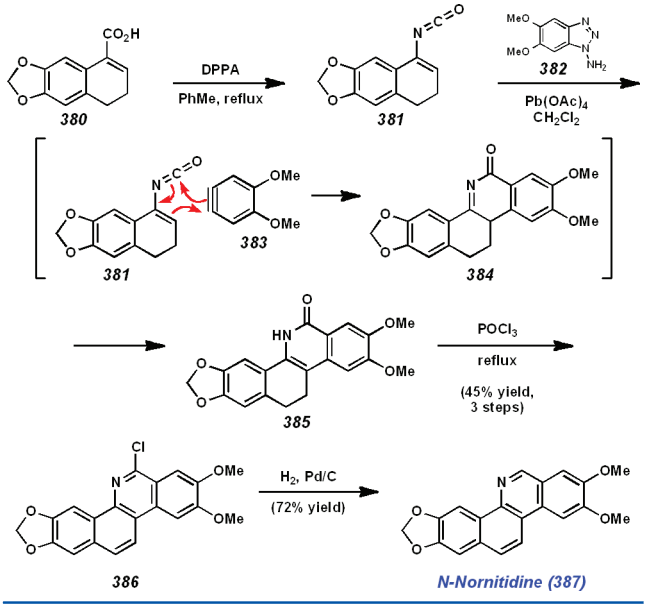
Scheme 64. Gribble's 1984 Synthesis of Ellipticine (374)



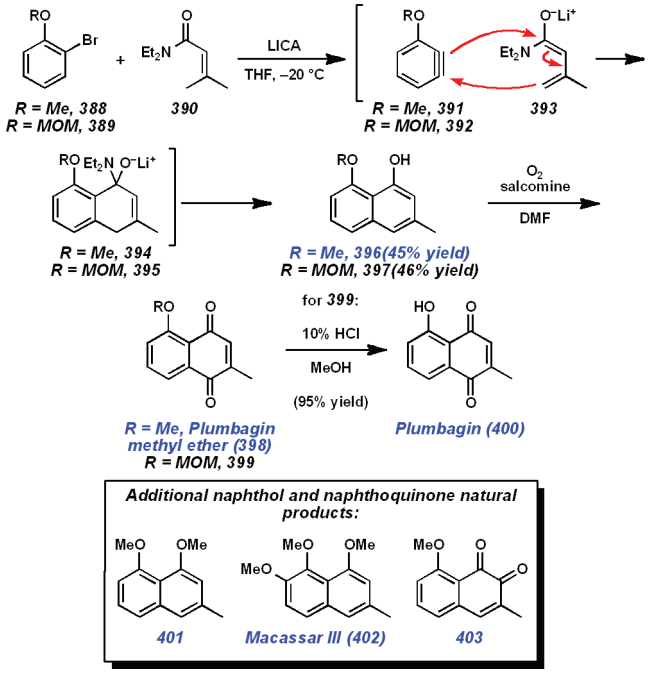
Scheme 65. Rigby's 1991 Synthesis of *N*-Nornitidine (387)



rare example of the use of an acyclic diene in an aryne [4 + 2]-cycloaddition. Subsequent exposure of the isoquinolone (**385**) to refluxing $POCl_3$ directly generated the fully aromatized chloroisoquinoline (**386**) in 45% yield for the three-step sequence beginning with acid **380**. Finally, hydrogenolysis of the chloride under standard conditions afforded *N*-nornitidine (**387**).

Departing from alkaloid synthesis, Watanabe and co-workers have targeted a variety of naphthol and naphthoquinone natural products by [4 + 2]-cycloadditions of arynes with acylic dienolate-type dienes (Scheme 66).[84] In the synthesis of plumbagin (**400**) and plumbagin methyl ether (**398**), treatment of either aryl bromide **388** or **389** with *N*,*N*-diethylsenecioamide (**390**) in the presence of LICA resulted in the regioselective intermolecular [4 + 2]-cycloaddition between aryne **391** or **392** and dienolate **393** to furnish naphthols **396** (itself an unnamed natural isolate of *Diospyros melanoxylon* ROXB) and **397**, respectively. These compounds were readily oxidized to their corresponding naphthoquinones with oxygen and salcomine, affording plumbagin methyl ether (**398**) and quinone **399**. The latter was converted to plumbagin (**400**) upon acidic hydrolysis of the methoxy methyl ether protective group. Additional

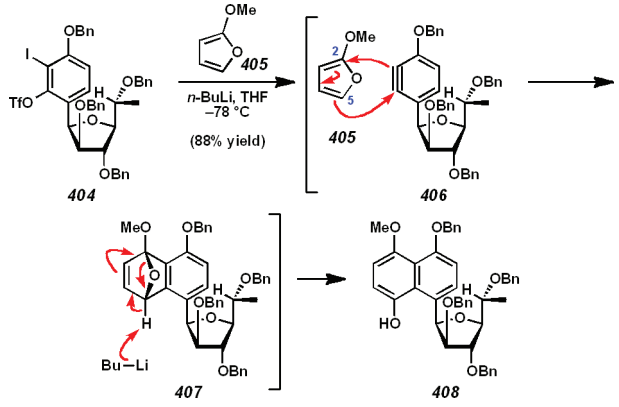
Scheme 66. Watanabe's 1986 Synthesis of Plumbagin Methyl Ether (398), Plumbagin (400), and Other Naphthol and Naphthoquinone Natural Products



naphthol and naphthoquinone natural products prepared by these methods are shown in Scheme 66.

In 1992, Suzuki and co-workers reported the synthesis of gilvocarcin M (**412**), a member of the *C*-glycoside antibiotics that bear a common aromatic core with pendant rare sugars.[85] This work, including Suzuki's later synthesis of gilvocarcin V (**416**), includes the first example of an intermolecular furan–aryne Diels–Alder reaction applied in total synthesis. More specifically, the [4 + 2]-cycloaddition between the aryne generated from *ortho*-iodotriflate **404** and 2-methoxyfuran (**405**) produced naphthol **408** as the principle product in 88% yield following aromatization (Scheme 67). Importantly, the

Scheme 67. Suzuki's 1992 Synthesis of Naphthol 408 En Route to the Gilvocarcin Antibiotics



selective formation of naphthol **408** in favor of the alternative isomeric cycloadduct (isolated in 7% yield) demonstrates the predominance of electronic factors over steric interactions in determining the regiochemical outcome of addition to unsymmetrical arynes. In this case, the more nucleophilic C(5) position

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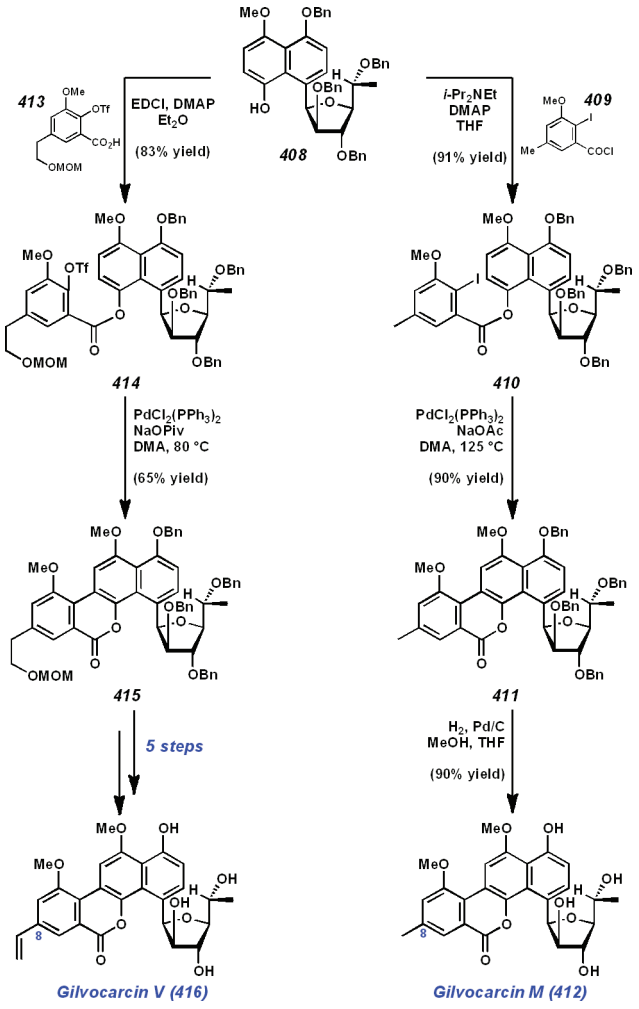
of the furan undergoes addition to the position *meta* to the inductively withdrawing benzyloxy group on the intermediate aryne (**406**). Under the basic reaction conditions, deprotonation of the initial cycloadduct (**407**) led to ring-opening aromatization, yielding naphthol **408**.

Naphthol **408** served as a key intermediate in the synthesis of both gilvocarcin M (**412**) and V (**416**), which differ only in the identity of the C(8) substituent. Acylation of the hydroxyl group of naphthol **408** with either acid chloride **409** or carboxylic acid **413** produced aryl esters **410** and **414**, respectively (Scheme 68). Treatment of iodide **410** or triflate **414**

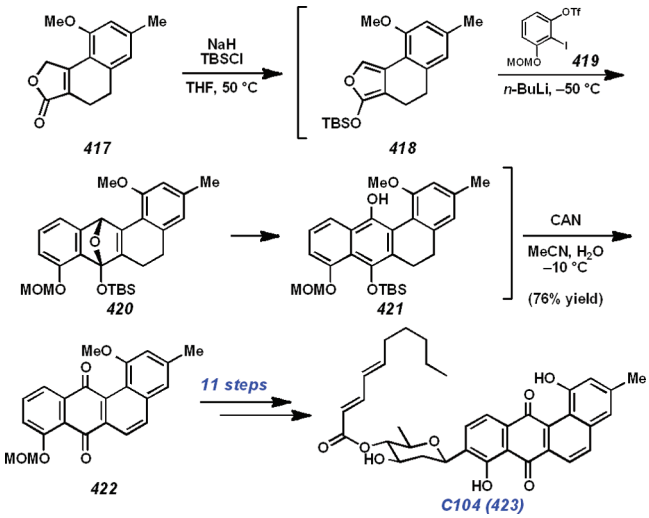
Scheme 68. Completion of Gilvocarcins M (412) and V (416) by Suzuki and Co-workers (1992)



with a palladium source resulted in ring-closing C−H functionalization to afford tetracycles **411** and **415**, respectively. Global deprotection of tetracycle **411** furnished gilvocarcin M (**412**), whereas tetracycle **415** required five additional steps for installation of the C(8) vinyl group and completion of gilvocarcin V (**416**). Furthermore, the synthesis of these two natural products determined the absolute configuration of the gilvocarcins to be the opposite of that originally proposed at the time of isolation.[86] The enantiomer prepared by Suzuki (shown in Schemes 67 and 68) was proven to be the non-natural enantiomer of the gilvocarcins.

Soon after their synthesis of the gilvocarcins, Suzuki and co-workers reported the total synthesis of antibiotic C104 (**423**), a member of the angucycline class of antibiotics.[87] The tetracyclic aromatic core of the natural product was prepared by a regioselective intermolecular aryne Diels−Alder cycloaddition with a functionalized furan serving as the diene. In fact, the authors were able to carry out a one-pot procedure consisting of in situ generation of silyloxyfuran **418** from butenolide **417**, followed by the [4 + 2]-cycloaddition with the aryne derived from iodoaryl triflate **419** (Scheme 69). The cycloadduct

Scheme 69. Suzuki's 1995 Synthesis of Antibiotic C104 (423)



initially formed by this sequence (**420**) undergoes ring-opening aromatization under the reaction conditions to yield tetracycle **421**. However, this intermediate was found to be unstable and was thus treated with CAN upon workup to give the quinone (**422**) as the final product of this sequence. Importantly, the aryne cycloaddition proceeded with a high degree of regioselectivity to provide quinone (**422**) in greater than a 14:1 ratio over the minor isomeric quinone. Over 11 subsequent synthetic operations, quinone **422** was advanced to antibiotic C104 (**423**), thereby establishing the absolute configuration of the natural product.

Many of the syntheses shown thus far relied upon aryne [4 + 2]-cycloadditions to build polycyclic ring systems lacking multiple stereogenic carbon atoms. In their 1995 synthesis of pseudopterosin A and E aglycon (**429**), however, Buszek and co-workers employed an aryne Diels−Alder reaction coupled with an olefin oxidative bond cleavage to set the relative stereochemistry of two of the four stereocenters of their target (Scheme 70). The authors found that, upon treatment of aryl bromide **424** with LDA, a [4 + 2]-cycloaddition of the intermediate aryne with the pendant cyclohexadiene yielded the cycloadduct as a mixture of two diastereomers (**426** and **427**) in a combined 63−71% yield. Although the selectivity was modest (1.4:1 ratio), the major diastereomer possessed the relative stereochemistry displayed in the pseudopterosins. Following dihydroxylation, oxidative diol cleavage, and aldehyde reduction, diol **428** was advanced to pseudopterosin A and E aglycon (**429**) over an additional 12 steps.

Among the examples in the literature of aryne [4 + 2]-cycloadditions in natural product synthesis that have employed acyclic dienes are Hoye and co-workers' syntheses of michellamines A−C (**449**−**451**),[88] korupensamine C (**445**), and ancistrobrevine B (**447**).[89] In each of these syntheses, the Diels−Alder reaction between the dienolate of *N,N*-diethylsenecioamide (**393**)

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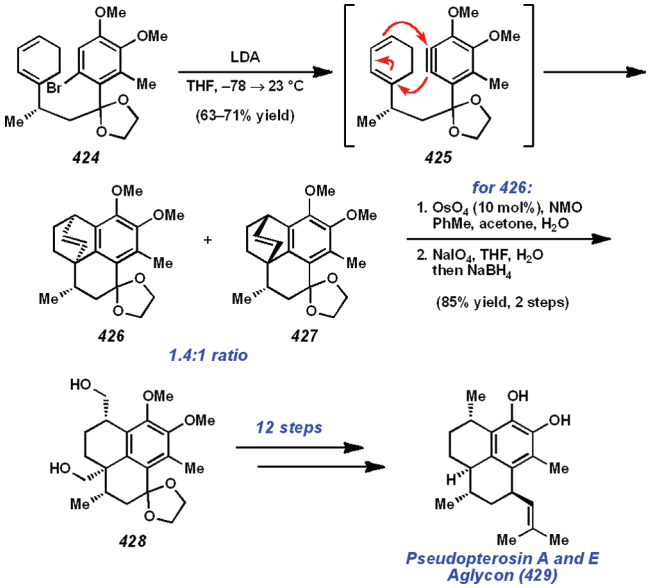
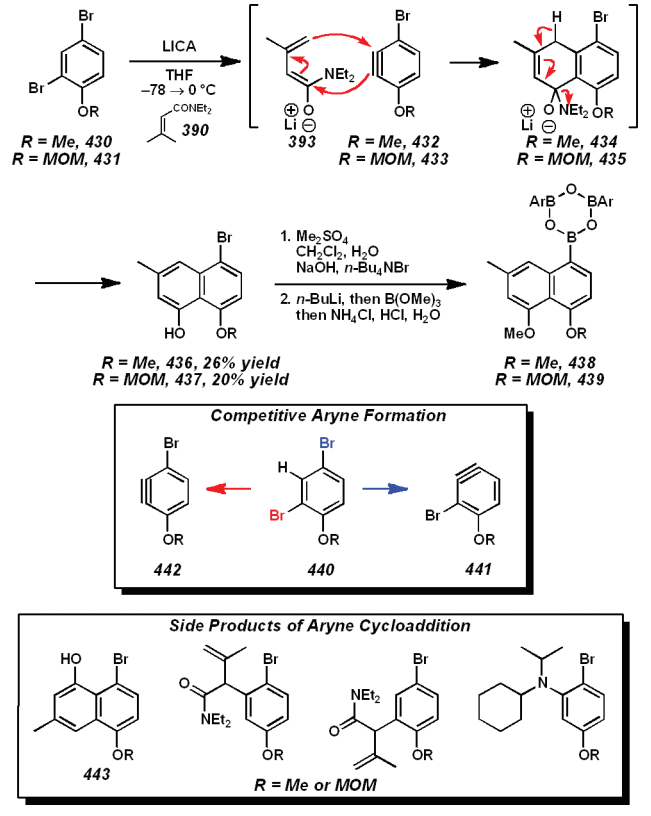
Scheme 70. Buszek's 1995 Synthesis of Pseudopterosin A and E Aglycon (429)



and the aryne generated in situ from 2,4-dibromo phenol derivatives **430** and **431** resulted in the selective formation of naphthols **436** and **437**, respectively (Scheme 71). Close

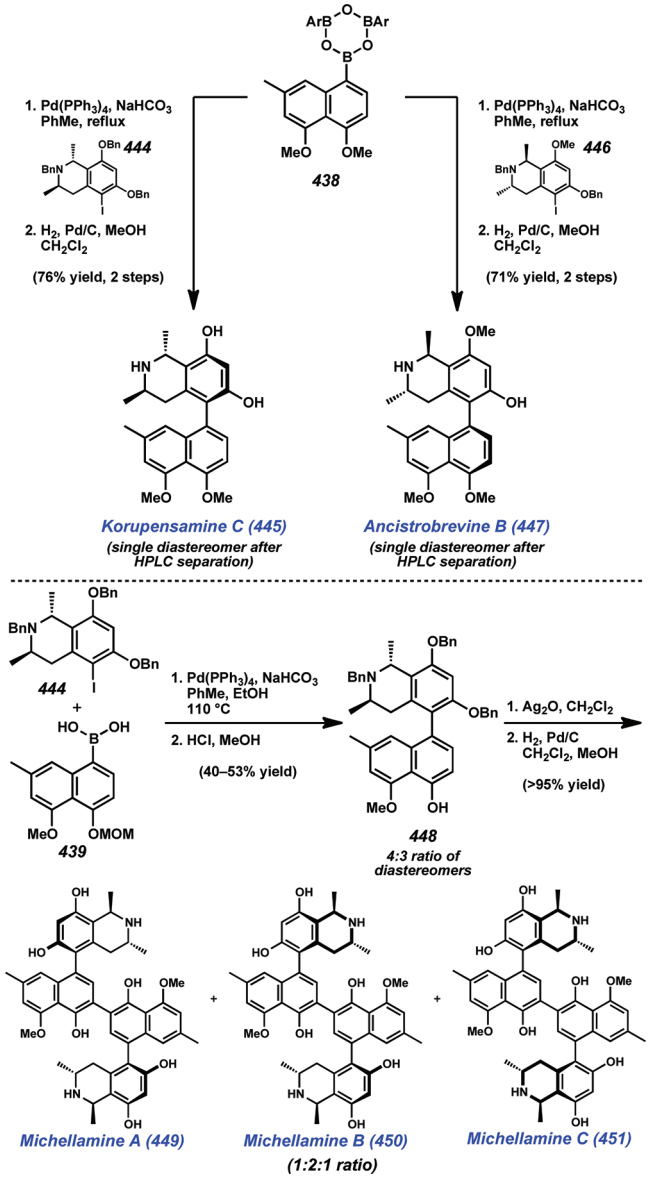
Scheme 71. Synthesis of Naphthyl Boroxines (438 and 439) by Aryne Diels–Alder Cycloadditions (1994)



examination of the aryne precursors (**430** and **431**) reveals that, upon removal of the proton between both bromides, two potential arynes could result from base-promoted dehydrohalogenation: **441** and **442**. Although a number of side-products are observed in this reaction in addition to the desired product, they all arise from reaction with the *para*-bromo aryne (**442**). Furthermore, the cycloaddition itself proceeds with good selectivity for naphthols **436** and **437** over isomeric naphthol **443** (5:1 ratio of **436**/**443**). The desired naphthol products (**436** and **437**) were subsequently converted to their respective boroxines (**438** and **439**) through methylation of the free phenol and borylation.

Upon synthesis of the required boroxines (**438** and **439**), palladium-catalyzed biaryl coupling with either iodotetrahydroisoquinoline **444** or **446** yielded a pair of naphthyl tetrahydroisoquinolines, which were separately advanced to korupensamine C (**445**) and ancistrobrevine B (**447**), respectively, upon cleavage of the benzyl groups and separation by HPLC (Scheme 72). Completion of the michellamines (**449**–**451**)

Scheme 72. Hoye's Syntheses of Korupensamine C (445), Ancistrobrevine B (447), and Michellamines A–C (449–451) (1994 and 1996)



(as an inseparable mixture) was achieved in a similar manner through coupling of boronic acid **439** with iodotetrahydroisoquinolines

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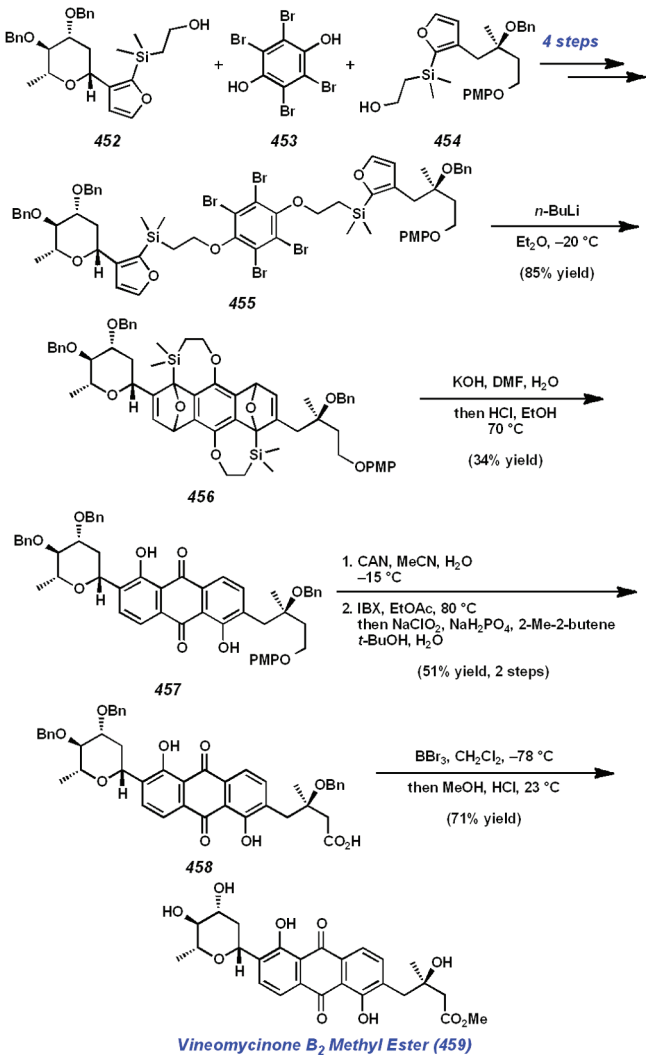
444 followed by removal of the methoxymethyl ether to yield naphthyl tetrahydroisoquinoline 448 as a 4:3 mixture of diastereomers. Oxidative dimerization, reduction/global deprotection, and HPLC separation provided michellamines A (449), B (450), and C (451) in a ratio of 1:2:1.

More recently, Martin and co-workers have employed aryne–furan Diels–Alder reactions en route to the glycosidic antibiotic vineomycinone B_2 methyl ester (459).[90] In this unique approach, the authors rely upon a tandem tethered [4 + 2]-cycloaddition strategy to append both aromatic rings of the tricyclic core to a central diaryne. To this end, a tandem cycloaddition precursor (455) was constructed by sequential Mitsunobu reactions beginning with phenol 453 and furanyl fragments 452 and 454 (Scheme 73). Treatment of tetrabromoarene

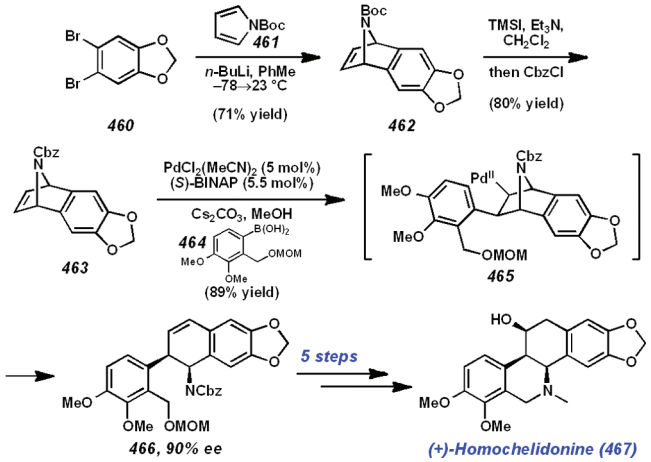
Scheme 73. Martin's 2006 Synthesis of Vineomycinone B_2 Methyl Ester (459) by Tandem Tethered Aryne Cycloadditions



455 with *n*-BuLi triggered a cascade sequence consisting of two separate intramolecular aryne–furan [4 + 2]-cycloadditions to yield cycloadduct 456 as an inconsequential mixture of diastereomers in excellent yield. Cleavage of the silyl tethers and oxidation of the system was accomplished by treatment of biscycloadduct 456 with base followed by acid, affording anthrarufin 457 upon air oxidation. Critically, use of the silyl tethers dictated the regioselectivity of the cycloadditions to provide only the desired anthrarufin isomer (457). Finally, the synthesis of vineomycinone B_2 methyl ester (459) was completed by a three-step sequence involving protecting group removal and alteration of the side-chain oxidation state. The concept of multiple aryne cycloadditions to construct the polycyclic aromatic cores of Sch 47554 and 5-hydroxyaloin A was also employed by Morton and Barrett[91] in 2006 and Martin and co-workers[92] in 2010, respectively.

Departing from aryne Diels–Alder reactions with furans, Lautens and co-workers utilized a [4 + 2]-cycloaddition between an aryne derived from dibromoarene 460 and *N*-Boc-pyrrole (461) to access azabicycle 462 en route to the alkaloid (+)-homochelidonine (467) (Scheme 74).[93] In this case, the

Scheme 74. Lautens' 2007 Synthesis of (+)-Homochelidonine (467)



tetracyclic product (462) does not undergo immediate ring-opening. Instead, following exchange of the carbamate, treatment of azabicycle 463 with a chiral palladium catalyst and arylboronic acid 464 resulted in an asymmetric migratory insertion of the *meso*-azabicycle (463) into an aryl palladium(II) species, forming intermediate 465. Following this insertion event, β-elimination of the bridging heteroatom afforded homoallylic carbamate 466 in 90% ee.[94] Finally, homoallylic carbamate 466 was converted into (+)-homochelidonine (467) over five synthetic steps.

In 2008, Stoltz and co-workers reported a unique annulation of *N*-acyl enamines and arynes to generate isoquinolines.[95] The reaction is believed to proceed through a formal [4 + 2]-addition reaction between the *N*-acyl enamine (468) and the aryne (469, derived from silyl aryl triflate 238) followed by dehydrative aromatization under the reaction conditions (Scheme 75). By this method, any position on the isoquinoline heterocyclic scaffold can be readily functionalized, rendering it ideal for use in natural product total synthesis. To date, the Stoltz group has reported two different syntheses employing this novel aryne annulation.

In the synthesis of the papaverine, a clinically used non-narcotic antispasmotic agent, annulation of the aryne generated in situ from silyl aryl triflate 474 with *N*-acyl enamine 473 (available in one step from homoveratric acid and serine methyl ester) produced tetrasubstituted isoquinoline 475 in good yield (Scheme 76).[95] Saponification and thermal decarboxylation furnished the natural product (476) in three steps.

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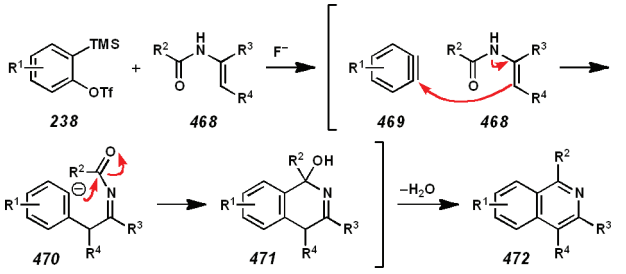
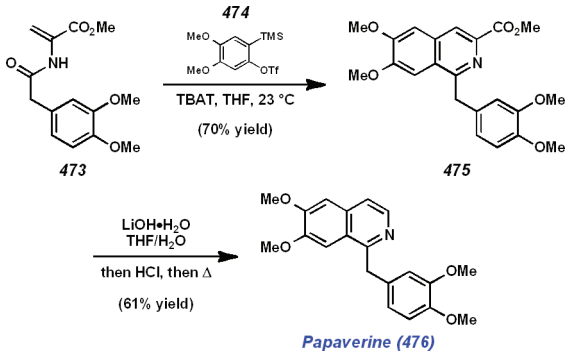
Scheme 75. Stoltz's Aryne Annulation with *N*-Acyl Enamines to Produce Isoquinolines

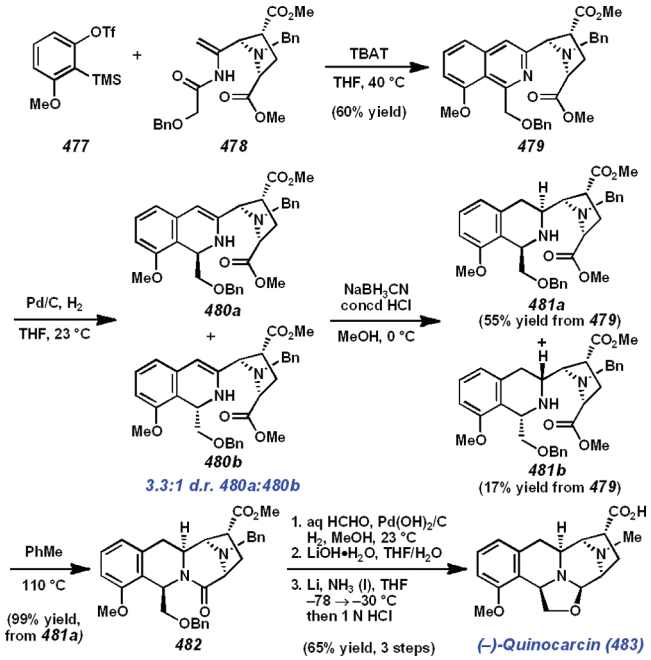


Scheme 76. Stoltz's 2008 Synthesis of Papaverine (476)



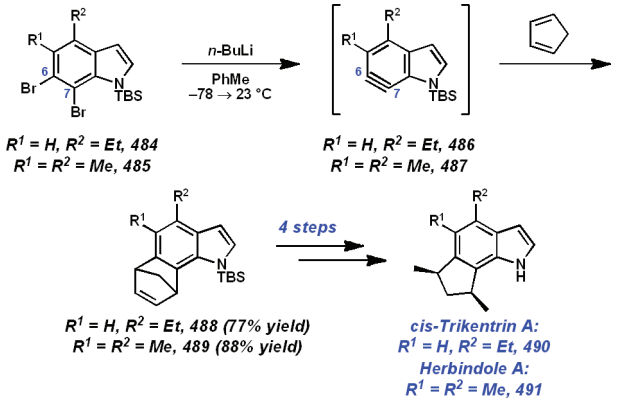
A greater extension of this work can be seen in Stoltz's synthesis of the tetrahydroisoquinoline antitumor antibiotic (−)-quinocarcin (**483**) (Scheme 77).[96] The success of the approach hinged on the sequential regioselective aryne annulation and diastereoselective reduction of the isoquinoline to generate the tetrahydroisoquinoline found in the natural product. Annulation of the aryne derived from 3-methoxy silyl aryl triflate **477** with enantioenriched *N*-acyl enamine **478** (available in 4 steps from known compounds) yielded isoquinoline **479** as a single isomer. Subsequent two-step reduction of the isoquinoline proceeded with 3.3:1 diastereoselectivity for the initial reduction and complete diastereoselectivity for the secondary reduction of the resulting enamine, affording tetrahydroisoquinoline **481a** as the major diastereomer in 55% yield. Following thermal lactamization to yield tetracycle **482**, (−)-quinocarcin (**483**) was completed by a three-step sequence involving debenzylation/reductive methylation, saponification, and reductive closure of the oxazolidine ring. Overall, this 11-step enantioselective synthesis of (−)-quinocarcin (**483**) is the shortest to date.

Scheme 77. Stoltz's 2008 Enantioselective Synthesis of (−)-Quinocarcin (483)



The most recent example of the application of an aryne [4 + 2]-cycloaddition to natural product synthesis is Buszek and co-workers' syntheses of *cis*-trikentrin A (**490**) and herbindole A (**491**).[97] This work significantly differs from the various syntheses described previously in that the aryne counterpart is a 6,7-indolyne. More specifically, elimination of 6,7-dibromoindoles **484** and **485** with *n*-BuLi generated the corresponding 6,7-indolynes (**486** and **487**), which, upon treatment with cyclopentadiene, underwent a [4 + 2]-cycloaddition to afford tetracycles **488** and **489**, respectively (Scheme 78). These intermediates were then advanced to *cis*-trikentrin A (**490**) and herbindole A (**491**), respectively, over four steps.

Scheme 78. Buszek's 2009 Syntheses of *cis*-Trikentrin A (490) and Herbindole A (491)



4.2. [2 + 2]-Aryne Cycloaddition Strategies

Aryne [2 + 2]-cycloadditions are some of the most poorly developed and underutilized methods, largely due to significant side-product formation. To date, there have been only two reported total syntheses employing an aryne [2 + 2]-cycloaddition. In 1982, Stevens and Bisacchi disclosed the synthesis of the quinone methide diterpene, taxodione (**500**), by a convergent route including a [2 + 2]-cycloaddition between an aryne and a ketene acetal (Scheme 79).[98] In this event, treatment of aryl bromide **492** with sodamide in THF in the presence of 1,1-dimethoxyethylene (**394**) resulted in regioselective formation of benzocyclobutene **495**, which was immediately hydrolyzed to benzocyclobutenone **496**. Addition of the organolithium reagent derived from vinyl chloride **497** to the benzocyclobutenone (**496**) and regioselective, yet contrasteric, ring fragmentation of the resulting benzocyclobutenol (**498**) yielded enone **499**, which was readily advanced to taxodione (**500**).

More recently, Suzuki and co-workers completed the synthesis of aquayamycin (**508**), in which an aryne [2 + 2]-cycloaddition was used to construct a key fragment of the natural product (Scheme 80).[99] Synthesis of phthalide **505** began with a regioselective [2 + 2]-aryne cycloaddition between silyl ketene acetal

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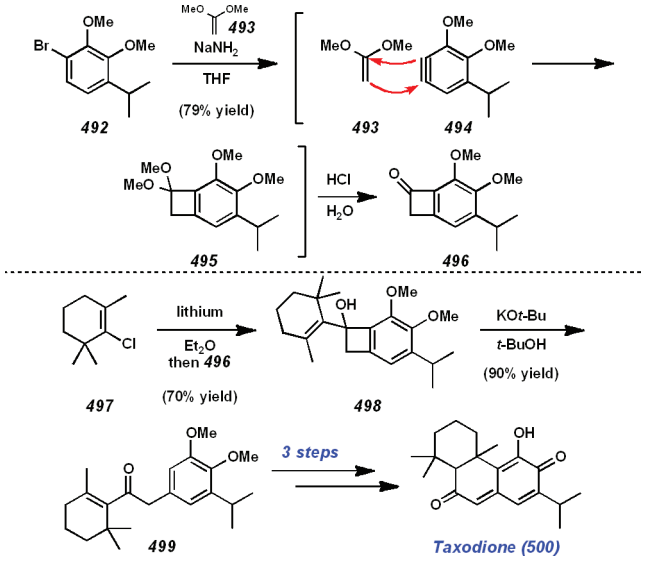
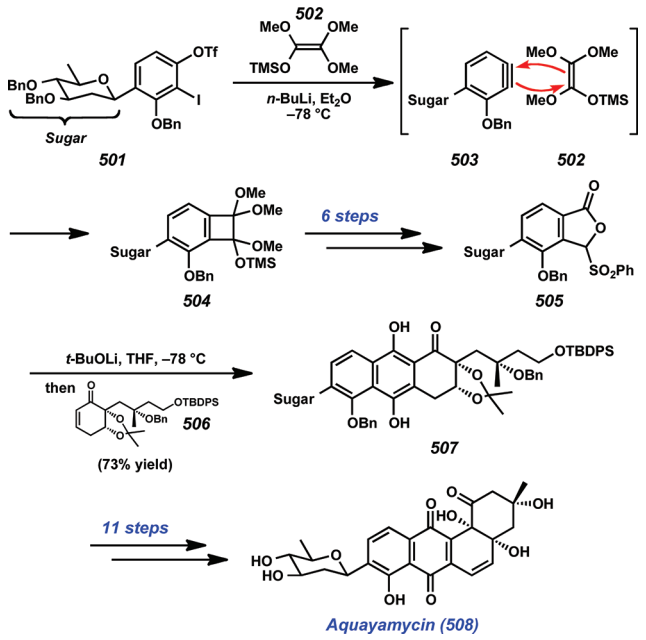
Scheme 79. Stevens' 1982 Synthesis of Taxodione (500)



Scheme 80. Suzuki's 2000 Synthesis of Aquayamycin (508)

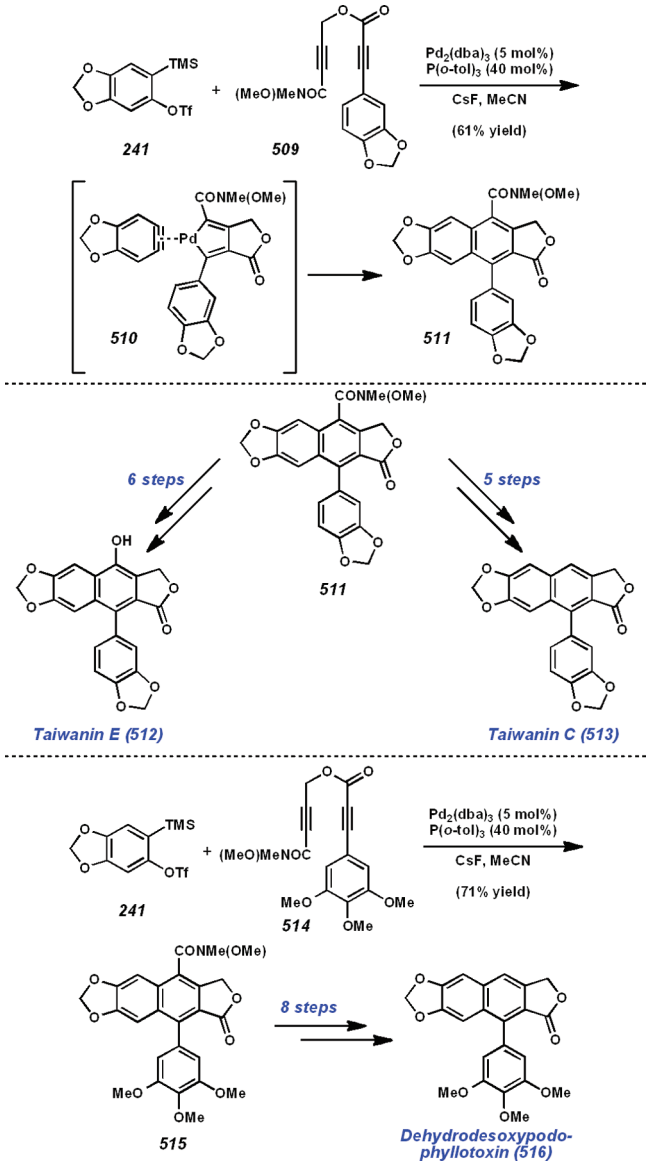


502 and the aryne generated in situ from iodo aryl triflate **501**. Over a series of six steps, the cycloadduct (**504**) was converted to the desired phthalide (**505**), which was subsequently coupled to enone **506**. From this point, completion of aquayamycin required an additional 11 transformations.

5. METAL-CATALYZED ARYNE REACTION STRATEGIES

Among all of the known reactions involving arynes, metal-catalyzed processes are still considered to be underdeveloped. In fact, metal-catalyzed reactions of arynes have only been employed in total synthesis on one occasion by Mori and co-workers en route to a series of arylnaphthalene lignans.[100] In this elegant approach, the naphthyl portions of taiwanins C (**513**) and E (**512**) and dehydrodesoxypodophyllotoxin (**516**) were targeted by a palladium-catalyzed [2 + 2 + 2]-cocyclization of an aryne and diyne. Cocyclization of sesamol-derived diyne **509** with the aryne generated in situ from silyl aryl triflate **241** resulted in formation of arylnaphthalene **511**, which was subsequently converted to taiwanin E (**512**) in six additional steps and taiwanin C (**513**) over five steps (Scheme 81).

Scheme 81. Mori's 2004 Synthesis of Taiwanin C (513), Taiwanin E (512), and Dehydrodesoxypodophyllotoxin (516)



Alternatively, use of diyne **514** (derived from 3-(trimethoxyphenyl)propiolic acid) in the palladium-catalyzed [2 + 2 + 2]-cocyclization afforded trimethoxyarylnaphthalene **515**, which was advanced to dehydrodesoxypodophyllotoxin (**516**) over eight synthetic transformations.

6. CONCLUDING REMARKS

When J. D. Roberts first assigned the structure of benzyne in 1953, few could have recognized the significant synthetic potential of this highly reactive intermediate. However, to the benefit of the synthetic organic chemistry community, the manifold types of reactivity possessed by arynes have been explored and exploited largely through efforts aimed at the

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synthesis of natural products. Since the first aryne-based total synthesis in 1967, there has been a progression from early strategies that monofunctionalize aryne intermediates to approaches that utilize the full potential of the uniquely reactive triple bond to generate 1,2-disubstituted arenes. Although there has been significant progress in expanding the utility of arynes in organic synthesis, there is still work that remains in increasing the yields of theses processes and minimizing background reactions. Fortunately, the recent resurgence in aryne research promises to improve what is already known while adding to the known compendium of aryne transformations.

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Notes

The authors declare no competing financial interest.

Biographies

Pamela M. Tadross was raised in Brooklyn, New York, and received her B.S. degree in chemistry in 2005 from New York University, where she conducted undergraduate research with Professor Marc A. Walters. She subsequently joined the laboratories of Professor Brian M. Stoltz as a graduate student at the California Institute of Technology, where she completed her Ph.D. in 2011. As a fellow of the California HIV/AIDS Research Program, her graduate research focused on the exploitation of aryne reactive intermediates in the synthesis of biologically active natural products. Pamela is currently an NIH Postdoctoral Fellow in the lab of Professor Eric N. Jacobsen at Harvard University.

Brian M. Stoltz was born in Philadelphia, PA, in 1970 and obtained his B.S. degree from the Indiana University of Pennsylvania in Indiana, PA. After graduate work at Yale Univeristy in the laboratories of John L. Wood and an NIH postdoctoral fellowship at Harvard in the Corey laboratories, he took a position at the California Institute of Technology. A member of the Caltech faculty since 2000, he currently is the Ethel Wilson Bowles and Robert Bowles Professor of Chemistry. His research interests lie in the development of new methodology for general applications in synthetic chemistry.

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ABBREVIATIONS

AIBN	azobisisobutyronitrile
BINAP	(1,1′-binaphthalene-2,2′-diyl)bis(diphenylphosphine)
Boc	*tert*-butoxycarbonyl
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DIBAL	diisobutyl aluminum hydride
DMA	dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphorylazide
EDCI	*N*-(3-dimethylaminopropyl)-*N*-2-ethylcarbodiimide hydrochloride
HMDS	hexamethyldisilamide or hexamethyldisilazide
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
IBX	2-iodoxybenzoic acid
KHMDS	potassium bis(trimethylsilyl)amide
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LICA	lithium isopropylcyclohexylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
MOM	methoxymethyl
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
PCC	pyridinium chlorochromate
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBS	*tert*-butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
tol	tolyl
TPAP	tetrapropylammonium perruthenate
Tr	triphenylmethane (trityl)

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