

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/221972314>

ChemInform Abstract: A Comprehensive History of Arynes in Natural Product Total Synthesis

ARTICLE *in* CHEMICAL REVIEWS · MARCH 2012

Impact Factor: 46.57 · DOI: 10.1021/cr200478h · Source: PubMed

CITATIONS

174

READS

90

2 AUTHORS, INCLUDING:



Brian M Stoltz

California Institute of Technology

248 PUBLICATIONS 7,962 CITATIONS

SEE PROFILE

A Comprehensive History of Arynes in Natural Product Total Synthesis

Pamela M. Tadross and Brian M. Stoltz*

The Warren and Katharine Schlinger Laboratory of Chemistry and Chemical Engineering, California Institute of Technology, Pasadena, California 91125, United States

CONTENTS

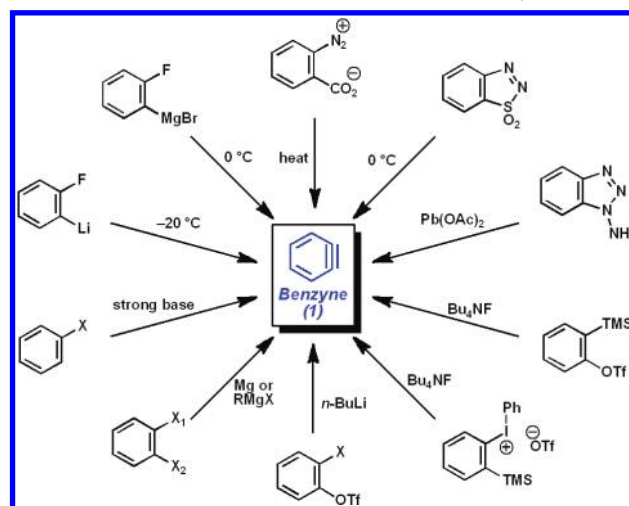
1. Introduction	A
2. Nucleophilic Addition and Multicomponent Reaction Strategies	B
2.1. Nucleophilic Additions to Arynes	B
2.2. Multicomponent Reactions of Arynes	H
3. Bond-Insertion Reaction Strategies	I
4. [4 + 2]- and [2 + 2]-Aryne Cycloaddition Strategies	N
4.1. [4 + 2]-Aryne Cycloaddition Strategies	N
4.2. [2 + 2]-Aryne Cycloaddition Strategies	W
5. Metal-Catalyzed Aryne Reaction Strategies	X
6. Concluding Remarks	X
Author Information	Y
Corresponding Author	Y
Notes	Y
Biographies	Y
Acknowledgments	Y
Abbreviations	Y
References	Y

1. INTRODUCTION

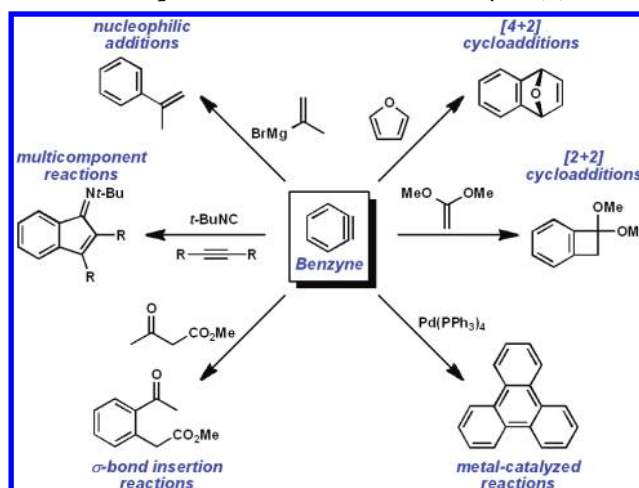
Within 14 years of the seminal experiments of J. D. Roberts leading to the first proposal of the structure of benzyne (1),¹ synthetic organic chemists recognized the potential to exploit this highly reactive intermediate (and its substituted variants) in the total synthesis of natural products. More 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

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



Scheme 2. Representative Reactions of Benzyne (1)⁶



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,

Received: December 22, 2011

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

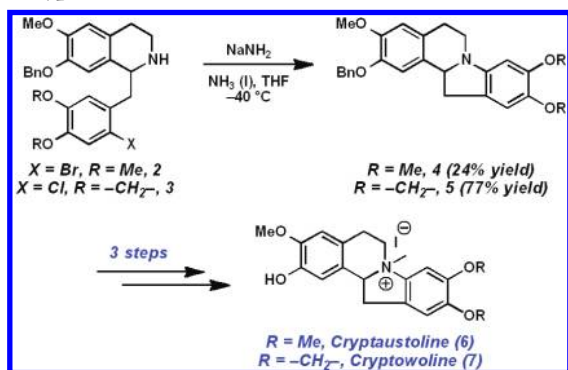
2. NUCLEOPHILIC ADDITION AND MULTICOMPONENT REACTION STRATEGIES

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

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

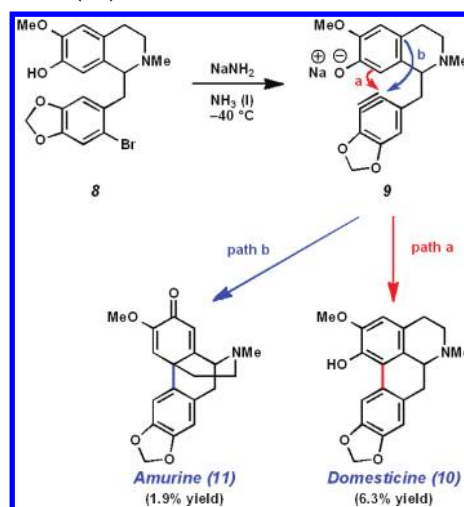


converted to cryptaustoline (6) over three steps, while tetracycle 5 afforded cryptowoline (7).

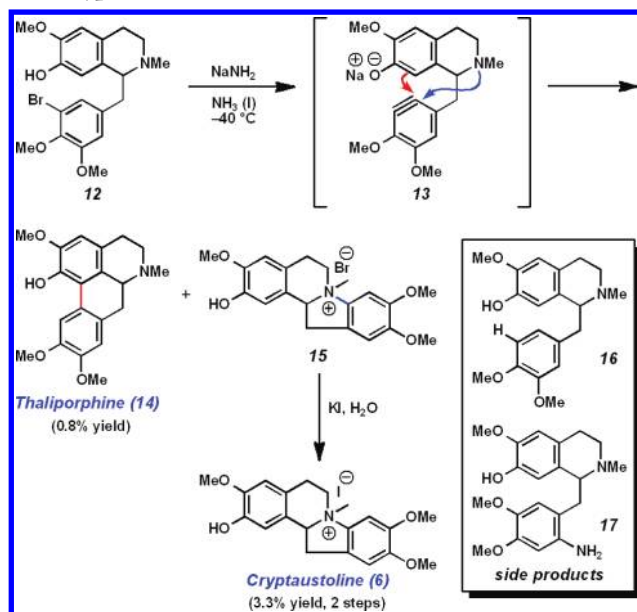
Building on this synthetic strategy, Kametani next reported the syntheses of domesticine (10) and amurine (11) (Scheme 4).^{8,9} N-Methylation of tetrahydroisoquinoline intermediates such as 2 and 3 and removal of the benzyl protective group led to alternative reactivity in the key aryne cyclization, 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)

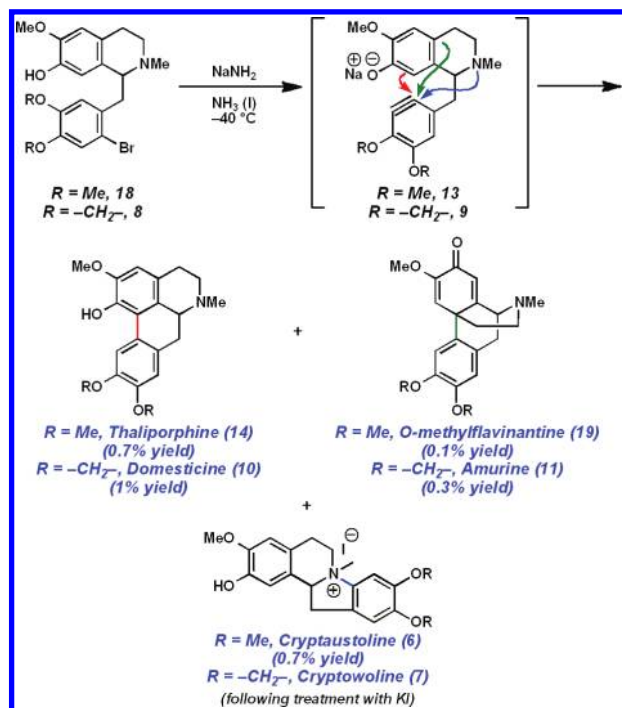


including thaliporphine (14) (Scheme 5).¹⁰ Following extraction of thaliporphine (14) and two additional side products (16 and 17), concentration of the aqueous washes and treatment with potassium iodide also afforded cryptaustoline (6).

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-methylflavanine (19), or cryptowoline (7) (following treatment with potassium iodide), domesticine (10), and amurine (11), respectively.

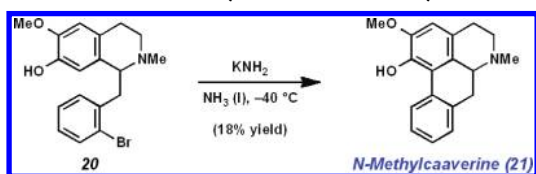
It should be noted that subsequent to Kametani's publication of the syntheses featured in Scheme 6, Kessar, Gandhi, and co-workers reported an identical approach to domesticine (10), cryptaustoline (6), cryptowoline (7), amurine (11), N-methylcaaverine (21), and thalimidine with similarly low yields.¹²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

Scheme 6. Kametani's 1973 One-Pot Synthesis of Cryptaustoline (6), Thaliporphine (14), and O-Methylflavanantine (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).

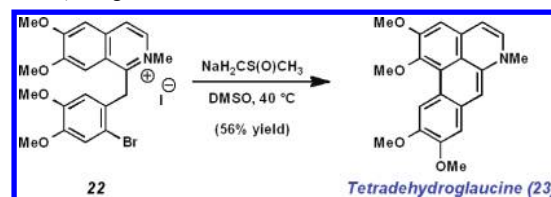
Scheme 7. Kessar's 1975 Synthesis of *N*-Methylcaaverine (21)



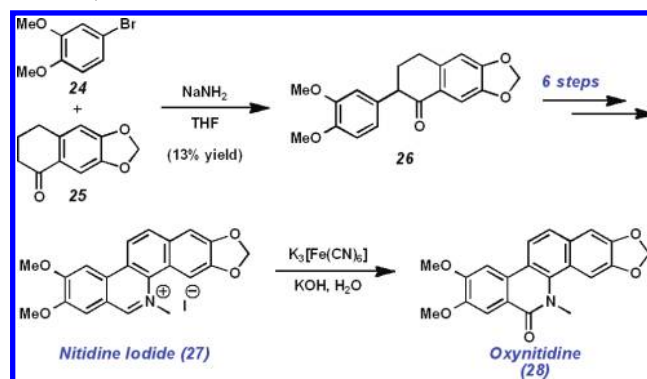
Furthermore, Castedo and co-workers extended this aryne cyclization method to include the synthesis of more oxidized relatives of natural products like thaliporphine (14) and domesticine (10). In the synthesis of tetrahydroglaucaine (23), aryne cyclization of *N*-methyl isoquinolinium iodide 22 directly 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 Tetrahydroglaucaine (23)

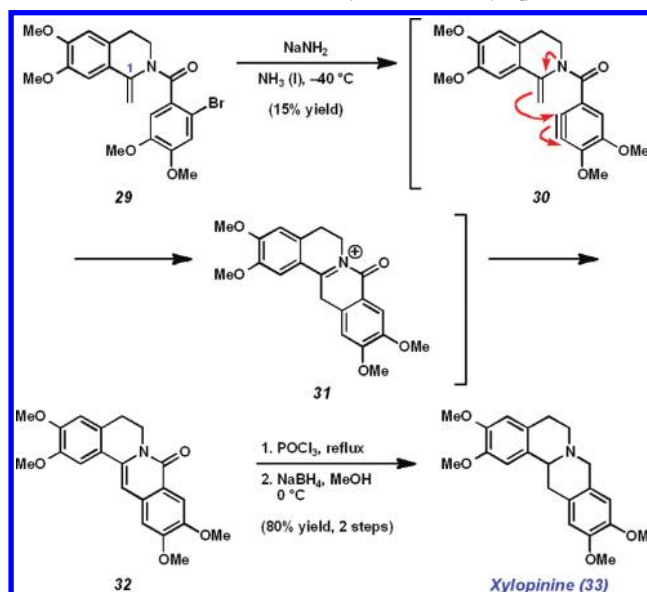


Scheme 9. Kametani's 1973 Synthesis of Nitidine Iodide (27) and Oxynitidine (28)



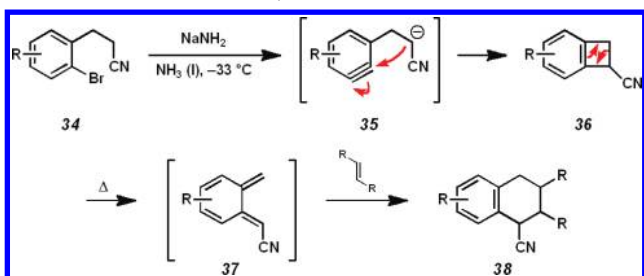
The final alkaloid synthesis in which Kametani and co-workers employed arynes deviates somewhat from the examples detailed above.¹⁵ In the synthesis of xylopinine (33), a protoberberine alkaloid, treatment of C(1)-methylene isoquinoline derivative 29 with sodamide in liquid ammonia resulted in enamine 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)



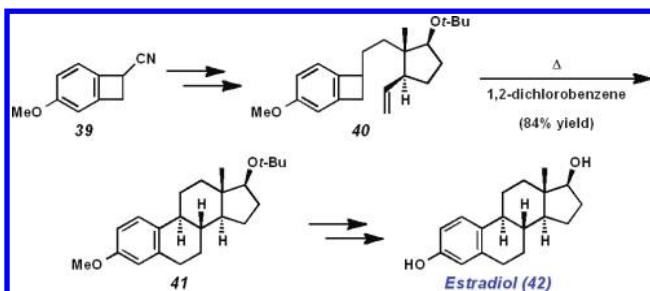
Outside the realm of alkaloid synthesis, Kametani also explored how arynes could expedite the synthesis of steroid structures. In one example, treatment of nitrile 34 with sodamide in liquid ammonia resulted in formation of benzocyclobutene 36 via intermediate aryne 35 (Scheme 11).¹⁶ Benzocyclobutenes,

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

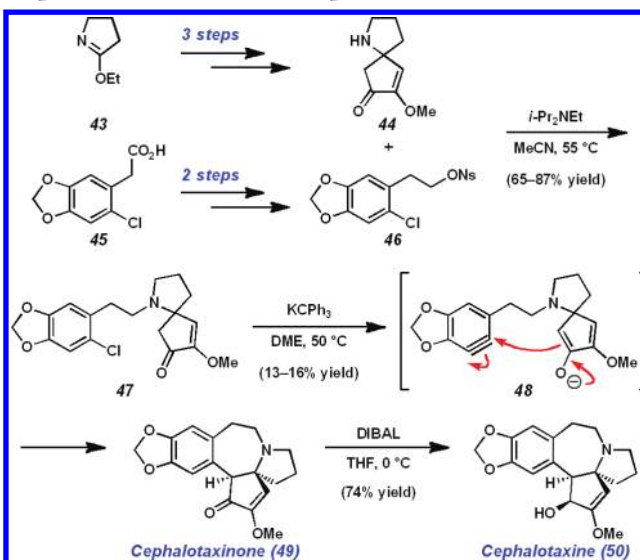
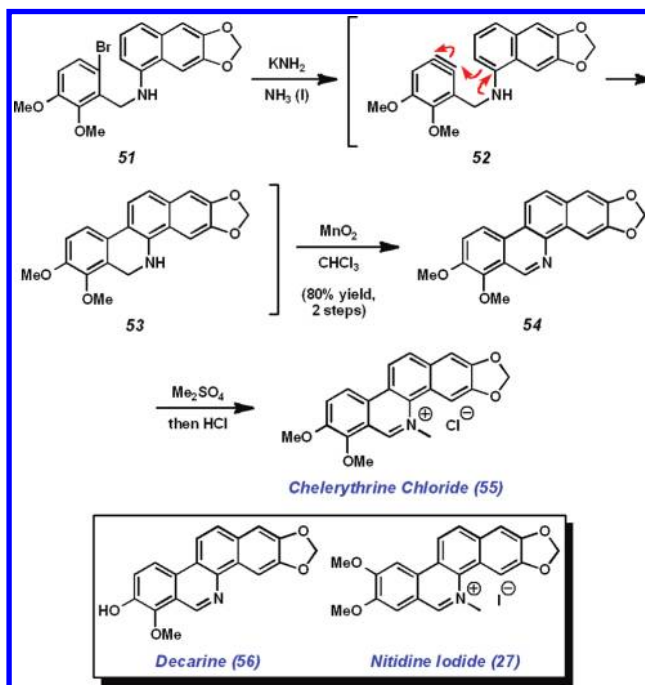
In the synthesis of estradiol (**42**), Kametani elaborated benzocyclobutene **39** to enantioenriched cyclopentane **40**, the precursor for the key Diels–Alder cycloaddition (Scheme 12).¹⁸

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

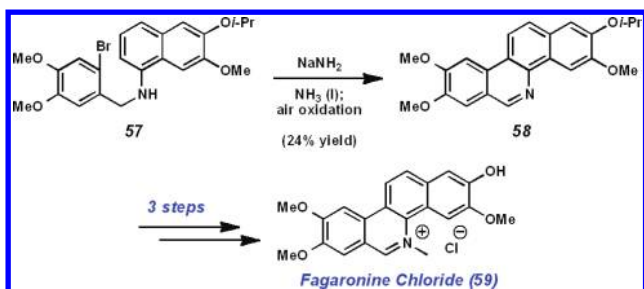
Scheme 13. Semmelhack's 1972 Synthesis of Cephalotaxinone (**49**) and Cephalotaxine (**50**)Scheme 14. Kessar's Synthesis of Chelerythrine Chloride (**55**) (1974), Decarine (**56**) (1984), and Nitidine Iodide (**27**) (1988)

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.

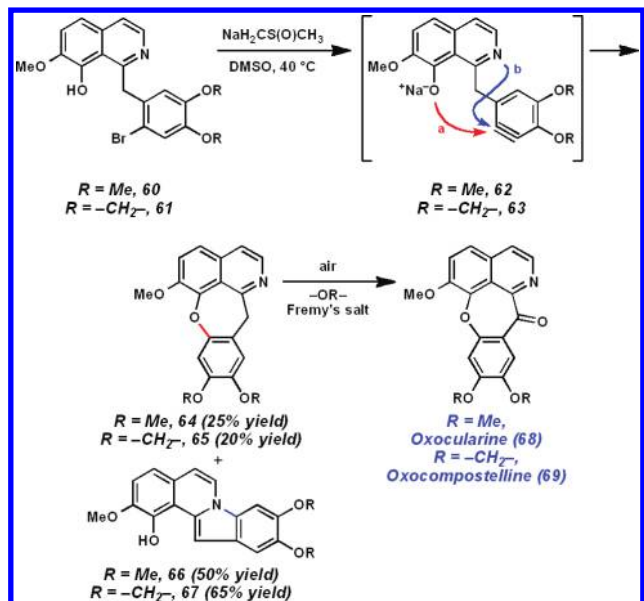
Whereas the previously described synthetic efforts all focused on the formation of new carbon–carbon and carbon–nitrogen bonds, Castedo and co-workers' synthesis of oxocularine (**68**) and oxocompostelline (**69**) sought to forge carbon–oxygen

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



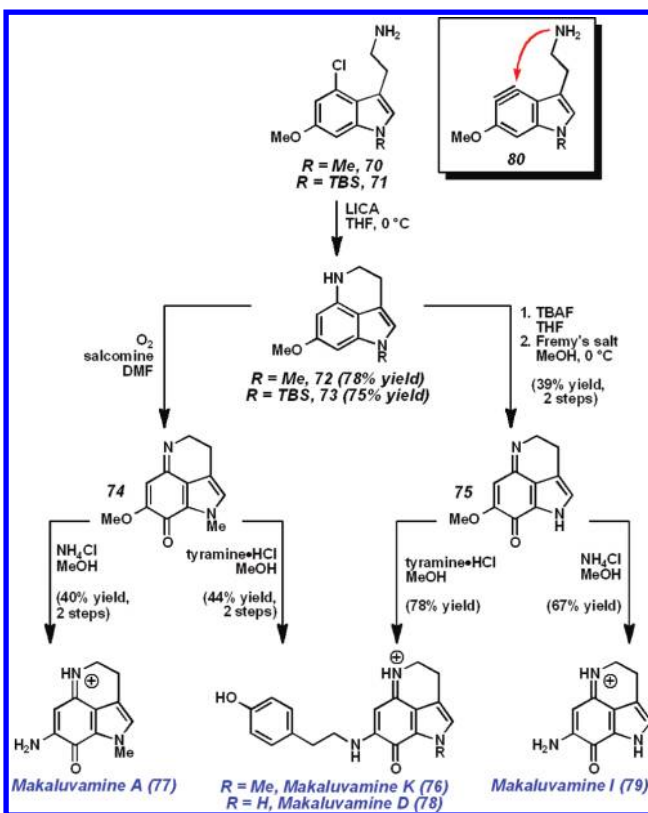
bonds between an intermediate aryne and a pendant phenolate.²⁴ In the key aryne cyclization, treatment of isoquinoline **60** or **61** with sodium dimsylate led to the isolation of two new products each (**64** and **66**, or **65** and **67**, respectively) resulting from competing addition of nitrogen 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 partner. 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 lithium 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**,

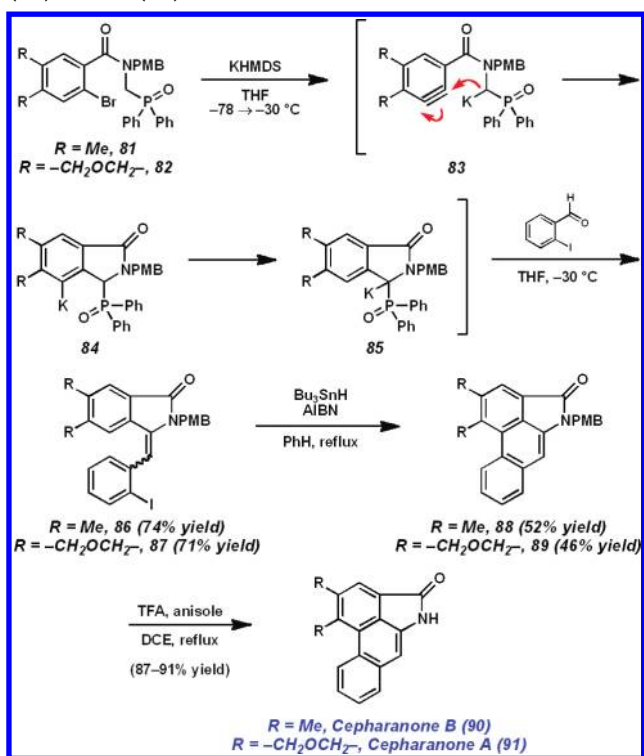
Scheme 17. Iwao's 1998 Synthesis of Makaluvamines A (**77**), D (**78**), I (**79**), and K (**76**)

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.

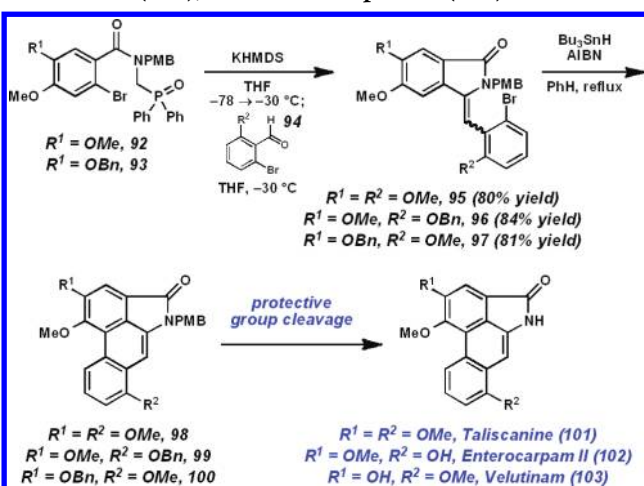
Beginning in the late 1990s, Couture and co-workers embarked on a research program aimed at the synthesis of the aristolactam alkaloids by a general route involving a tandem aryne cyclization/olefination and radical cyclization. Their initial report focused on the synthesis of cepharanones A (**91**) 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 olefination. 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 Bu₃SnH 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**).

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

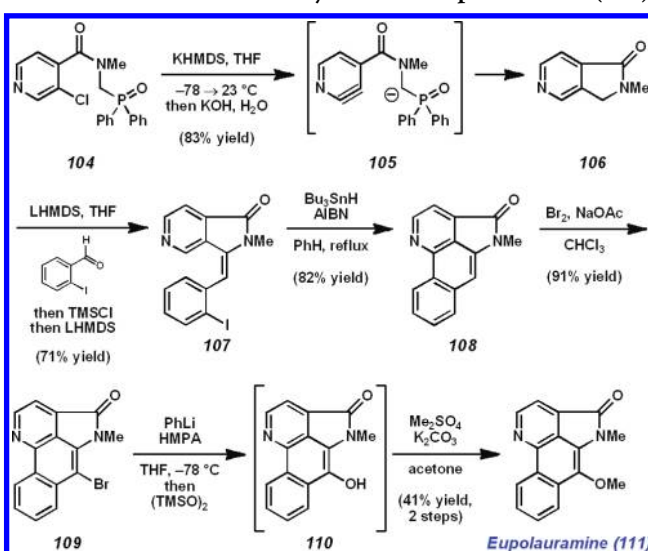


Scheme 19. Couture's 1998 Synthesis of Velutinam (103), Taliscanine (101), and Enterocarpam II (102)



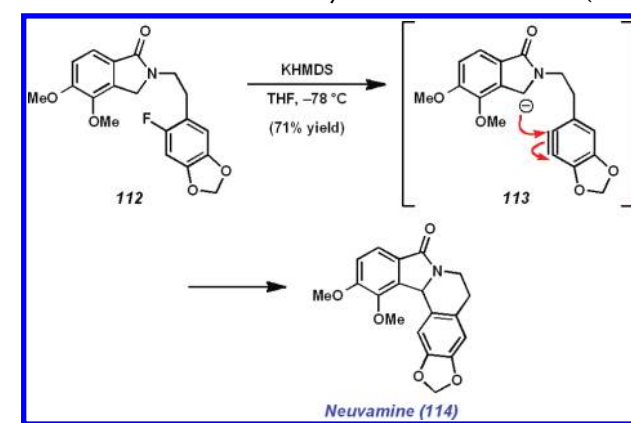
A final natural product synthesis reported by Couture and co-workers utilizing the aryne cyclization/olefination/radical cyclization sequence was that of eupolauramine (111) (Scheme 20).²⁸ This work is distinguished by the intermediacy of a 2,3-pyridyne (105) in place of the standard aryne employed above; 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).

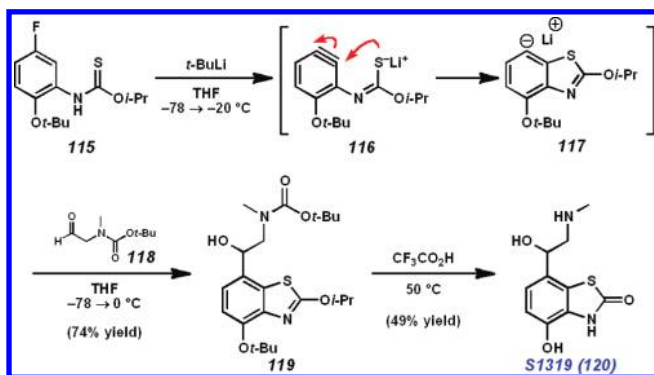
Scheme 21. Couture's 2004 Synthesis of Neuvamine (114)



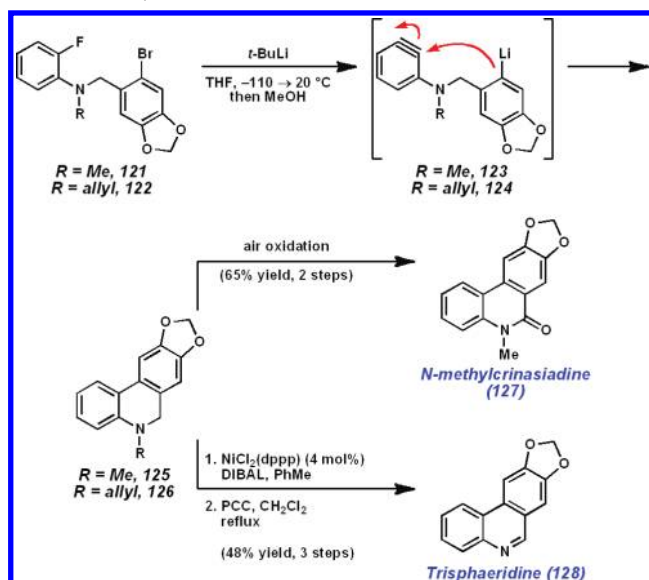
To this point, all instances of nucleophilic additions to arynes in natural product synthesis have employed solely carbon, nitrogen, or oxygen nucleophiles. In 2005, Fairhurst and co-workers reported the synthesis of the thiazolone natural product S1319 (120), which relies upon an intramolecular nucleophilic 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, tri-sphaeridine (128) and *N*-methylcrinasiadine (127), was reported in 2007 by Sanz and co-workers.³¹ Their strategy relies upon the

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



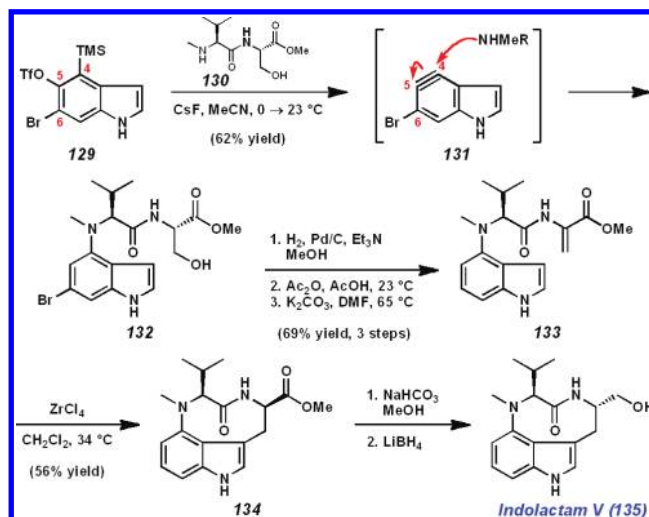
generation of an aryne through dehydrofluorination with concomitant lithium–halogen exchange of a pendant aryl bromide (Scheme 23). In this event, treatment of either *N*-methyl

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)

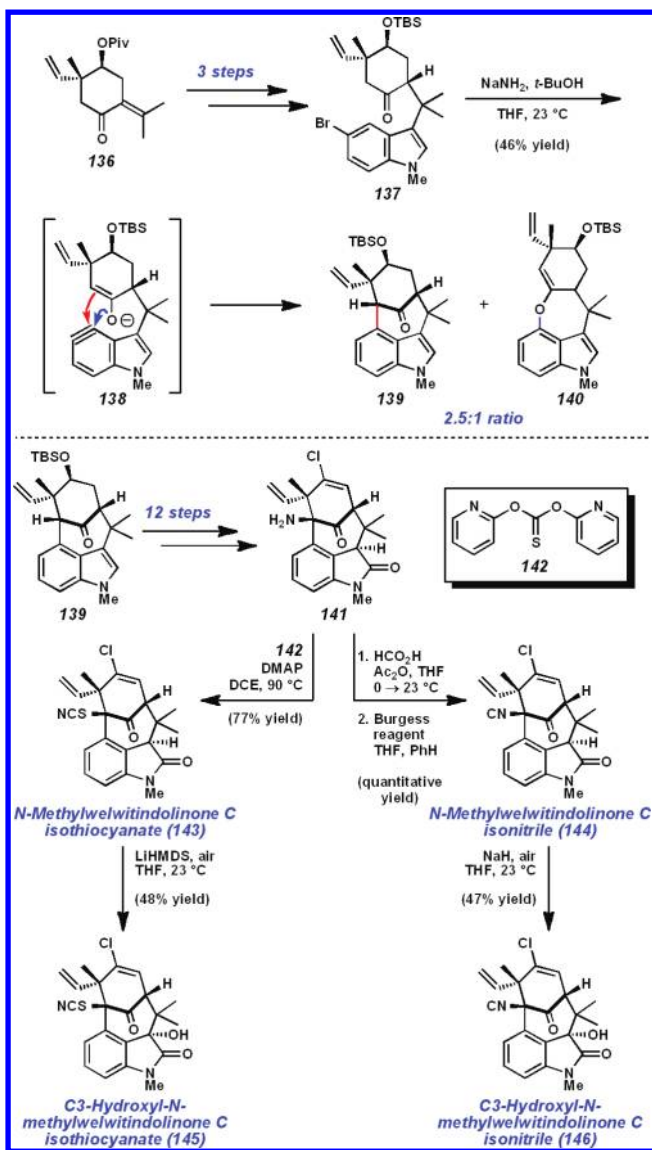


(i.e., addition to the 5-position) for nucleophilic additions to 4,5-indolyne.^{34a,b} At this point, reduction of the bromide and elimination of the primary alcohol produced enamide 133, which underwent conjugate addition with diastereoselective protonation upon treatment with $ZrCl_4$ to generate macrocycle 134. Finally, epimerization of the newly formed C(9) stereo-center 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 quantities 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.

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



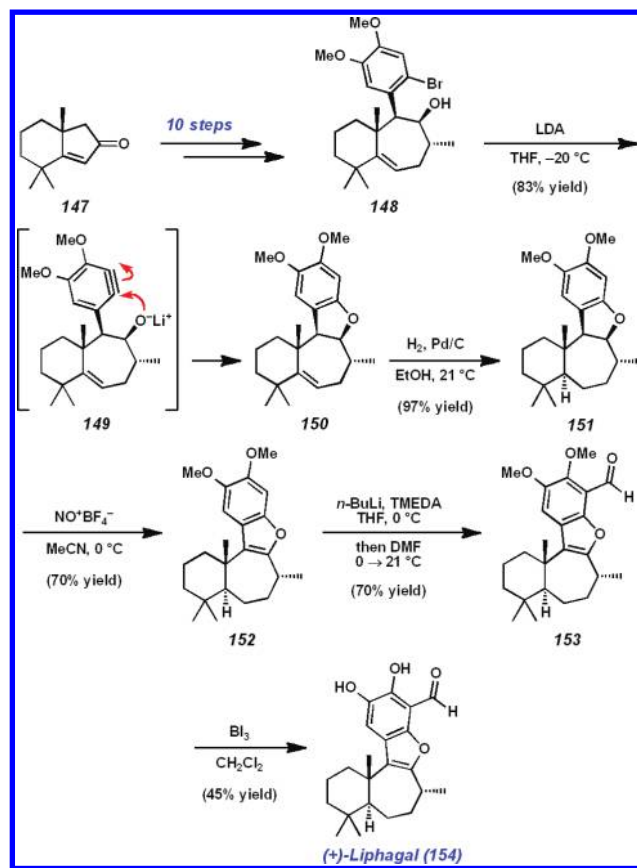
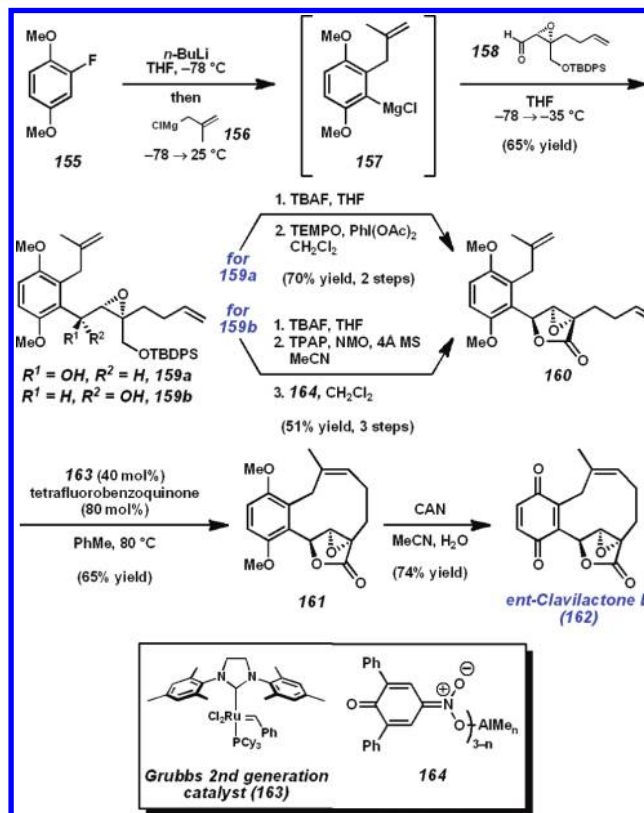
From this point, the synthesis of (+)-liphagal (154) was completed by oxidation of the dihydrobenzofuran (151), formylation, and demethylation.

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

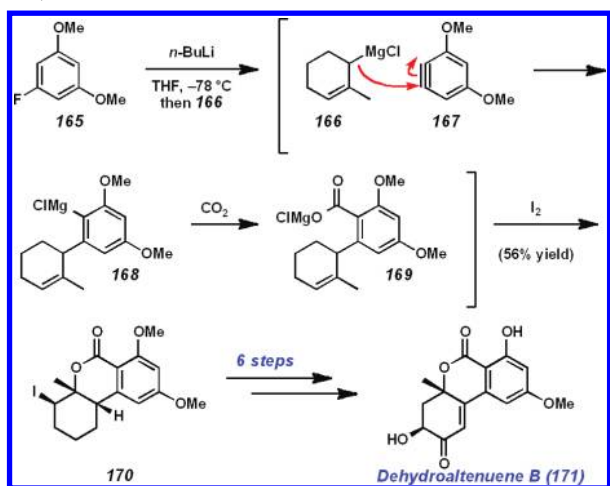
Scheme 26. Stoltz's 2011 Synthesis of (+)-Liphagal (154)

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

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**)



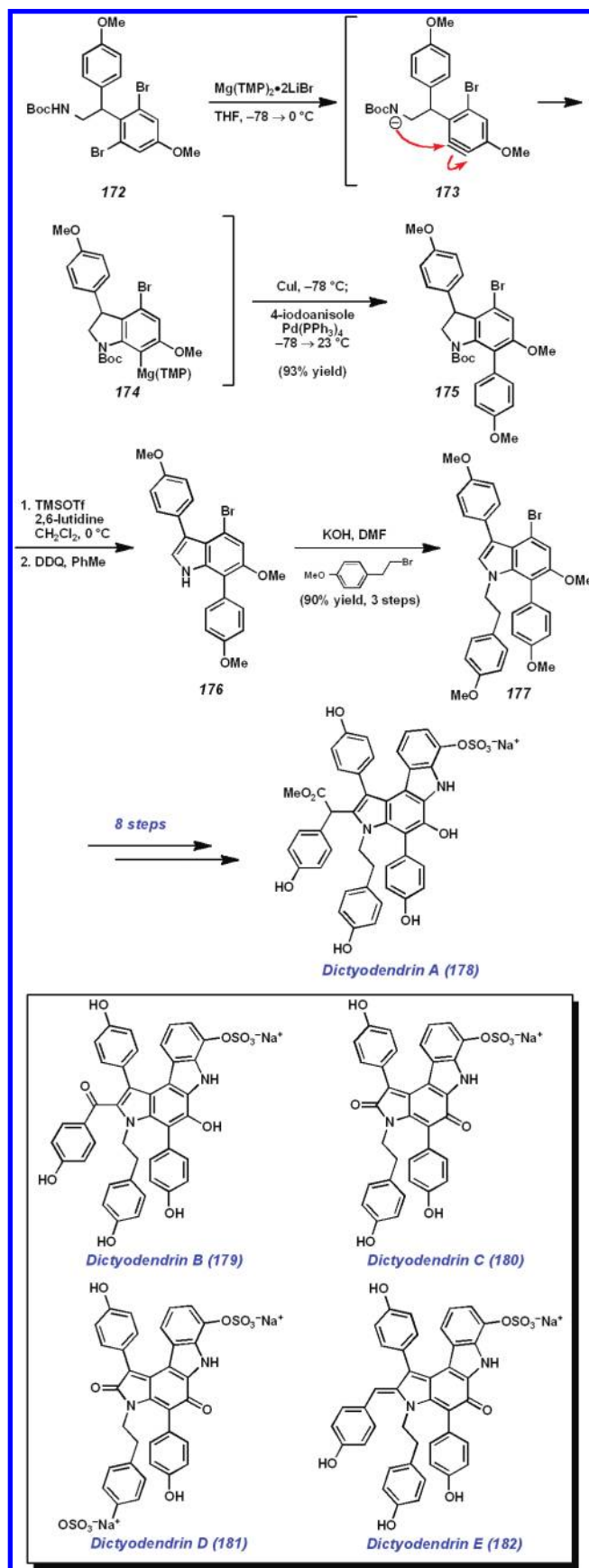
of fluoroarene **165** to generate arynes **166**, sequential addition of cyclohexenylmagnesium chloride **166**, carbon dioxide, and iodine generated iodolactone **170**. The authors propose that the reaction proceeds through addition of organomagnesium reagent **166** to arynes **167**, followed by 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 dictyodendrin A–E (**178**–**182**).⁴¹ In this case, an initial intramolecular nucleophilic addition of a nitrogen anion into a pendant aryne (**172** \rightarrow **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 dictyodendrin B (**179**), C (**180**), D (**181**), and E (**182**).

3. BOND-INSERTION REACTION STRATEGIES

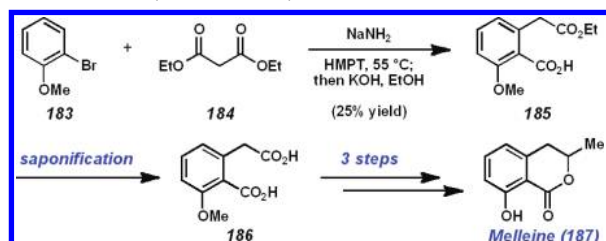
Carbon–carbon bond-insertion reactions are some of the most recent methodologies to emerge from the aryne literature. Remarkably, their use was first reported in the context of total synthesis, whereas generalized methods were not disclosed until 2005.^{6a,42,43} Since these initial reports, a number 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 Dictyodendrin A–E (**178**–**182**)



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

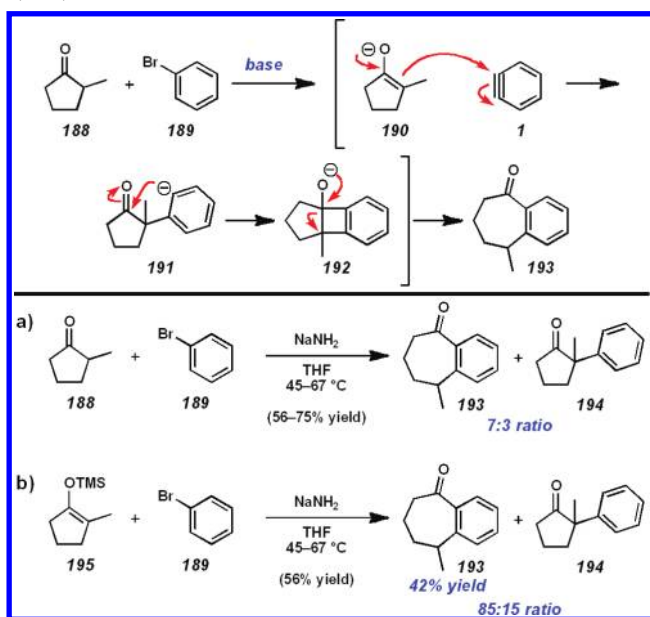
Scheme 30. Guyot's 1973 Synthesis of Melleine (187)



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

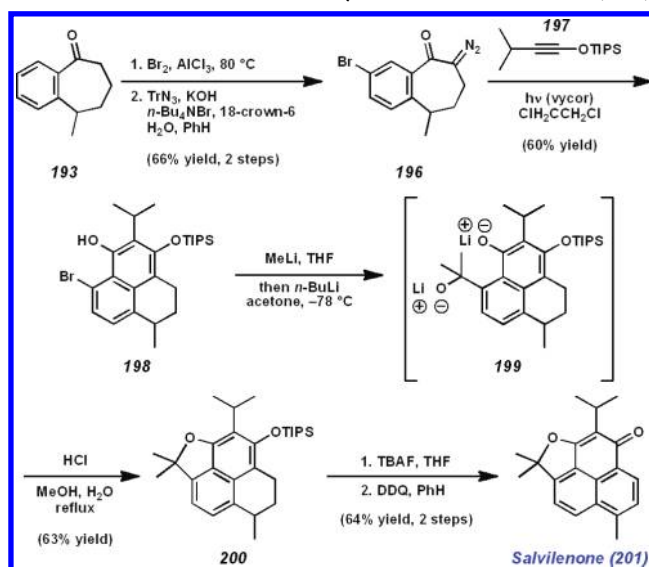
It was not until 1994 that an aryne σ -bond insertion reaction was used again in natural product synthesis. In their total synthesis of salvilenone (**201**), Danheiser and Helgason employed a ring-expansive carbon–carbon bond-insertion reaction between an aryne and a ketone enolate (Scheme 31).⁴⁶ More

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)

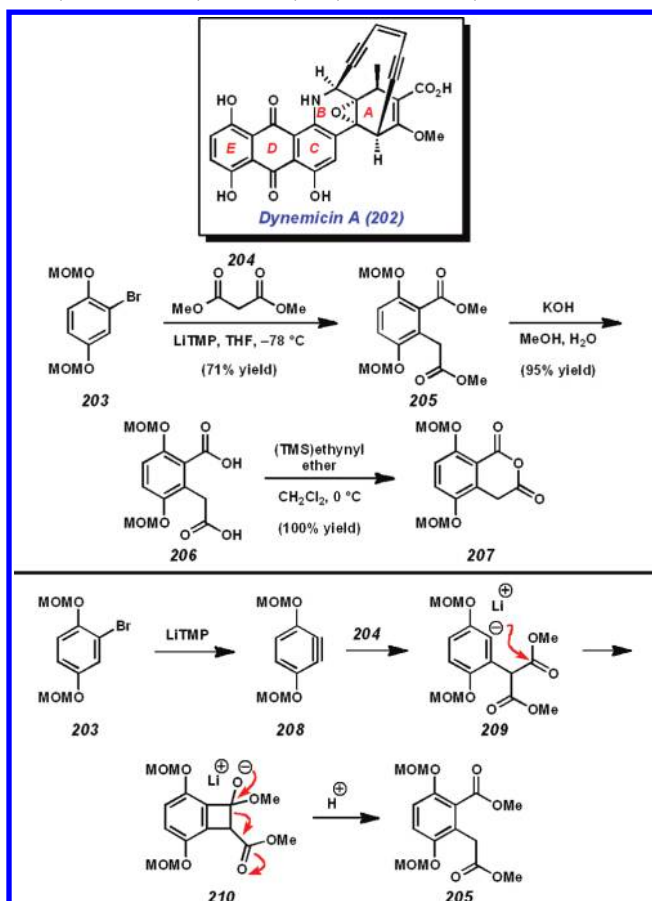


alkyne **197** resulted in a cascade reaction consisting of Wolff rearrangement, $[2 + 2]$ -ketene cycloaddition, 4π electrocyclic ring-opening, and 6π electrocyclic ring-closing to furnish tricycle **198**. From this point, completion of salvilenone (**201**) was readily accomplished by annulation of 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 calicheamicin⁴⁸ 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**)

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

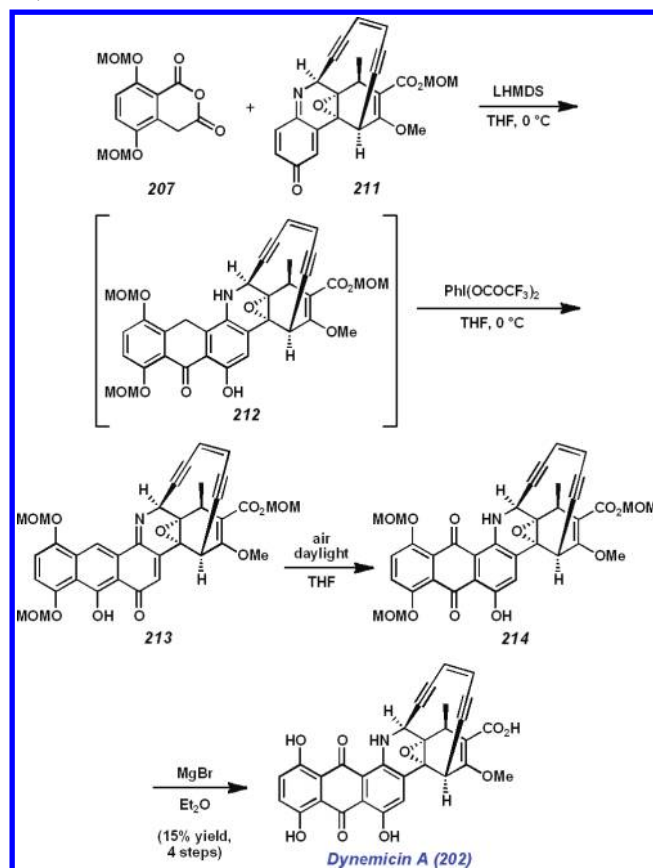


followed by global deprotection yielded dynemicin A (202) in 15% yield over the final four steps.

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 regioselectivity 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 CO₂ 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)



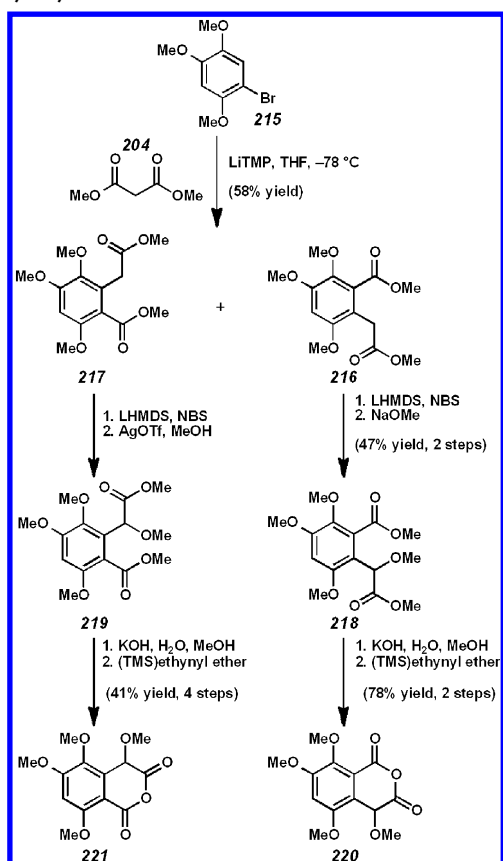
Ultimately, Kita and co-workers determined that the compound bearing the *S* absolute configuration at the single stereocenter was the naturally occurring fredericamycin.

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 carboxyalkylation 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).

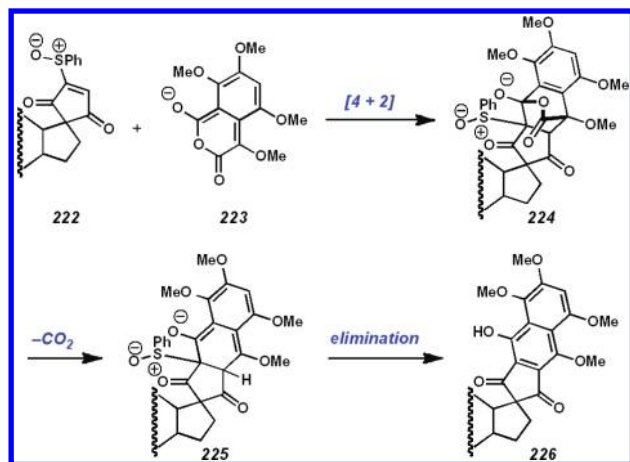
Despite the previous five examples of aryne acyl-alkylation with malonate-derived nucleophiles, a thorough examination of this specific reactivity was not undertaken until 2005 when Stoltz and co-workers reported the reaction of arynes derived from silyl aryl triflates³ (e.g., 238) with β -ketoesters (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

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

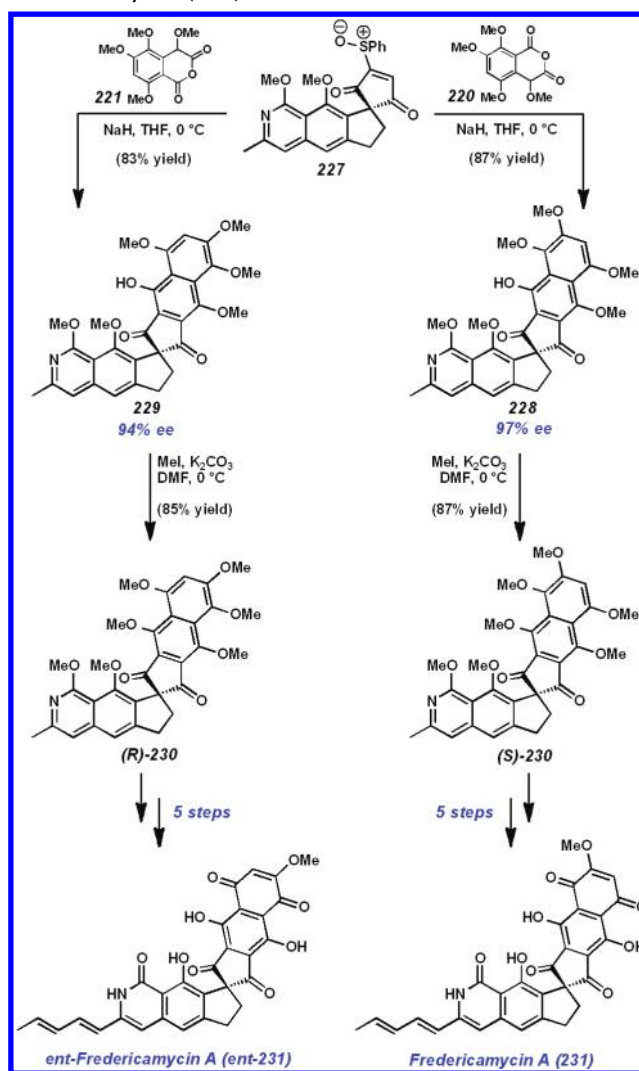
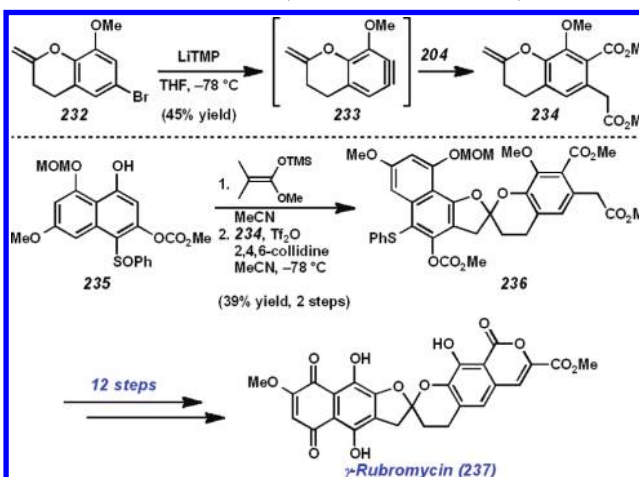


Scheme 36. Mechanism for Coupling of the AB-Ring Fragment and CDEF-Ring Fragment

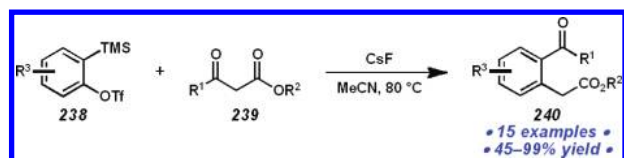


In this case, the aryne formation and the subsequent acyl-alkylation are triggered by a mild fluoride source, instead of the strong bases used in prior examples. The resulting tetracycle (243) contained all but one of carbons present in the natural product. To render the synthesis enantioselective, Stoltz 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 (\pm)-244 provided enantioenriched alcohol ($-$)-244 in 47% yield and >99% ee, corresponding to a selectivity factor

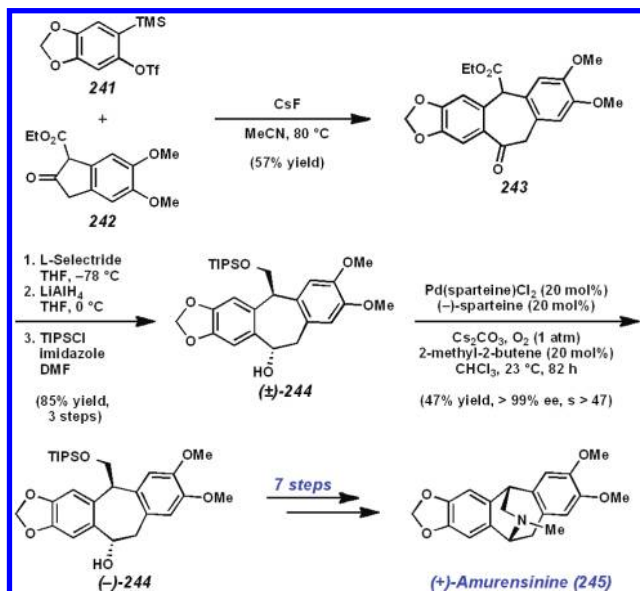
Scheme 37. Kita's 1999 Stereodivergent Approach to Fredericamycin (231)

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.

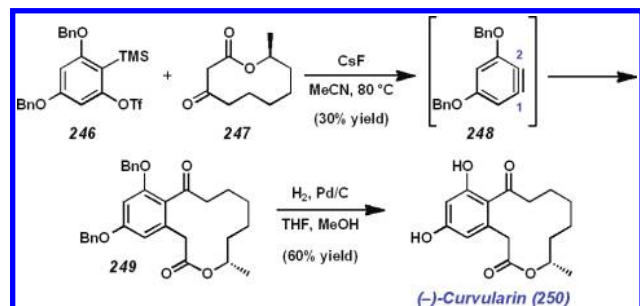
Scheme 39. Stoltz's Acyl-alkylation of Arynes with β -Ketoesters

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,

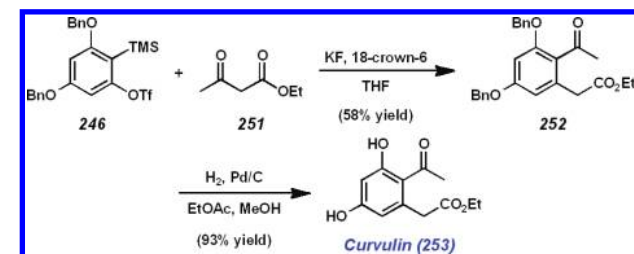
Scheme 41. Stoltz's 2010 Enantioselective Synthesis of (–)-Curvularin (250)



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, debenzoylation revealed the resorcinol core, completing (–)-curvularin (**250**) in six steps from known compounds.

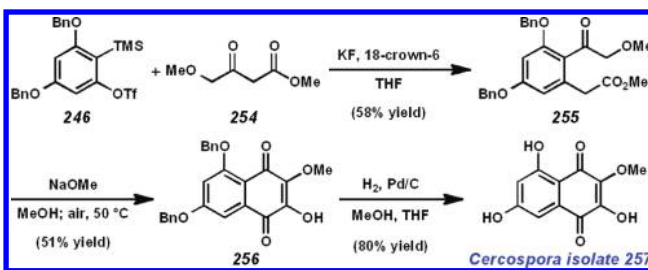
Concurrent with their report on (–)-curvularin, Stoltz and co-workers reported two additional syntheses of natural products utilizing the same protected resorcinyl silyl aryl triflate (**246**).⁵⁶ Acyl-alkylation of silyl aryl triflate **246** with ethyl acetoacetate (**251**) under modified conditions followed by debenzoylation 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)



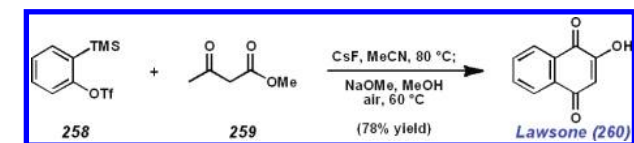
with γ -methoxy- β -ketoester **254**, followed by base-mediated cyclization and aerobic oxidation yielded hydroxynaphthoquinone **256** (Scheme 43). Debzoylation of this intermediate (**256**) provided *Cercospora* isolate **257**.

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



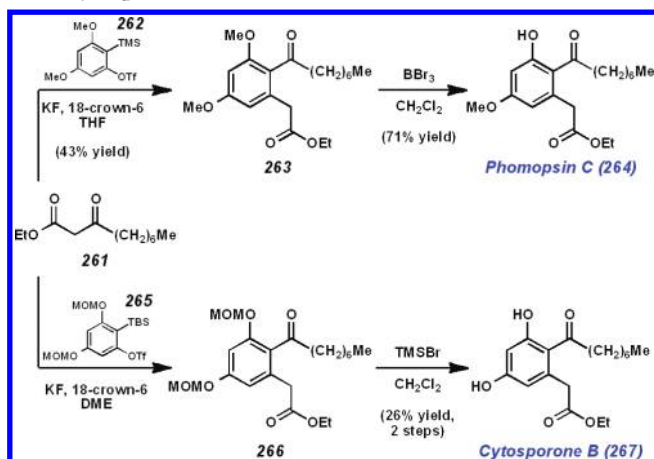
The acyl-alkylation/condensation/air oxidation method for the formation of hydroxynaphthoquinones was further developed into a one-pot procedure by Stoltz and co-workers.⁵⁷ This streamlined method was demonstrated by the one-step synthesis of lawsone (**260**) from unsubstituted silyl aryl triflate **258** 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 phomopsis C (**264**) (Scheme 45).⁵⁸ Acyl-alkylation of ethyl 3-oxodecanoate (**261**) with unsymmetrical dimethoxy aryne precursor **262** regioselectively yielded arene **263** as a single isomer in modest yield. Subsequent selective monodemethylation then afforded phomopsis C (**264**). Alternatively, acyl-alkylation of silyl aryl triflate **265** with ethyl 3-oxodecanoate (**261**) provided arene **266**, which was converted into

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

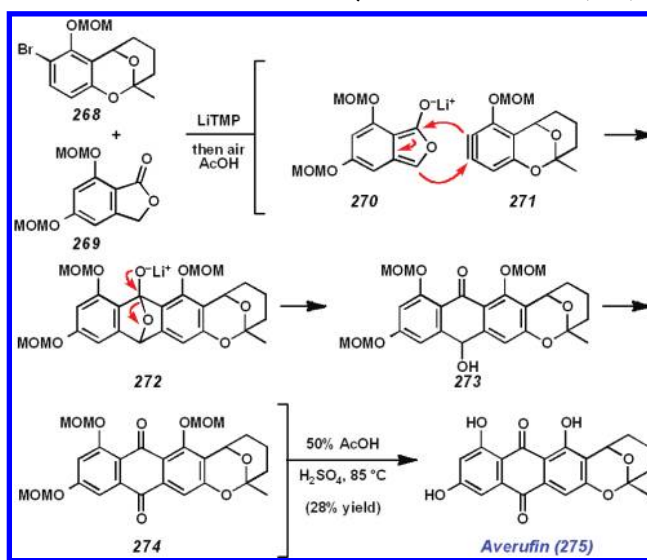
The prevalence of [4 + 2]-aryne cycloadditions as a strategy for natural product total synthesis is second in the literature only to the use of nucleophilic additions. However, despite the large volume of such approaches, there remain significant limitations to the application of aryne [4 + 2]-cycloadditions. 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.

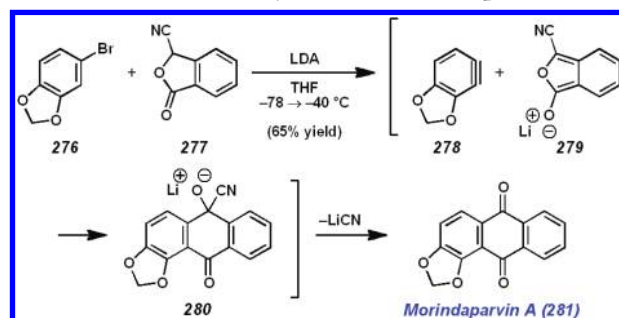
The first example of the application of an aryne [4 + 2]-cycloaddition (formal, stepwise, or concerted) in the synthesis of a natural product comes from Townsend and co-workers' preparation of averufin (275) in 1981 (Scheme 46).⁵⁹ Averufin (275) was targeted by a formal aryne [4 + 2]-cycloaddition reaction 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)

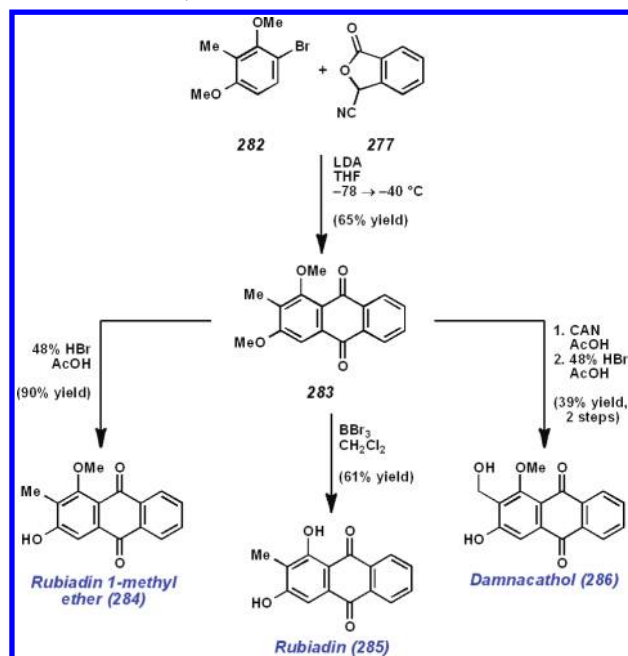


Notably, the use of a 3-cyanophthalide (277) in place of a simpler lactone removed the need for subsequent air oxidation as in the case of averufin. Instead, cycloaddition and fragmentation generated cyanohydrin 280, which furnished the anthraquinone (281) directly upon ejection of cyanide.

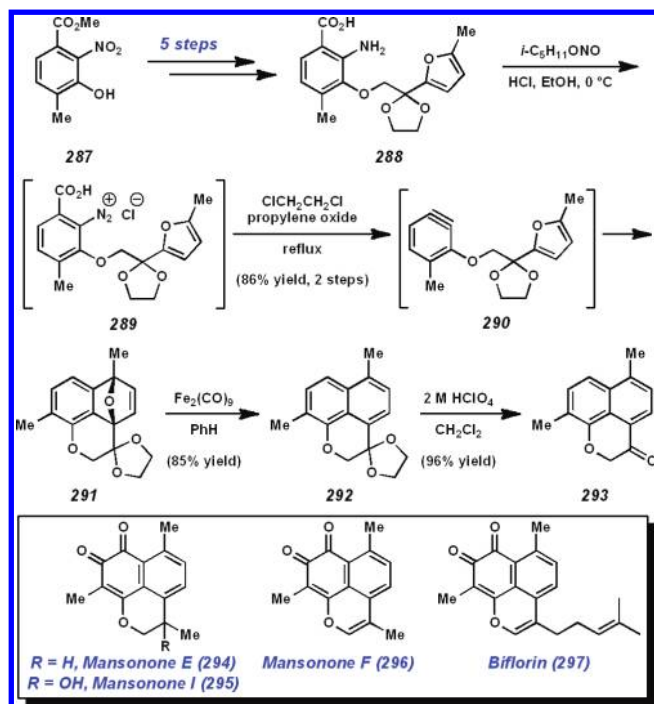
The second of Biehl's reports applied this same method to the synthesis of rubiadin (285), rubiadin 1-methyl ether (284), and damnacathol (286) (Scheme 48).⁶¹ Replacing dioxolane 276 with trisubstituted bromoarene 282 led to anthraquinone 283, the point of divergence from which the three products were targeted. Monodemethylation with HBr in acetic acid produced rubiadin 1-methyl ether (284), whereas bisdemethylation with excess BBr₃ 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

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 E Precursor 293

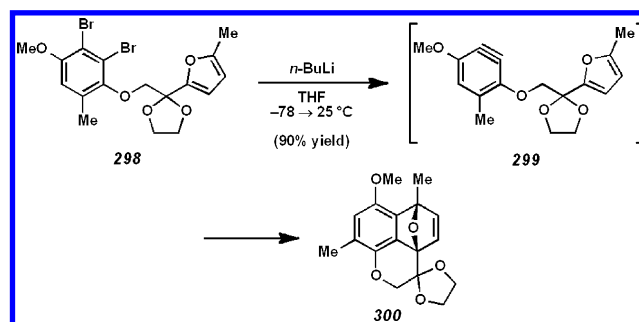


treatment of anthranilic acid 288 with $i\text{-C}_5\text{H}_{11}\text{ONO}$ in acidic ethanol, an intermediate diazonium hydrochloride (289) was generated that then underwent spontaneous thermal decomposition to the aryne (290). Cycloaddition between the aryne and the pendant furan then produced pentacyclic 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

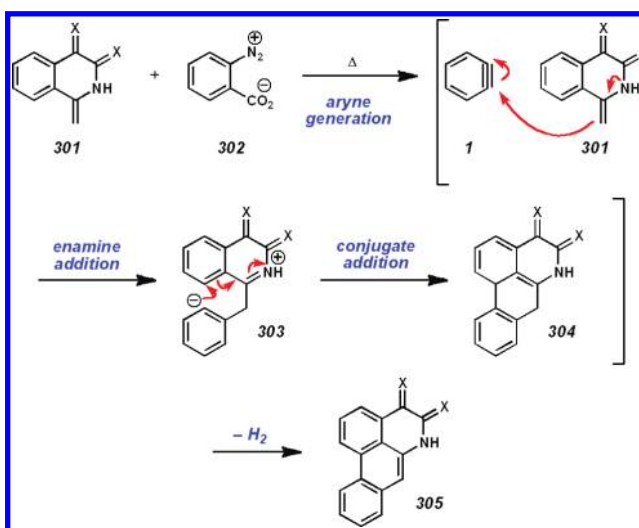
that the key intramolecular Diels–Alder cycloaddition can also be performed by elimination of the corresponding *o*-dibromide compound (298) with $n\text{-BuLi}$, producing cycloadduct 300 in 90% yield (Scheme 50).

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

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

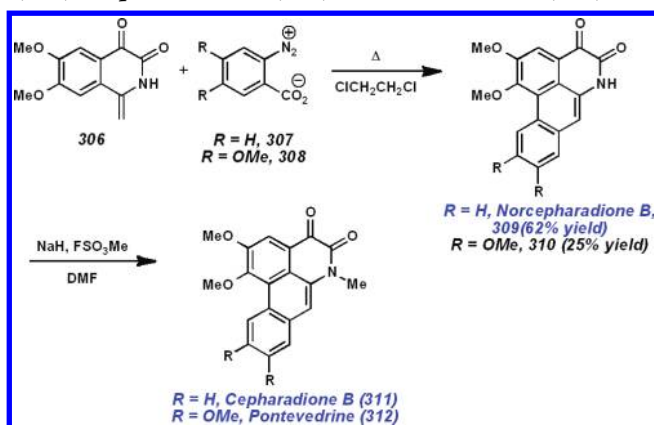


annulation can be envisioned to proceed in a stepwise fashion beginning with an enamine addition of isoquinoline derivative 301 to an aryne (1) to generate an intermediate aryl anion (303). The aryl anion (303) can then undergo a dearomatizing conjugate addition to the pendant iminium ion to produce 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),

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).

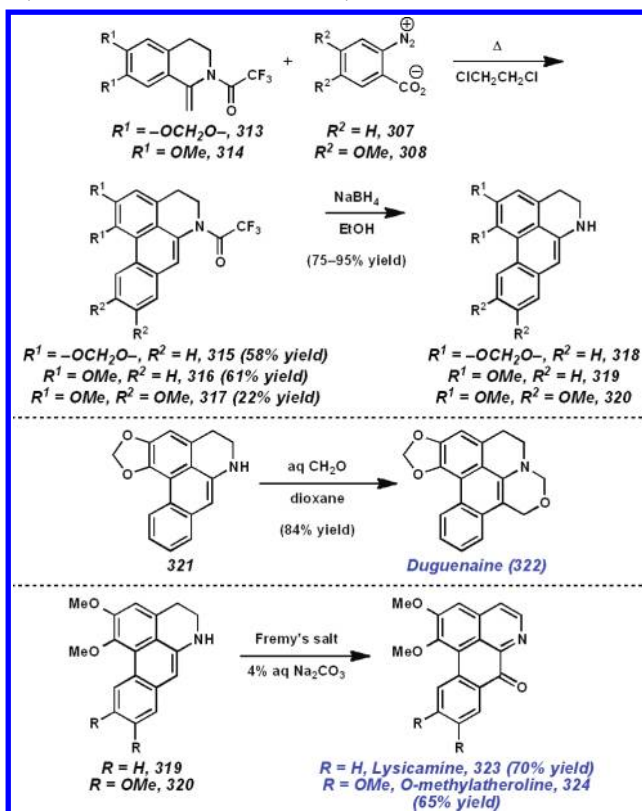
A variation on this theme produced duguenaine (322), lysicamine (323), and *O*-methylatheroline (324) by employing differentially substituted 1-methylene-3,4-dihydroisoquinoline cycloaddition partners (313 and 314) (Scheme 53).^{68a} The cycloadducts of these aryne [4 + 2]-reactions (315–317) were each 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).

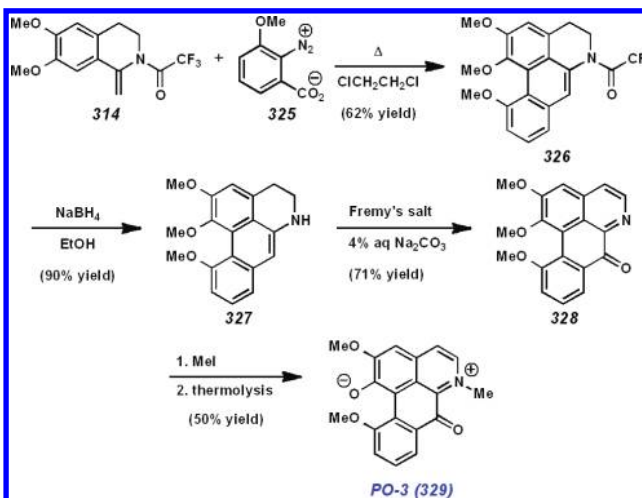
As part of their ongoing program aimed at the development of new aryne [4 + 2]-cycloadditions for alkaloid total synthesis, Castedo and co-workers targeted another class of isoquinoline-derived natural products—the protoberberines—by the cycloaddition of isoquinolinepyrrolinediones (e.g., 330) with arynes (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)



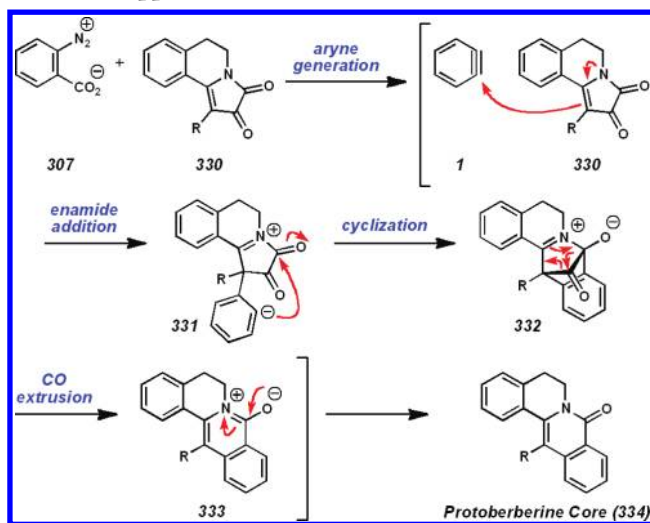
Scheme 54. Castedo's 1985 Synthesis of PO-3 (329)



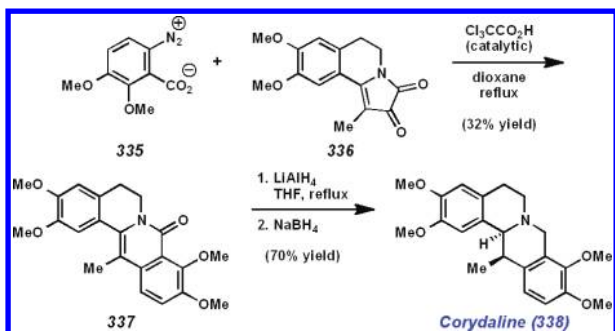
tetracycle 337 in modest yield (Scheme 56).⁶⁹ Amide reduction followed by treatment of the resulting enamine with $NaBH_4$ furnished corydaline (338).

Analogous to corydaline, 8-oxypseudopalmitine (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 extrusion. Hydrogenolysis of the bromide provided 8-oxypseudopalmitine (341).

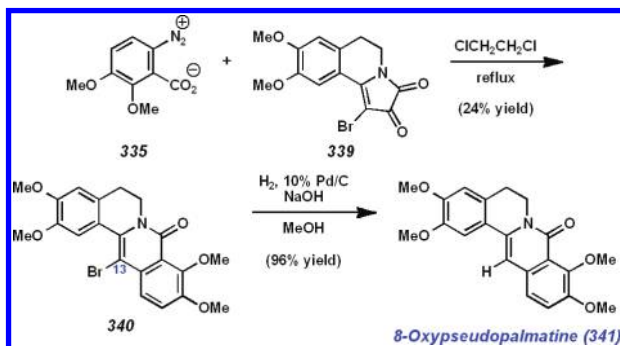
Scheme 55. Castedo's Tandem [4 + 2]-Cycloaddition/CO Extrusion Approach to the Protoberberine Alkaloids



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



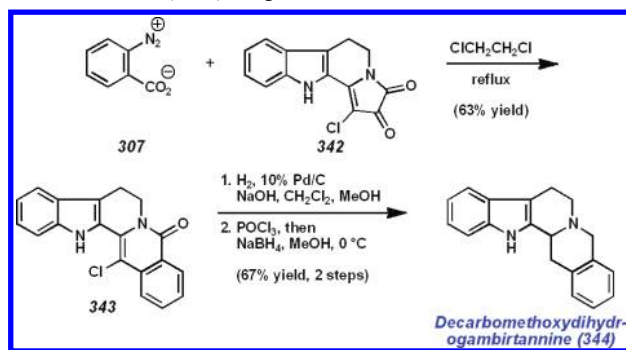
Scheme 57. Castedo's 1988 Synthesis of 8-Oxypseudopalmitine (341)



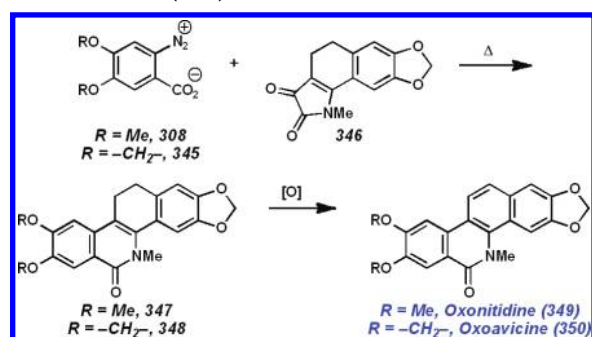
In the synthesis of decarbomethoxydihydrogambirtannine (344), the reaction of β -carboline-derived chloropyrrolinedione 342 and benzenediazonium-2-carboxylate (307) generated pentacyclic intermediate 343 in good yield (Scheme 58).^{70b} Upon hydrogenolysis of the chloride and reduction of the amide,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

Similarly, oxoavicine (350) and oxonitidine (349) could be accessed by [4 + 2]-cycloaddition and CO extrusion with pyrrolinedione 346 and arylene 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)

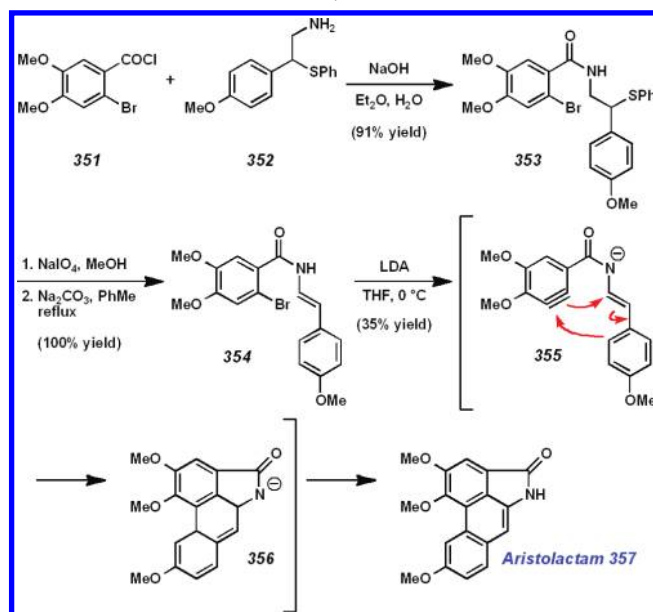


Scheme 59. Castedo's 1989 Synthesis of Oxoavicine (350) and Oxonitidine (349)



In 1989, Castedo and co-workers reported syntheses of the aristolactam and phenanthrene alkaloids featuring novel arylene [4+2]-cycloaddition strategies.⁷² In these examples, the cycloaddition occurs between a tethered arylene–diene pair in an intramolecular arylene 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

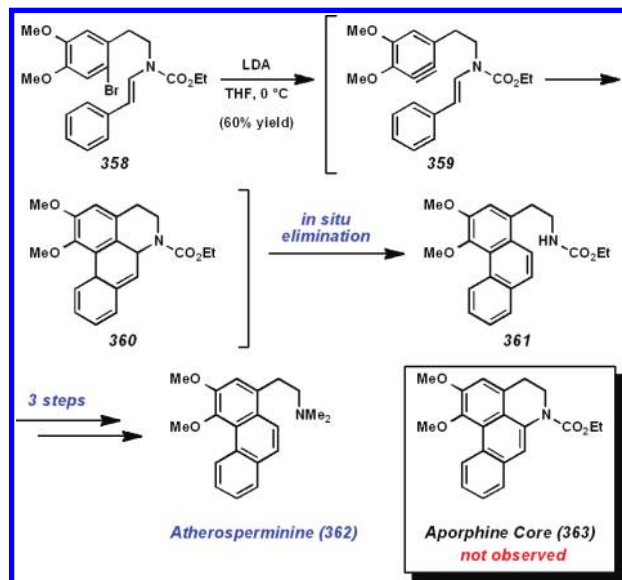
Scheme 60. Castedo's 1989 Synthesis of Aristolactam 357



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)



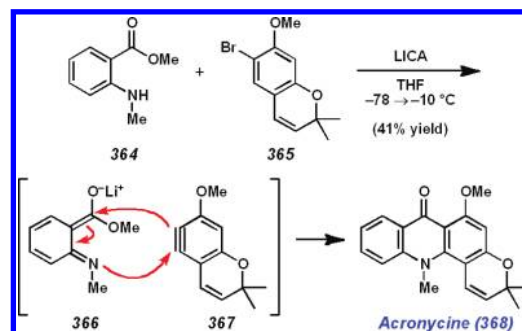
361 was isolated as the major product in 60% yield. Presumably this product arises from a pathway beginning with the desired intramolecular $[4 + 2]$ -cycloaddition following aryne generation; however, the initial adduct (360) then undergoes fragmentation during aromatization to form phenanthrene 361. 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 amaryllidaceae alkaloid ring system,⁷⁴ the ergot alkaloid framework,⁷⁵ the benzophenanthridine alkaloid 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 Moody⁷⁹ and Gribble⁸⁰ 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

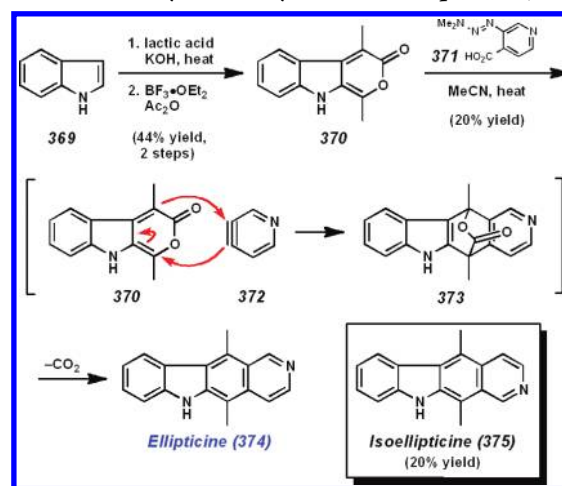
Scheme 62. Watanabe's 1984 Synthesis of Acronycine (368)



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)

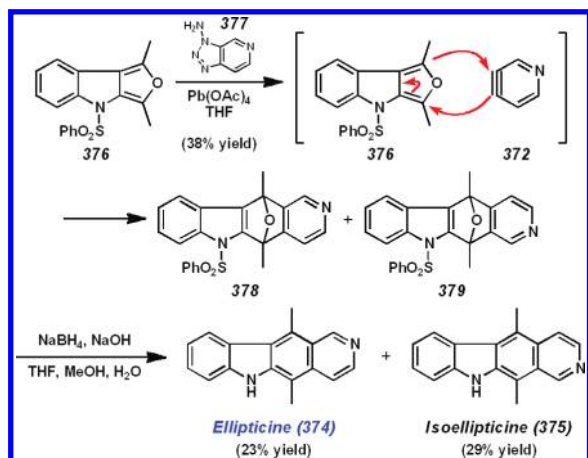
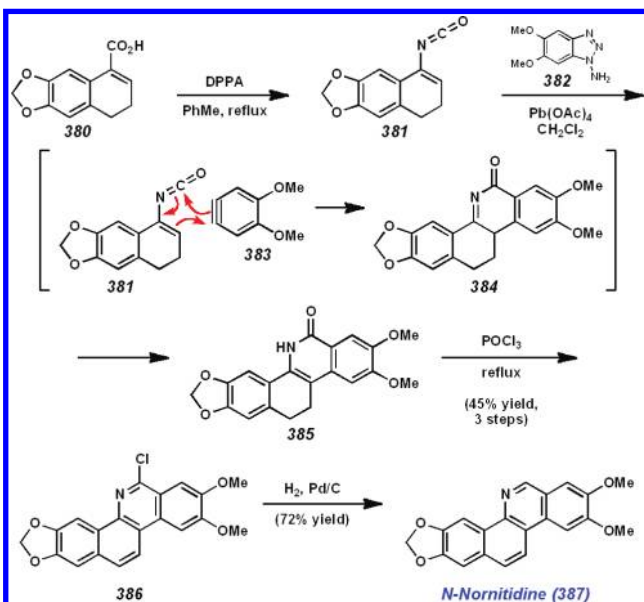


Upon thermal decomposition of triazine 371, nonselective $[4 + 2]$ -cycloaddition of pyrone 370 with 3,4-pyridyne (372) yielded a 1:1 separable mixture of ellipticine (374) and isoellipticine (375), following extrusion of CO₂.

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*-normitidine (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

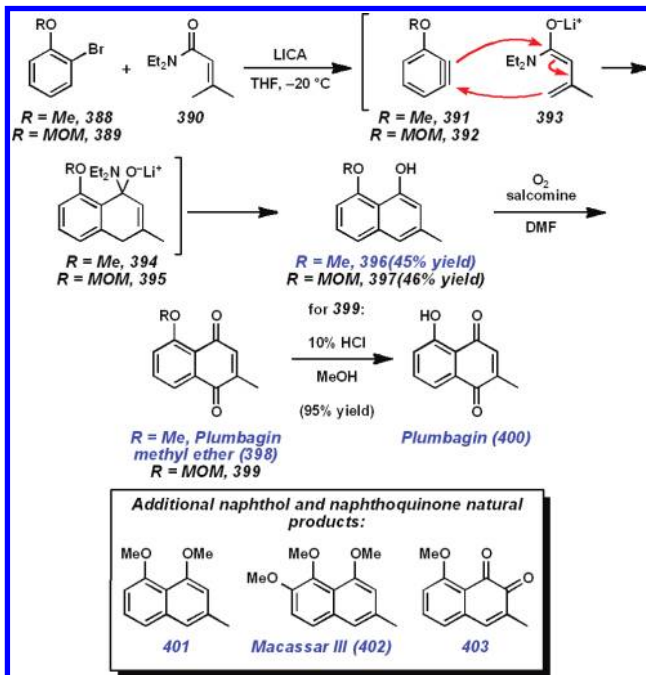
Scheme 64. Gribble's 1984 Synthesis of Ellipticine (374)

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 POCl₃ 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 acyclic 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

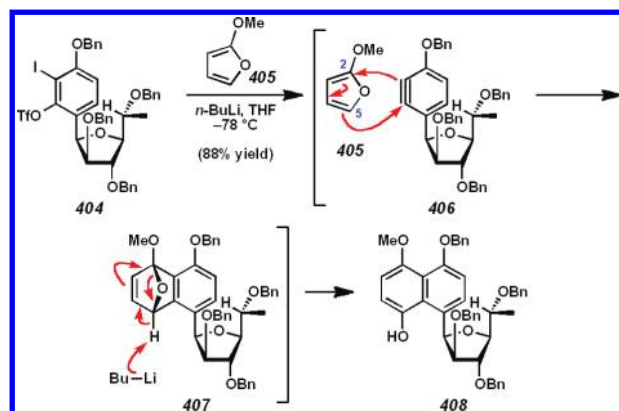
Scheme 66. Watanabe's 1986 Synthesis of Plumbagin Methyl Ether (398), Plumbagin (400), and Other Naphthol and Naphthoquinone Natural Products



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

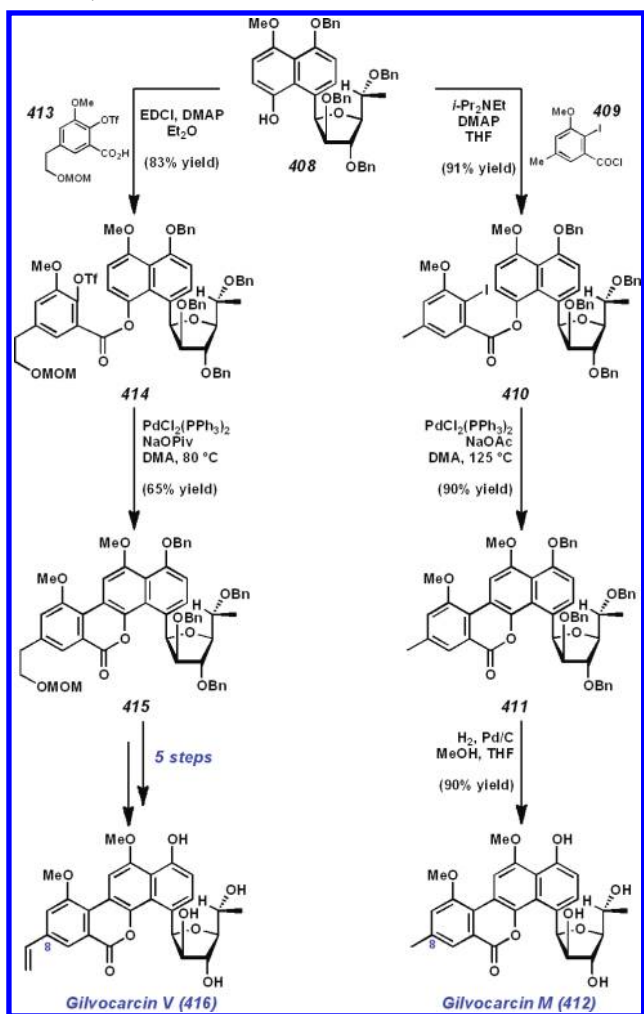


selective formation of naphthol 408 in favor of the alternative isomeric cycloadduct (isolated in 7% yield) demonstrates the predominance of electronic factors over steric interactions in determining the regiochemical outcome of addition to unsymmetrical arynes. In this case, the more nucleophilic C(5)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

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)**

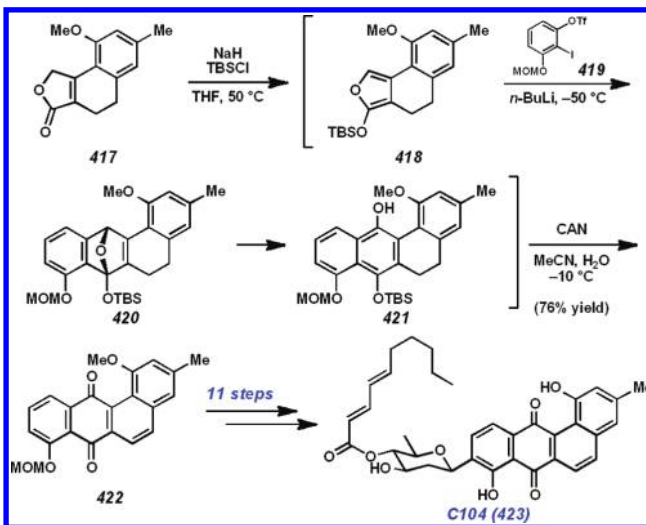


with a palladium source resulted in ring-closing C–H functionalization to afford tetracycles **411** and **415**, respectively. Global deprotection of tetracycle **411** furnished gilvocarcin M (**412**), whereas tetracycle **415** required five additional steps for installation of the C(8) vinyl group 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**)**

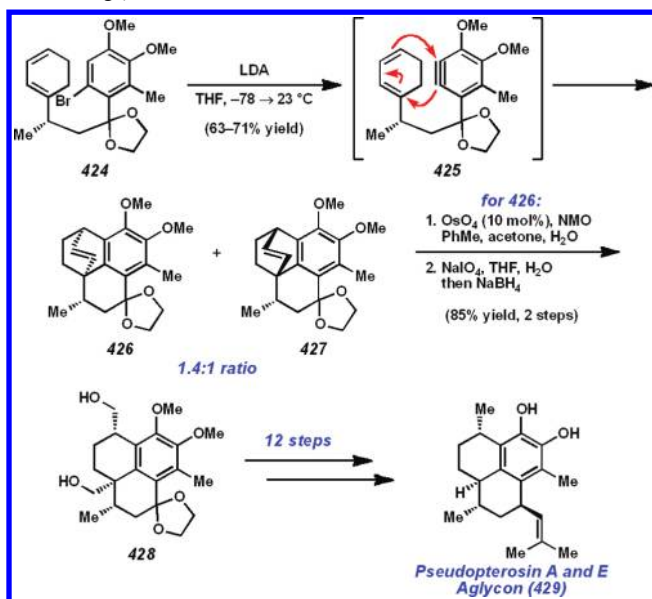


initially formed by this sequence (**420**) undergoes ring-opening aromatization under the reaction conditions to yield tetracycle **421**. However, this intermediate was found to be unstable and was thus treated with CAN upon workup to give the quinone (**422**) as the final product of this sequence. 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.

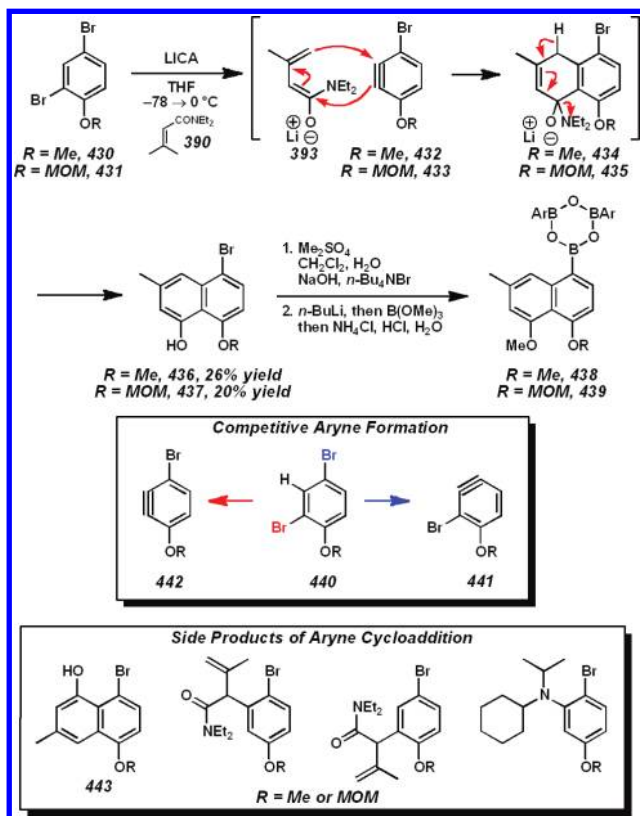
Among the examples in the literature of aryne [4 + 2]-cycloadditions in natural product synthesis that have employed acyclic dienes are Hoyer and co-workers' syntheses of michelamines A–C (**449–451**),⁸⁸ korupensamine C (**445**), and ancistrobrevine B (**447**).⁸⁹ In each of these syntheses, the Diels–Alder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

Scheme 70. Buszek's 1995 Synthesis of Pseudopterisin 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)

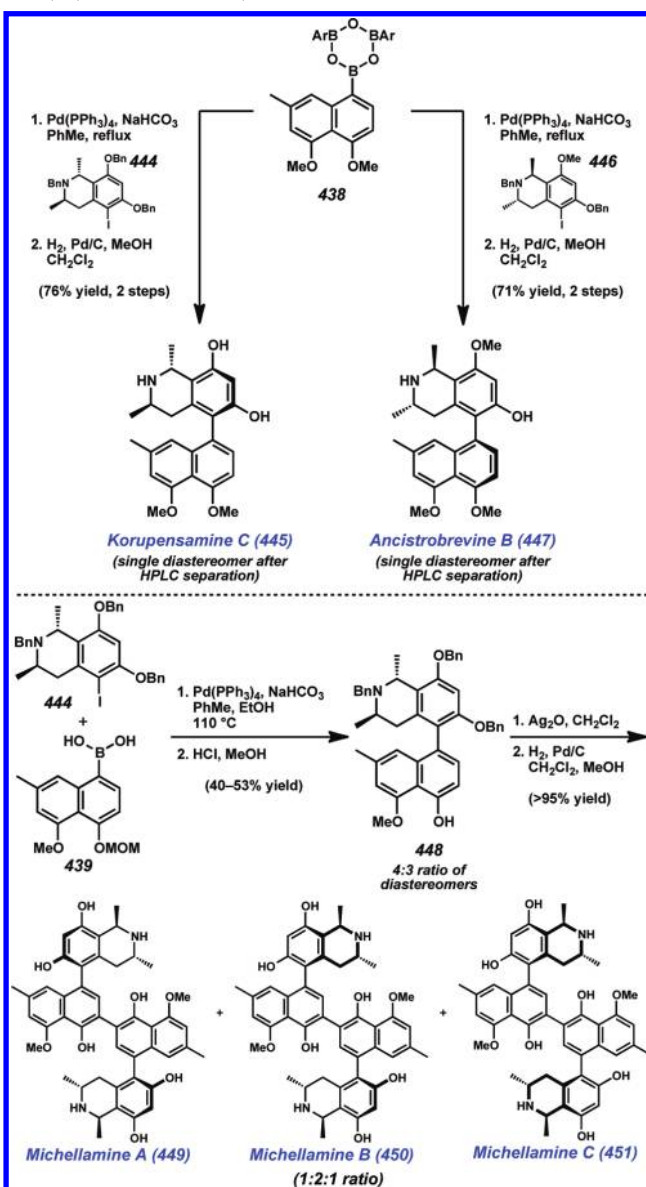


examination of the aryne precursors (430 and 431) reveals that, upon removal of the proton between both bromides, two potential arynes could result from base-promoted dehydrohalogenation: 441 and 442. Although a number of side-products

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 ancistrobreve 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), Ancistrobreve B (447), and Michellamines A–C (449–451) (1994 and 1996)

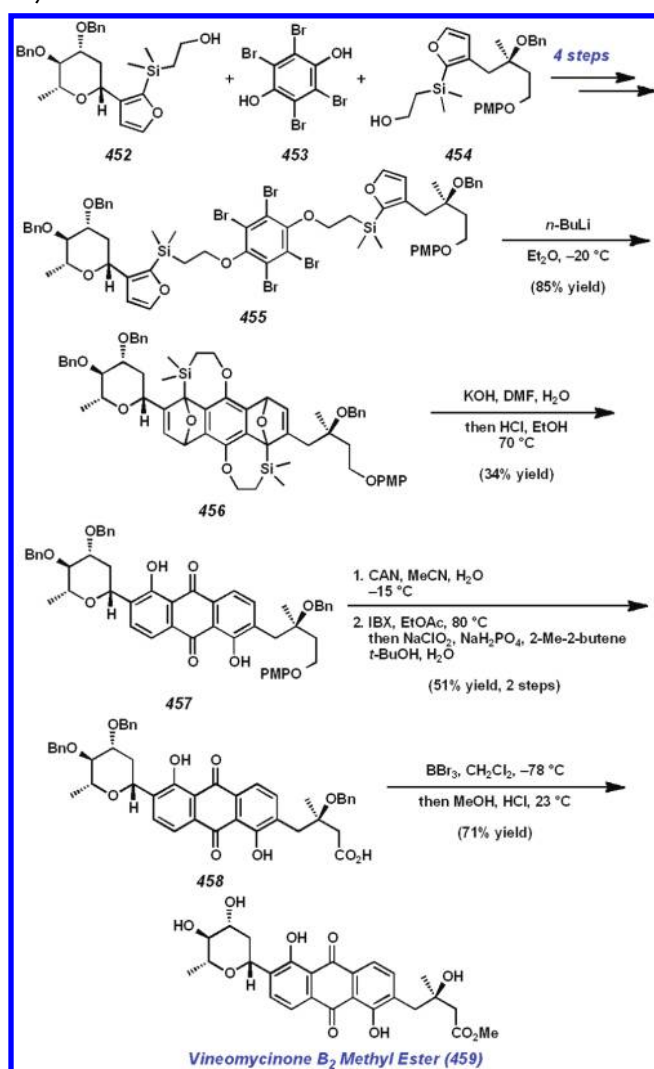


(as an inseparable mixture) was achieved in a similar manner through coupling of boronic acid 439 with iodotetrahydroisoquinolines

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 B₂ 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 B₂ Methyl Ester (459**) by Tandem Tethered Aryne Cycloadditions**

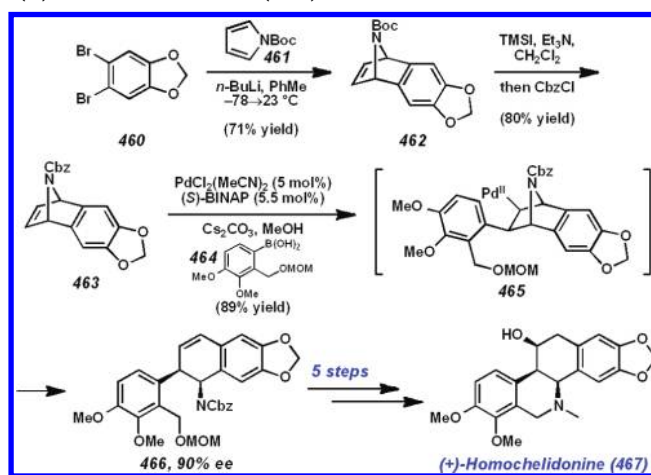


455 with *n*-BuLi triggered a cascade sequence consisting of two separate intramolecular aryne–furan [4 + 2]-cycloadditions to yield cycloadduct **456** as an inconsequential mixture of diastereomers in excellent yield. Cleavage of the silyl tethers and oxidation of the system was accomplished by treatment of bicyclic adduct **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 B₂ 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 Barrett⁹¹ in 2006 and Martin and co-workers⁹² 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 azabicyclic **462** en route to the alkaloid (+)-homochelidonine (**467**) (Scheme 74).⁹³ In this case, the

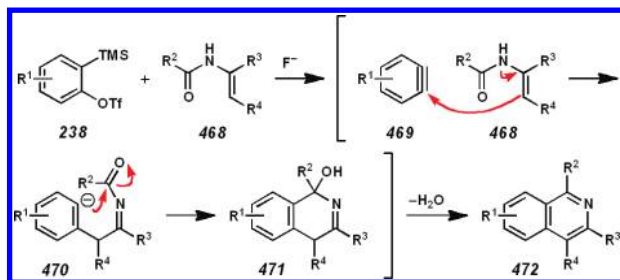
Scheme 74. Lautens' 2007 Synthesis of (+)-Homochelidonine (467**)**



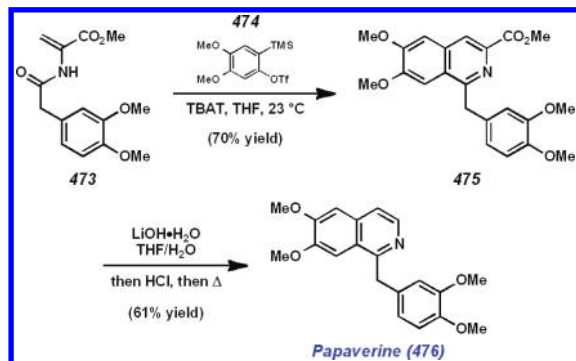
tetracyclic product (**462**) does not undergo immediate ring-opening. Instead, following exchange of the carbamate, treatment of azabicyclic **463** with a chiral palladium catalyst and arylboronic acid **464** resulted in an asymmetric migratory insertion of the *meso*-azabicyclic (**463**) into an 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 antispasmodic 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.

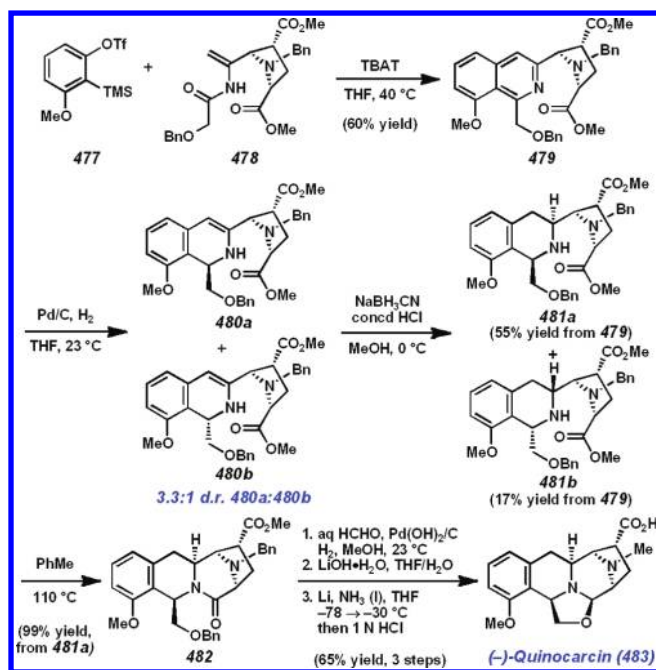
Scheme 75. Stoltz's Aryne Annulation with *N*-Acyl Enamines to Produce Isoquinolines

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

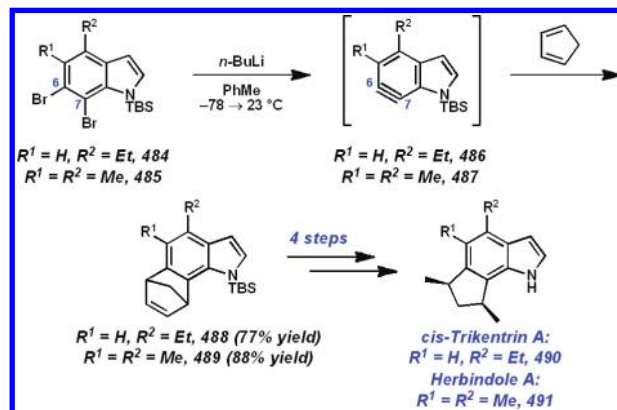
Scheme 77. Stoltz's 2008 Enantioselective Synthesis of (–)-Quinocarcin (483)



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 debenzoylation/reductive methylation, saponification, and reductive closure of the oxazolidine ring. Overall, this 11-step enantioselective synthesis of (–)-quinocarcin (483) is the shortest to date.

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-indolynes. 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

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

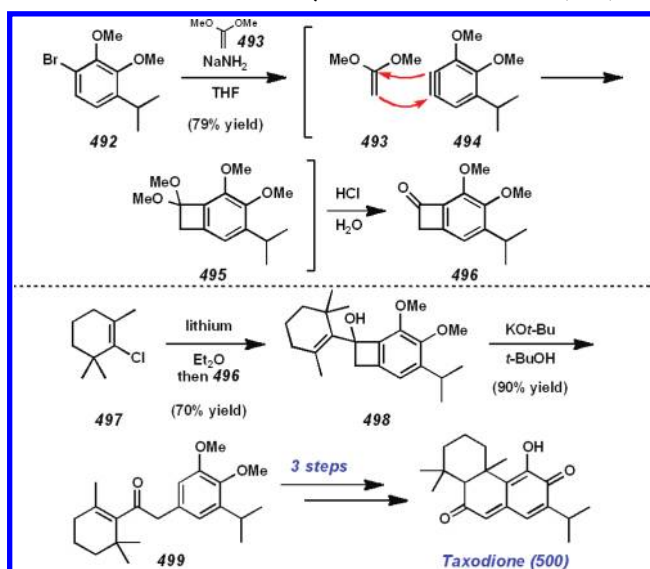
intermediates were then advanced to *cis*-trikentrin A (490) and herbindole A (491), respectively, over four steps.

4.2. [2 + 2]-Aryne Cycloaddition Strategies

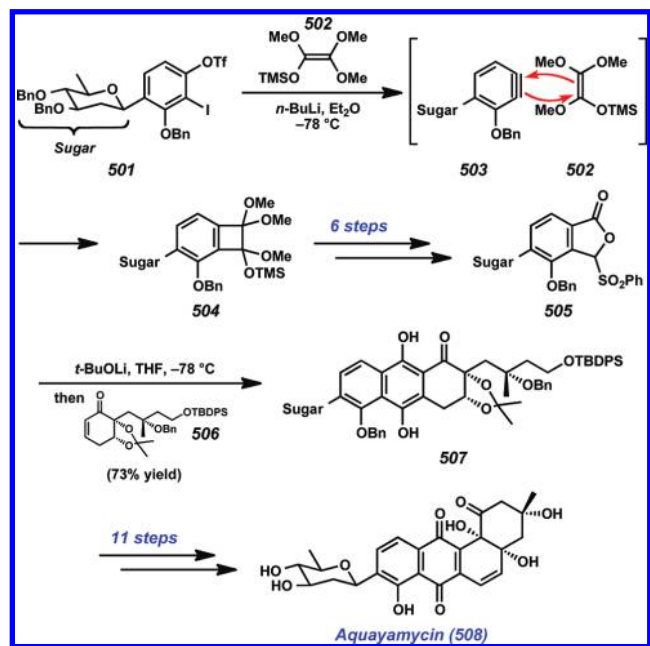
Aryne [2 + 2]-cycloadditions are some of the most poorly developed and underutilized methods, largely due to significant side-product formation. To date, there have been only two reported total syntheses employing an aryne [2 + 2]-cycloaddition. In 1982, Stevens and Bisacchi disclosed the synthesis of 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

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



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



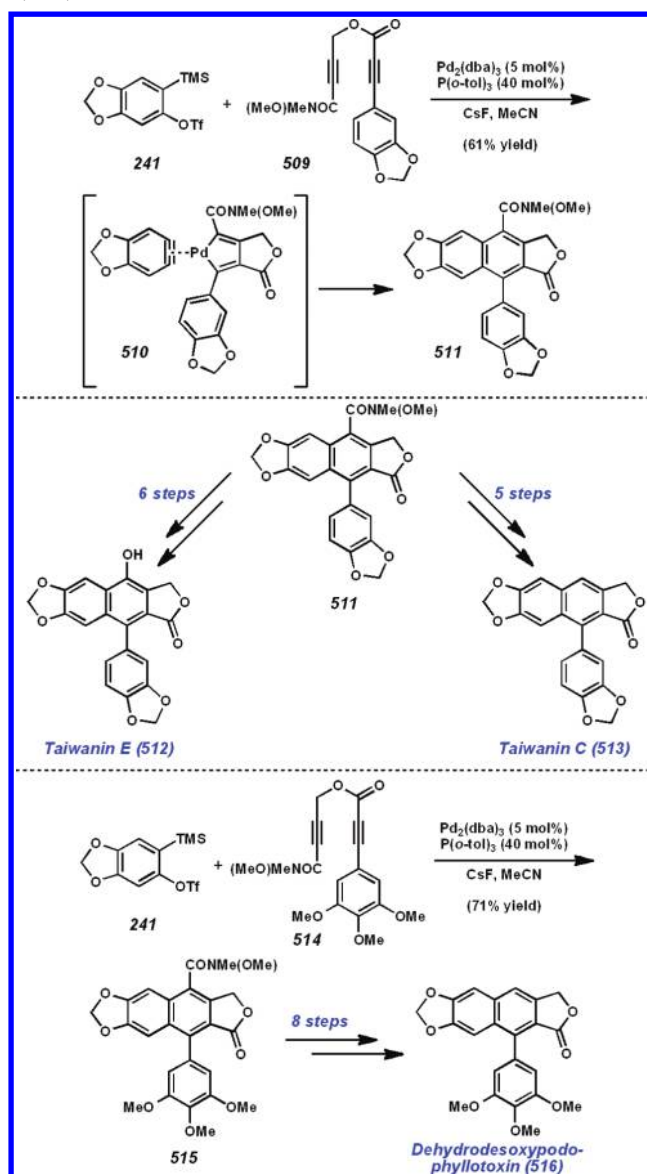
502 and the aryne generated in situ from iodo aryl triflate 501. Over a series of six steps, the cycloadduct (504) was converted to the desired phthalide (505), which was subsequently coupled to enone 506. From this point, completion of aquayamycin required an additional 11 transformations.

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 arynaphthalene lignans.¹⁰⁰ In this elegant approach, the naphthyl portions of taiwanins C (513) and E (512) and dehydrosesoxypodophyllotoxin (516) were targeted by a palladium-catalyzed [2 + 2 + 2]-cycloaddition of an aryne and diyne. Cycloaddition of sesamol-derived diyne 509

with the aryne generated in situ from silyl aryl triflate 241 resulted in formation of arynaphthalene 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 Dehydrosesoxypodophyllotoxin (516)



Alternatively, use of diyne 514 (derived from 3-(trimethoxyphenyl)propionic acid) in the palladium-catalyzed [2 + 2 + 2]-cycloaddition afforded trimethoxyarylnaphthalene 515, which was advanced to dehydrosesoxypodophyllotoxin (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

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 these 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.

AUTHOR INFORMATION

Corresponding Author

*E-mail: stoltz@caltech.edu.

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 University 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.

ACKNOWLEDGMENTS

The authors thank Abbott, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Merck, Sigma-Aldrich, Teva, and Caltech for financial support and Dr. Kevin Allan, Dr. Kun-Liang (Phil) Wu, and Mr. Christopher Haley for editorial assistance.

ABBREVIATIONS

AIBN	azobisisobutyronitrile
BINAP	(1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine)
Boc	<i>tert</i> -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	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
DPPA	diphenylphosphoryl azide
EDCI	<i>N</i> -(3-dimethylaminopropyl)- <i>N</i> -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	<i>N</i> -bromosuccinimide
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
PCC	pyridinium chlorochromate
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAT	tetra- <i>n</i> -butylammonium difluorotriphenylsilicate
TBS	<i>tert</i> -butyldimethylsilyl
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
tol	tolyl
TPAP	tetrapropylammonium perruthenate
Tr	triphenylmethane (trityl)

REFERENCES

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

- (2) For methods of benzyne generation, see: (a) Kitamura, T.; Yamane, M. *J. Chem. Soc., Chem. Commun.* **1995**, 983. (b) Campbell, C. D.; Rees, C. W. *J. Chem. Soc., C* **1969**, 742. (c) Matsumoto, T.; Hosoya, T.; Katsuki, M.; Suzuki, K. *Tetrahedron Lett.* **1991**, 32, 6735. (d) Friedman, L.; Logullo, F. M. *J. Am. Chem. Soc.* **1963**, 85, 1792. (e) Logullo, F. M.; Seitz, A. H.; Friedman, L. *Org. Synth.* **1968**, 48, 12. (f) Wittig, G.; Hoffmann, R. W. *Org. Synth.* **1967**, 47, 4. (g) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967. (h) Kitamura, T. *Aust. J. Chem.* **2010**, 63, 987. (i) Dyke, A. M.; Hester, A. J.; Lloyd-Jones, G. C. *Synthesis* **2006**, 4093.
- (3) Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.
- (4) For reviews on the general reactivity of arynes, see: (a) Wenk, H. H.; Winkler, M.; Sander, W. *Angew. Chem., Int. Ed.* **2003**, 42, 502. (b) Pellissier, H.; Santelli, M. *Tetrahedron* **2003**, 59, 701. (c) Kessar, S. V. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, pp 483–515. (d) Sanz, R. *Org. Prep. Proced. Int.* **2008**, 40, 215. (e) Yoshida, H.; Joji, O. *Yuki Gosei Kagaku Kyokaiishi* **2011**, 69, 877.
- (5) The lack of yields in some examples throughout this review is due to the omission of such information by the original authors.
- (6) For examples of the reactivity highlighted in Scheme 2, see: (a) Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, 5, 4673. (b) Allan, K. M.; Gilmore, C. D.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, 50, 4488. (c) Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, 127, 5340. (d) Wittig, G.; Pohmer, L. *Chem. Ber.* **1956**, 89, 1334. (e) Stevens, R. W.; Bisacchi, G. S. *J. Org. Chem.* **1982**, 47, 2393. (f) Peña, D.; Escudero, S.; Pérez, D.; Guitián, E.; Castedo, L. *Angew. Chem., Int. Ed.* **1998**, 37, 2659.
- (7) Kametani, T.; Ogasawara, K. *J. Chem. Soc., C* **1967**, 2208.
- (8) Kametani, T.; Shibuya, S.; Kigasawa, K.; Hiiragi, M.; Kusama, O. *J. Chem. Soc., C* **1971**, 2712.
- (9) It should be noted that Kano and co-workers later reported a synthesis of domesticine (10) employing an almost identical aryne cyclization. See: Kano, S.; Takahagi, Y.; Komiyama, E.; Yokomatsu, T.; Shibuya, S. *Heterocycles* **1976**, 4, 1013.
- (10) (a) Kametani, T.; Fukumoto, K.; Nakano, T. *J. Heterocycl. Chem.* **1972**, 9, 1363. (b) Kametani, T.; Shibuya, S.; Kano, S. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1212.
- (11) Kametani, T.; Ujiie, A.; Takahashi, K.; Nakano, T.; Suzuki, T.; Fukumoto, K. *Chem. Pharm. Bull.* **1973**, 21, 766.
- (12) Kessar, S. V.; Batra, S.; Nadir, U. K.; Gandhi, S. S. *Indian J. Chem.* **1975**, 13, 1109.
- (13) Rodríguez de Lera, A.; Aubourg, S.; Suau, R.; Castedo, L. *Heterocycles* **1987**, 26, 675.
- (14) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Kusama, O. *J. Heterocycl. Chem.* **1973**, 10, 31.
- (15) Kametani, T.; Sugai, T.; Shoji, Y.; Honda, T.; Satoh, F.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1151.
- (16) Kametani, T.; Kato, Y.; Honda, T.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, 98, 8185.
- (17) (a) Nemoto, H.; Nagai, M.; Moizumi, M.; Kohzaki, K.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1639. (b) Nemoto, H.; Nagai, M.; Moizumi, M.; Kohzaki, K.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1988**, 29, 4959. (c) Nemoto, H.; Nagai, M.; Abe, Y.; Moizumi, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1727. (d) Nemoto, H.; Nagai, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1621. (e) Nemoto, H.; Nagai, M.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1985**, 26, 4613. (f) Nemoto, H.; Nagai, M.; Abe, Y.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1985**, 1316. (g) Nemoto, H.; Nagai, M.; Fukumoto, K.; Kametani, T. *Tetrahedron* **1985**, 41, 2361. (h) Nemoto, H.; Nagai, M.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1985**, 50, 2764. (i) Kametani, T.; Suzuki, K.; Nemoto, H. *J. Org. Chem.* **1982**, 47, 2331. (j) Kametani, T. *Stud. Org. Chem.* **1981**, 6, 113. (k) Kametani, T.; Matsumoto, H.; Honda, T.; Nagai, M.; Fukumoto, K. *Tetrahedron* **1981**, 37, 2555. (l) Kametani, T.; Nemoto, H. *Tetrahedron* **1981**, 37, 3. (m) Kametani, T.; Suzuki, K.; Nemoto, H. *J. Am. Chem. Soc.* **1981**, 103, 2890. (n) Kametani, T.; Nemoto, H. *Tetrahedron Lett.* **1979**, 35, 3309. (o) Kametani, T.; Suzuki, K.; Nemoto, H. *J. Chem. Soc., Chem. Commun.* **1979**, 1127. (p) Kametani, T. *Pure Appl. Chem.* **1979**, 51, 747. (q) Kametani, T.; Nemoto, H.; Ishikawa, H.; Shiroyama, K.; Matsumoto, H.; Fukumoto, K. *J. Am. Chem. Soc.* **1977**, 99, 3461.
- (18) Kametani, T.; Matsumoto, H.; Nemoto, H.; Fukumoto, K. *J. Am. Chem. Soc.* **1978**, 100, 6218.
- (19) (a) Semmelhack, M. F.; Chong, B. P.; Jones, L. D. *J. Am. Chem. Soc.* **1972**, 94, 8629. (b) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, 97, 2507.
- (20) Kessar, S. V.; Singh, M.; Balakrishnan, P. *Indian J. Chem.* **1974**, 12, 323.
- (21) Kessar, S. V.; Gupta, Y. P.; Mohammad, T.; Khurana, A.; Sawal, K. K. *Heterocycles* **1984**, 22, 2723.
- (22) Kessar, S. V.; Gupta, Y. P.; Balakrishnan, P.; Sawal, K. K.; Mohammad, T.; Dutt, M. *J. Org. Chem.* **1988**, 53, 1708.
- (23) Gillespie, J. P.; Amoros, L. G.; Stermitz, F. R. *J. Org. Chem.* **1974**, 39, 3239.
- (24) Boente, J. M.; Castedo, L.; Rodríguez de Lera, A.; Saá, J. M.; Suau, R.; Vidal, M. C. *Tetrahedron Lett.* **1983**, 24, 2295.
- (25) Iwao, M.; Motoi, O.; Fukuda, T.; Ishibashi, F. *Tetrahedron* **1998**, 54, 8999.
- (26) Couture, A.; Deniau, E.; Grandclaude, P.; Lebrun, S. *Synlett* **1997**, 1475.
- (27) Couture, A.; Deniau, E.; Glandclaude, P.; Hoarau, C. *J. Org. Chem.* **1998**, 63, 3128.
- (28) Hoarau, C.; Couture, A.; Cornet, H.; Deniau, E.; Grandclaude, P. *J. Org. Chem.* **2001**, 66, 8064.
- (29) Moreau, A.; Couture, A.; Deniau, E.; Grandclaude, P.; Lebrun, S. *Tetrahedron* **2004**, 60, 6169.
- (30) Fairhurst, R. A.; Janus, D.; Lawrence, A. *Org. Lett.* **2005**, 7, 4697.
- (31) Sanz, R.; Fernández, Y.; Castroviejo, M. P.; Pérez, A.; Fañanás, F. *J. Eur. J. Org. Chem.* **2007**, 62.
- (32) (a) Barluenga, J.; Fañanás, F. J.; Sanz, R.; Fernández, Y. *Tetrahedron Lett.* **1999**, 40, 1049. (b) Barluenga, J.; Fañanás, F. J.; Sanz, R.; Fernández, Y. *Chem.—Eur. J.* **2002**, 8, 2034. (c) Sanz, R.; Fernández, Y.; Castroviejo, M. P.; Pérez, A.; Fañanás, F. *J. Org. Chem.* **2006**, 71, 6291.
- (33) Bronner, S. M.; Goetz, A. E.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, 133, 3832.
- (34) For additional studies on the reactivity of indolynes by Garg and co-workers, see: (a) Im, G.-Y. J.; Bronner, S. M.; Goetz, A.; Paton, R. S.; Cheong, P. H.-Y.; Houk, K. N.; Garg, N. K. *J. Am. Chem. Soc.* **2010**, 132, 17933. (b) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y. J.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, 132, 1267. (c) Bronner, S. M.; Bahnck, K. B.; Garg, N. K. *Org. Lett.* **2009**, 11, 1007.
- (35) (a) Tian, X.; Hutters, A. D.; Douglas, C. J.; Garg, N. K. *Org. Lett.* **2009**, 11, 2349. (b) Hutters, A. D.; Quasdorf, K. W.; Styduhar, E. D.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, 133, 15797. (c) Quasdorf, K. W.; Hutters, A. D.; Lodewyk, M. W.; Tantillo, D. J.; Garg, N. K. *J. Am. Chem. Soc.* **2012**, 134, 1396.
- (36) Day, J. J.; McFadden, R. M.; Virgil, S. C.; Kolding, H.; Alleva, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2011**, 50, 6814.
- (37) For early examples of multicomponent aryne reactions, see: (a) Wittig, G.; Pieper, G.; Fuhrmann, G. *Ber. Dtsch. Chem. Ges.* **1940**, 73, 1193. (b) Wittig, G.; Fuhrmann, G. *Ber. Dtsch. Chem. Ges.* **1940**, 73, 1197. (c) Wittig, G. *Naturwissenschaften* **1942**, 30, 696. (d) Meyers, A. I.; Pansegrau, P. D. *Tetrahedron Lett.* **1983**, 24, 4935. (e) Meyers, A. I.; Pansegrau, P. D. *J. Chem. Soc., Chem. Commun.* **1985**, 690.
- (38) For select examples of multicomponent aryne methodologies to generate 1,2-disubstituted arenes, see: (a) Pawlas, J.; Begtrup, M. *Org. Lett.* **2002**, 4, 2687. (b) Yoshida, H.; Watanabe, M.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2004**, 6, 4049. (c) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *J. Am. Chem. Soc.* **2006**, 128, 11040. (d) Huang, X.; Xue, J. *J. Org. Chem.* **2007**, 72, 3965. (e) Xie, C.; Zhang, Y. *Org. Lett.* **2007**, 9, 781. (f) Yoshida, H.; Morishita, T.; Fukushima, H.; Ohshita, J.; Kunai, A. *Org. Lett.* **2007**, 9, 3367. (g) Morishita, T.; Fukushima, H.; Yoshida, H.; Ohshita, J.; Kunai, A.

- J. Org. Chem.* **2008**, *73*, 5452. (h) Xie, C.; Zhang, Y.; Xu, P. *Synlett* **2008**, 3115. (i) Yoshida, H.; Morishita, T.; Ohshita, J. *Org. Lett.* **2008**, *10*, 3845. (j) Huang, X.; Zhang, T. *Tetrahedron Lett.* **2009**, *50*, 208. (k) Sha, F.; Guang, X. *Angew. Chem., Int. Ed.* **2009**, *48*, 3458. (k) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3935. (l) Yoshida, H.; Fukushima, H.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2004**, *45*, 8659. (m) Jeganmohan, M.; Cheng, C.-H. *Chem. Commun.* **2006**, 2454.
- (39) Larrosa, I.; Da Silva, M. I.; Gómez, P. M.; Hannen, P.; Ko, E.; Lenger, S. R.; Linke, S. R.; White, A. J. P.; Wilton, D.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2006**, *128*, 14042.
- (40) Soorukram, D.; Qu, T.; Barrett, A. G. M. *Org. Lett.* **2008**, *10*, 3833.
- (41) (a) Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5925. (b) Tokuyama, H.; Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T. *Chem. Asian J.* **2011**, *6*, 560.
- (42) Ebner, D. C.; Tambar, U. K.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 161.
- (43) Soon after Stoltz's initial publication, Yoshida, Kunai, and co-workers reported similar reactivity: Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2005**, 3292.
- (44) For additional examples of carbon–carbon bond insertions by arynes, see: (a) Yoshida, H.; Watanabe, M.; Ohshita, J.; Kunai, A. *Tetrahedron Lett.* **2005**, *46*, 6729. (b) Peña, D.; Pérez, D.; Guitián, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579. (c) Yoshida, H.; Watanabe, M.; Morishita, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 1505. (d) Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 5691. (e) Zhang, T.; Huang, X.; Xue, J.; Sun, S. *Tetrahedron Lett.* **2009**, *50*, 1290. (f) Yoshida, H.; Ohshita, J.; Kunai, A. *Bull. Chem. Soc. Jpn.* **2010**, *83*, 199. (g) Yoshida, H.; Ito, Y.; Yoshikawa, Y.; Ohshita, J.; Takaki, K. *Chem. Commun.* **2011**, 47, 8664.
- (45) Guyot, M.; Molho, D. *Tetrahedron Lett.* **1973**, *14*, 3433.
- (46) Danheiser, R. L.; Helgason, A. L. *J. Am. Chem. Soc.* **1994**, *116*, 9471.
- (47) (a) Shair, M. D.; Yoon, T.-Y.; Danishefsky, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1721. (b) Shair, M. D.; Yoon, T.-Y.; Mosny, K. K.; Chou, T. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509.
- (48) (a) Lee, M. D.; Dunne, T. S.; Siegel, M. M.; Chang, C. C.; Morton, G. O.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3464. (b) Lee, M. D.; Dunne, T. S.; Chang, C. C.; Ellestad, G. A.; Siegel, M. M.; Morton, G. O.; McGahren, W. J.; Borders, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 3466. (c) Zein, N.; Sinha, A.; McGahren, W. J.; Ellestad, G. A. *Science* **1988**, *240*, 1198. (d) Casza, A. M.; Kelley, S. L. Biological Properties of Esperamicin and Other Endiayne Antibiotics. In *Endiayne Antibiotics as Antitumor Agents*; Doyle, T. W., Borders, D. B., Eds., Marcel–Dekker: New York, 1994; pp 283–299.
- (49) (a) Golik, J.; Clardy, J.; Dubay, G.; Groenwold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkum, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3461. (b) Golik, J.; Dubay, G.; Groenwold, G.; Kawaguchi, H.; Konishi, M.; Krishnan, B.; Ohkum, H.; Saitoh, K.; Doyle, T. W. *J. Am. Chem. Soc.* **1987**, *109*, 3462.
- (50) (a) Konishi, M.; Ohkuma, H.; Matsumoto, K.; Tsuno, T.; Kamei, H.; Miyaki, T.; Oki, T.; Kawaguchi, H.; VanDuyne, G. D.; Clardy, J. *J. Antibiot.* **1989**, *42*, 1449. (b) Konishi, M.; Ohkuma, H.; Tsuno, T.; Oki, T.; VanDuyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3715.
- (51) (a) Kita, Y.; Higuchi, K.; Yoshida, Y.; Iio, K.; Kitagaki, S.; Akai, S.; Fujioka, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 683. (b) Kita, Y.; Higuchi, K.; Yoshida, Y.; Iio, K.; Kitagaki, S.; Ueda, K.; Akai, S.; Fujioka, H. *J. Am. Chem. Soc.* **2001**, *123*, 3214.
- (52) Akai, S.; Kakiguchi, K.; Nakamura, Y.; Kuriwaki, I.; Dohi, T.; Harada, S.; Kubo, O.; Morita, N.; Kita, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 7458.
- (53) Tambar, U. K.; Ebner, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 11752.
- (54) (a) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2001**, *123*, 7725. (b) Ebner, D. C.; Bagdanoff, J. T.; Ferreira, E. M.; McFadden, R. M.; Caspi, D. D.; Trend, R. M.; Stoltz, B. M. *Chem.—Eur. J.* **2009**, *15*, 12978. (c) Krishnan, S.; Bagdanoff, J. T.; Ebner, D. C.; Ramtohl, Y. K.; Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 13745.
- (55) Tadross, P. M.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1612.
- (56) Tadross, P. M.; Gilmore, C. D.; Bugga, P. B.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1224.
- (57) Allan, K. M.; Hong, B. D.; Stoltz, B. M. *Org. Biomol. Chem.* **2009**, *7*, 4960.
- (58) Yoshida, H.; Morishita, T.; Ohshita, J. *Chem. Lett.* **2010**, 39, 508.
- (59) Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885.
- (60) Khanapure, S. P.; Biehl, E. R. *J. Nat. Prod.* **1989**, *52*, 1357.
- (61) Zhao, H.; Biehl, E. R. *J. Nat. Prod.* **1995**, *58*, 1970.
- (62) Khanapure, S. P.; Biehl, E. R. *Synthesis* **1991**, 33.
- (63) (a) Kaiser, F.; Schwink, L.; Velder, J.; Schmalz, H.-G. *J. Org. Chem.* **2002**, *67*, 9248. (b) Kaiser, F.; Schwink, L.; Velder, J.; Schmalz, H.-G. *Tetrahedron* **2003**, *59*, 3201.
- (64) Best, W. M.; Wege, D. *Tetrahedron Lett.* **1981**, *22*, 4877.
- (65) Best, W. M.; Wege, D. *Aust. J. Chem.* **1986**, *39*, 647.
- (66) It should be noted that anthranilic acid-derived arynes precursors are extremely dangerous and prone to spontaneous explosion when dried. Their use is not recommended by the authors.
- (67) (a) Castedo, L.; Guitián, E.; Saá, J. M.; Suau, R. *Tetrahedron Lett.* **1982**, *23*, 457. (b) Castedo, L.; Guitián, E.; Saá, C.; Suau, R.; Saá, J. M. *Tetrahedron Lett.* **1983**, *24*, 2107.
- (68) (a) Atanes, N.; Castedo, L.; Guitián, E.; Saá, C.; Saá, J. M.; Suau, R. *J. Org. Chem.* **1991**, *56*, 2984. (b) Saá, C.; Guitián, E.; Castedo, L.; Saá, J. M. *Tetrahedron Lett.* **1985**, *26*, 4559.
- (69) Saá, C.; Guitián, E.; Castedo, L.; Suau, R.; Saá, J. H. *J. Org. Chem.* **1986**, *51*, 2781.
- (70) (a) Cobas, A.; Guitián, E.; Castedo, L.; Saá, J. M. *Tetrahedron Lett.* **1988**, *29*, 2491. (b) Cobas, A.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1992**, *57*, 6765.
- (71) While this work was never formally published with full experimental details, it was highlighted by the authors in a review as unpublished results. See: Castedo, L.; Guitián, E. In *Studies in Natural Products Chemistry*; Atta-ur, R., Ed.; Elsevier: Amsterdam, 1989; Vol. 3 (Stereoselective Synthesis Part B), pp 417–454.
- (72) (a) Estévez, J. C.; Estévez, R. J.; Guitián, E.; Villaverde, M. C.; Castedo, L. *Tetrahedron Lett.* **1989**, *30*, 5785. (b) Estévez, J. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1995**, *51*, 10801.
- (73) Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Seijas, J. A.; Castedo, L. *Can. J. Chem.* **1990**, *68*, 964.
- (74) (a) González, C.; Guitián, E.; Castedo, L. *Tetrahedron Lett.* **1996**, *37*, 405. (b) González, C.; Pérez, D.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1995**, *60*, 6318. (c) Meirás, D. P.; Guitián, E.; Castedo, L. *Tetrahedron Lett.* **1990**, *31*, 2331.
- (75) Gómez, B.; Guitián, E.; Castedo, L. *Synlett* **1992**, 903.
- (76) (a) Pérez, D.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1992**, *57*, 5911. (b) Martín, G.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1992**, *57*, 5907.
- (77) Estévez, J. C.; Estévez, R. J.; Castedo, L. *Tetrahedron Lett.* **1992**, *33*, 6883.
- (78) Watanabe, M.; Kurosaki, A.; Furukawa, S. *Chem. Pharm. Bull.* **1984**, *32*, 1264.
- (79) May, C.; Moody, C. J. *Chem. Soc., Chem. Commun.* **1984**, 926.
- (80) Gribble, G. W.; Saulnier, M. G.; Sibi, M. P.; Obaza-Nutiatis, J. A. *J. Org. Chem.* **1984**, *49*, 4518.
- (81) Mal, D.; Senapati, B. K.; Pahari, P. *Synlett* **2005**, 994.
- (82) Sha, C.-K.; Yang, J.-F. *Tetrahedron* **1992**, *48*, 10645.
- (83) Rigby, J. H.; Holsworth, D. D. *Tetrahedron Lett.* **1991**, *32*, 5757.
- (84) Watanabe, M.; Hisamatsu, S.; Hotokezaka, H.; Furukawa, S. *Chem. Pharm. Bull.* **1986**, *34*, 2810.
- (85) (a) Matsumoto, T.; Hosoya, T.; Suzuki, K. *J. Am. Chem. Soc.* **1992**, *114*, 3568. (b) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004.
- (86) (a) Hirayama, N.; Takahashi, K.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1338. (b) Balitz, D. M.; O'Herron, F. A.; Bush, J.; Vyas, D. M.; Nettleton, D. E.; Grulich, R. E.;

- Bradner, W. T.; Doyle, T. W.; Arnold, E.; Clardy, J. J. *Antibiot.* **1981**, *34*, 1544. (c) Jain, T. C.; Simolike, G. C.; Jackman, L. M. *Tetrahedron* **1983**, *39*, 599.
- (87) (a) Matsumoto, T.; Sohma, T.; Yamaguchi, H.; Kurata, S.; Suzuki, K. *Synlett* **1995**, 263. (b) Matsumoto, T.; Sohma, T.; Yamaguchi, H.; Kurata, S.; Suzuki, K. *Tetrahedron* **1995**, *51*, 7347.
- (88) Hoye, T. R.; Chen, M.; Mi, L.; Priest, O. P. *Tetrahedron Lett.* **1994**, *35*, 8747.
- (89) (a) Hoye, T. R.; Mi, L. *Tetrahedron Lett.* **1996**, *37*, 3097. (b) Hoye, T. R.; Chen, M.; Hoang, B.; Mi, L.; Priest, O. P. *J. Org. Chem.* **1999**, *64*, 7184.
- (90) (a) Chen, C.-L.; Sparks, S. M.; Martin, S. F. *J. Am. Chem. Soc.* **2006**, *128*, 13696. (b) Sparks, S. M.; Chen, C.-L.; Martin, S. F. *Tetrahedron* **2007**, *63*, 8619.
- (91) Morton, G. E.; Barrett, A. G. M. *Org. Lett.* **2006**, *8*, 2859.
- (92) Procko, K. J.; Li, H.; Martin, S. F. *Org. Lett.* **2010**, *12*, 5632.
- (93) McManus, H. A.; Fleming, M. J.; Lautens, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 433.
- (94) Lautens, M.; Dockendorff, C. *Org. Lett.* **2003**, *5*, 3695.
- (95) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558.
- (96) Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 17270.
- (97) Buszek, K. R.; Brown, N.; Luo, D. *Org. Lett.* **2009**, *11*, 201.
- (98) Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* **1982**, *47*, 2396.
- (99) (a) Matsumoto, T.; Yamaguchi, H.; Hamura, T.; Tanabe, M.; Kuriyama, Y.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 8383. (b) Yamaguchi, H.; Konegawa, T.; Tanabe, M.; Nakamura, T.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 8389. (c) Matsumoto, T.; Yamaguchi, H.; Tanabe, M.; Yasui, Y.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 8393.
- (100) (a) Sato, Y.; Tamura, T.; Mori, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2436. (b) Sato, Y.; Tamura, T.; Kinbara, A.; Mori, M. *Adv. Synth. Catal.* **2007**, *349*, 647.