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Natural Product Synthesis

Arynes and Cyclohexyne in Natural Product Synthesis

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This Minireview highlights recent advances in the field of aryne and cyclohexyne chemistry that have allowed the extraordinary reactivity of these entities to be harnessed during the course of natural product syntheses. The syntheses presented rely on the use of these reactive species in chemoselective transformations and follow unprecedented synthetic strategies that are inspiring for the practitioners of synthetic organic chemistry.

1. Introduction

The simplest alkyne, C_2H_2, was first discovered by Davy in 1836 and rediscovered by Berthelot in 1857, who named it acetylene.[1] It is the stereotype of a class of functional groups that is characterized by its linear structure.[2] In 1933 Leopold Ruzicka wrote that "*up to now no carbon cycle that incorporates a triple bond is known*."[3] This statement would only hold true for another decade, when a number of cyclic alkynes were characterized. However, arynes and cyclohexynes have only been observed as highly reactive transient species. As a consequence of their fleeting lifetime and the harsh reaction conditions required for their generation, their applications in synthetic chemistry have been drastically limited. In the 1940s Wittig and Roberts first hypothesized that triple bonds could be formed in carbon cycles small enough to significantly bend the C–C triple bond.[4] It was noted that the smaller the ring size, the more reactive the incorporated triple bond. For example, cycloheptyne has a half-life of 1 h at −78 °C.[5] The much more reactive cyclohexyne could only be trapped in a matrix at −100 °C and characterized by IR spectroscopy.[6] The best-studied "cyclic alkyne" to date is benzyne, or 1,2-didehydrobenzene. Infrared, UV, photoelectron, mass, microwave, and NMR spectral data of benzyne trapped in matrixes and molecular cages are available.[7] The increased reactivity of strained cycloalkynes became manifest in the world of naturally occurring, bioactive compounds: the enediynes. These have been the subject of extensive in-depth studies, among others by the research groups of Myers,[8a,b] Danishefsky,[8c,d] Nicolaou,[8f] and Magnus.[8e,f]

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To date, a large number of quantum chemical calculations have shed light on the underlying reasons for the dramatically changed reactivity of cyclic alkynes and arynes compared to their stable, linear counterparts:[4,9] Bending of the C–C triple bond results in reduced overlap of the in-plane p orbitals and thus lower energy of the triple bond (Figure 1). For example, it has been calculated that the bond strength of the triple bond diminishes from 76 kcal mol^{-1} in acetylene to about 35 kcal mol^{-1} in cyclohexyne.[9h] Moreover, computations revealed that the geometric constrictions result in a significant reduction in the LUMO energy from 6.41 eV for 2-butyne to 1.33 eV for benzyne; interestingly the energy of the HOMO orbital remains essentially unchanged.[9a] Similar estimates have been made for cyclohexyne, and it follows that strained cycloalkynes and arynes typically react as electrophiles. However, theoretical studies revealed that arynes and angle-strained cycloalkynes can behave as diradicals or dicarbenes, and hence their representation as traditional Lewis structures is an oversimplification.

Arynes and cycloalkynes have intrigued chemists for more than seven decades, and a large body of literature has been accumulated from studies of these molecules. It is not our intention to review the entire field, and instead refer the reader to a number of excellent reviews.[4,10] However, in the recent past a number of novel reactions of arynes, indolynes, and cyclohexyne have been disclosed that are worth highlighting, as they offer new opportunities for synthesis. Additional significant improvements have been developed in the

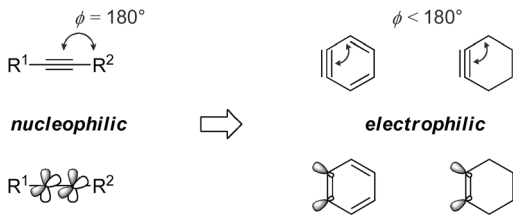


Figure 1. Bending of triple bonds results in reduced orbital overlap and increased reactivity.

methods for generating these reactive intermediates under conditions that are compatible with the more intricate structures typical of intermediates in multistep syntheses of complex natural products.[11] In this Minireview we highlight recent successful applications of benzynes, indolynes, and cyclohexyne in natural product syntheses, all of which are highly instructive for the practitioners of organic synthesis.

2. Arynes

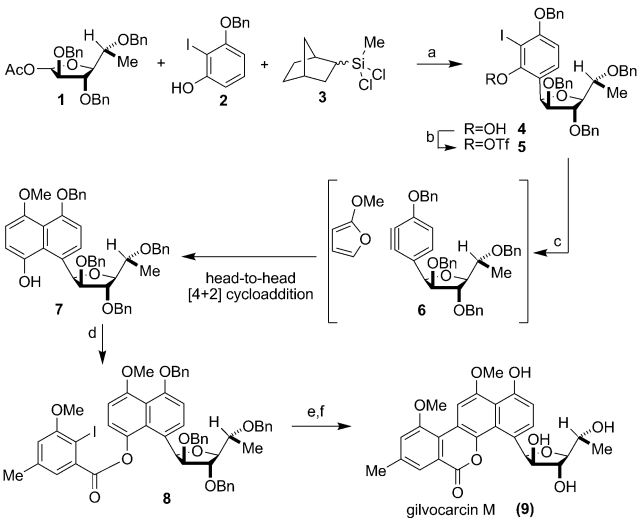
2.1. Background

The possible existence of 1,2-didehydrobenzene, or benzyne, as an intermediate in the reaction of fluorobenzene with phenyllithium was first considered by Wittig in 1942.[12] This initial report sparked tremendous activity in the field of aryne chemistry. The existence of 1,2-didehydrobenzene and the benzyne mechanism of aromatic substitution is now commonly accepted. Substituted benzynes have been prepared from various precursors and allowed to undergo cycloaddition reactions.[4,10] Despite the tremendous research efforts, the field of benzyne chemistry is still a work in progress, as evidenced by the intriguing natural product syntheses highlighted in this section.[13]

2.2. Benzynes in [4+2] and [3+2] Cycloadditions

2.2.1. Synthesis of Gilvocarcin M

The gilvocarcins are a family of tetracyclic C glycosides that have enjoyed much attention because of their broad biological activity.[14] Members of this family of natural products have been identified as bactericidal, virucidal, and cytotoxic, and also display antitumor activity. The first gilvocarcins were isolated from *Streptomycetes* in 1955, however, their structural assignment remained ambiguous for nearly four decades until the total synthesis of gilvocarcin M (**9**) and V finally clarified their true constitution and configuration (Scheme 1). The report by Suzuki and coworkers thus constitutes a landmark synthesis and the perfect starting point for a discussion of developments in aryne chemistry.[15] In addition to providing valuable structural information, this study is remarkable because of the application of a benzyne in the synthesis of a complex molecule. Whereas Diels–Alder reactions of benzyne and substituted



Scheme 1. Reagents and conditions: a) $AgClO_4$, −10 °C, MS 4 Å, CH_2Cl_2, 86%, d.r. = 26:1; b) Tf_2O, iPr_2NEt, CH_2Cl_2, −78 °C, 1 h, 99%; c) *n*BuLi, 2-methoxyfuran, THF, −78 °C, 10 min, 88%; d) 2-iodo-3-methoxy-5-methylbenzoyl chloride, iPr_2NEt, DMAP, THF, RT, 2 h, 91%; e) $[(Ph_3P)PdCl_2]$ (26 mol%), NaOAc, DMA, 125 °C, 5 h, 90%; f) H_2, Pd/C (10 mol%), MeOH, THF, RT, 5 h, 90%. Bn = benzyl; MS = molecular sieves; Tf_2O = trifluoromethanesulfonic acid anhydride; DMAP = *N*,*N*-dimethylaminopyridine; DMA = *N*,*N*-dimethylacetamide.

benzynes had previously been studied, the research group of Suzuki first utilized the highly functionalized benzyne **6**, bearing a benzyloxy and a furanose substituent, in a [4+2] cycloaddition with a 2-methoxyfuran.[16] This synthetic strategy was chosen because the regioselective formation of the aryl C glycoside from a naphthalene proved difficult. It was reasoned that the challenging glycosylation could perhaps be performed with a phenol as a reacting partner, which in turn would be further elaborated into the targeted naphthalene. For the successful implementation of this key step, however, reaction conditions needed to be established that would generate benzyne **6** efficiently. It is worth noting that successful implementation of the benzyne strategy required that the aryne undergoes regioselective cycloaddition with 2-methoxyfuran.

Glycoside **4** was prepared by contrasteric C-glycoside formation involving initial O-glycosylation of phenol **2** followed by 1,2-rearrangement to give **4**. Experimentation revealed that norbornylsilane **3** along with $AgClO_4$ promoted the desired glycosylation/rearrangement sequence in high

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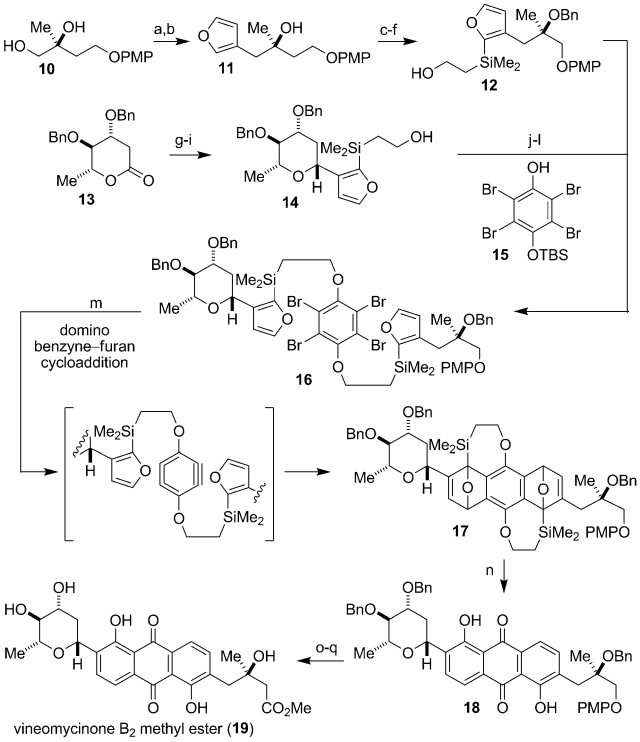
yield (86%) and an excellent α selectivity of 26:1. Conversion of phenol **4** into triflate **5** paved the way for the controlled formation of benzyne by lithiation/elimination. Halogen/lithium exchange with *n*BuLi at −78°C in the presence of 2-methoxyfuran was followed by elimination of lithium triflate to give **6**. Benzyne **6** and 2-methoxyfuran reacted preferentially in a head-to-head fashion to give naphthol **7** in 88% yield after aromatization of the intermediate cycloadduct. The excellent regioselectivity in this step can be understood by considering inductive effects of the proximal benzyloxy substituent on the benzyne. Attack of the sterically less encumbered 4-position of the furan is directed to the aryne β-carbon atom, thereby leading to a fleeting intermediate bearing partial negative charge at the benzyne α-carbon atom. Naphthol **7** was then acylated with a benzoic acid derivative to give **8**. Palladium-catalyzed formation of the biaryl axis followed by global deprotection provided the first total synthesis of glivocarcin M (**9**). A similar sequence gave access to glivocarcin V.

2.2.2. Synthesis of Vineomycinone B_2 Methyl Ester

Vineomycinone B_2 methyl ester (**19**, Scheme 2) is the aglycon of vineomycin B_2, which belongs to the vineomycin glycosidic antibiotics, isolated from *Streptomyces matensis vineus*. Besides their antibacterial properties, the vineomycins show cytotoxicity against sarcoma-180 solid tumor cells in mice.[17] This intriguing biological activity along with the structural complexity of the vineomycins evoked vibrant activity in the community of synthetic organic chemists, culminating in the disclosure of a number of total syntheses of vineomycin B_2 methyl ester.[18] One of the shortest syntheses (16 linear steps) was described by Martin and co-workers.[19] The concise synthesis of **19** was achieved by execution of an intramolecular, silane-tethered domino-benzyne-furan cycloaddition as the key step to connect the eastern and western parts of the molecule and create the central anthraquinone.

The synthesis commenced with the preparation of two furan derivatives **12** and **14** that acted as precursors for the substituents of the anthraquione core (Scheme 2). The known diol **10** was monotosylated and treated with 3-lithiofuran to give **11** in 76% yield. Benzyl protection was followed by bromination of the furan, which allowed installation of the C3-silyl group by lithiation and quenching with vinyldimethylchlorosilane. Hydroboration/oxidation provided furan **12** in 71% yield from **11**. C Glycoside **14** was readily available from known lactone **13**. The lactol arising from the nucleophilic addition of 3-lithiofuran to **13** was converted into its ethoxy acetal (HCl, EtOH), which was reduced stereoselectively with $NaCNBH_3$. The silane tether was then installed in a procedure similar to the one used previously.

Furans **12** and **14** were both coupled to phenol **15** under Mitsunobu conditions, setting the stage for the key domino benzyne cycloaddition (54% over 3 steps). The optimized conditions involve the slow addition of an excess of *n*BuLi to tetrabromide **16** in Et_2O at −20°C to obtain cycloadduct **17** in 85% yield. Removal of the silyl tethers was achieved with KOH in DMF/H_2O, and subsequent treatment with HCl induced regioselective hydrolysis of the oxy bridges to give

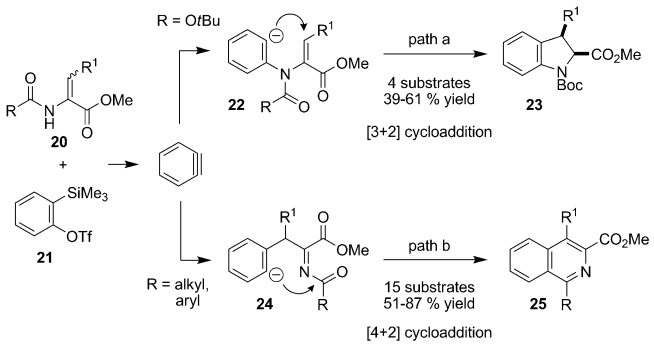


Scheme 2. Reagents and conditions: a) TsCl, NEt_3, DMAP, CH_2Cl_2; b) *n*BuLi, −78°C, 3-lithiofuran, BF_3OEt_2, THF, 76% (2 steps); c) KH, BnBr, DMF, 99%; d) NBS, DMF, 86%; e) *n*BuLi, THF, −78°C, $Me_2Si(Cl)CH{=}CH_2$, 87%; f) 9-BBN, THF, H_2O_2, NaOH, 96%; g) 3-lithiofuran, THF, −78°C; HCl, EtOH then $NaCNBH_3$, HCl, 50°C, 80%; h) LDA, THF, −78°C, $Me_2Si(Cl)CH{=}CH_2$, 70%; i) 9-BBN, THF, H_2O_2, NaOH, 94%; j) **12**, **15**, DIAD, PPh_3, THF, 75%; k) HF·py, THF, 85%; l) **14**, DIAD, PPh_3, THF, 85%; m) *n*BuLi (3.0 equiv), Et_2O, −20°C, 85%; n) KOH, DMF/H_2O; HCl, EtOH, 34%; o) CAN, MeCN, H_2O, −15°C, 74%; p) IBX, EtOAC, 80°C; $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, 70%; q) BBr_3, CH_2Cl_2, −78°C; MeOH, HCl, 71%. TsCl = tosyl chloride; NBS = *N*-bromosuccinimide; DMF = Me_2NCHO; 9-BBN = 9-borabicyclononane; THF = tetrahydrofuran; LDA = lithium diisopropylamide; DIAD = diisopropyl diazodicarboxylate; py = pyridine; CAN = $(NH_4)_2Ce(NO_3)_6$; IBX = 2-iodoxybenzoic acid; PMP = *p*-methoxyphenyl; TBS = *tert*-butyldimethylsilyl.

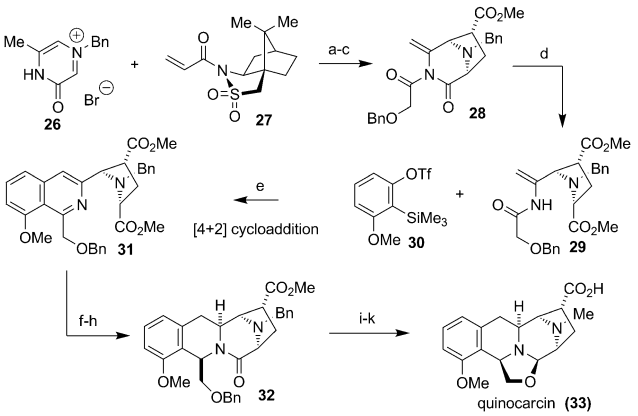
1,5-dihydroxyanthraquinone **18** in 34% yield after oxidation in air. Oxidative cleavage of the PMP ether was followed by oxidation of the resulting primary alcohol. Treatment of the resulting carboxylate with BBr_3, followed by HCl in MeOH, induced cleavage of the benzyl group and installed the methyl ester to give vineomycinone B2 methyl ester (**19**, 37% yield over 3 steps).

2.2.3. Access to Indolines and Isoquinolines and Synthesis of Quinocarcin

Stoltz and co-workers have recently disclosed a new type of formal [2+3] and [2+4] cycloadditions of benzynes with enamine derivatives.[20] It was found that *N*-Boc-dehydroalanine esters react with benzyne—generated from *o*-TMS-aryl triflates under Kobayashi conditions[21]—to give indolines (path a, Scheme 3). The reaction was envisioned to proceed via phenyl carbanion **22**, formed from attack of the depro-



Scheme 3. Reagents and conditions: **21** (2 equiv), TBAT (2 equiv), THF, RT, 6–8 h. TBAT = $Bu_4N^+F_2Ph_3Si^-$; THF = tetrahydrofuran; Boc = *tert*-butoxycarbonyl.



Scheme 4. Reagents and conditions: a) *N*-methylmorpholine, MeCN, −20 °C; b) NaOMe, MeOH, RT, 74% (over 2 steps); c) 2-(benzyloxy)-acetyl chloride, DMAP, NEt_3, CH_2Cl_2, RT to reflux, 93%; d) $Yb(OTf)_3$, MeOH, CH_2Cl_2, reflux, 69%; e) TBAT, THF, 40 °C, 60%; f) H_2, Pd/C, THF, RT; g) $NaBH_3CN$, conc. HCl, MeOH, 0 °C; h) toluene, 110 °C, 55% (over 3 steps); i) HCHO, H_2O, $Pd(OH)_2/C$, H_2, MeOH, 80%; j) LiOH, THF, H_2O, RT; k) Li, NH_3 (liq.), THF, −78 °C to −30 °C, then 1 M HCl, 81% (over 2 steps).

tonated carbamate at benzyne, followed by 5-*endo*-trig cyclization. This operationally simple (TBAT, THF, RT) procedure enables rapid access to 1,2- and 1,2,3-substituted indolines. However, the initial substrate scope reported was narrow (four substrates) and the yields were modest (39–61%). Furthermore, the cycloaddition lacked regioselectivity in the case of unsymmetrically substituted benzynes. A search for various other dehydroamino ester substrates led Stoltz and co-workers to discover yet another unprecedented reaction of benzynes. It was found that switching from *N*-carbamoylenamines to *N*-acylenamines resulted in the reaction pathway changing entirely, and led to the generation of isoquinolines (path b, Scheme 3). It was presumed that, this time, attack of the enamine carbon atom at benzyne initiated the reaction sequence to give intermediate **24**, which cyclized and underwent dehydration to give isoquinolines. The scope of this transformation proved to be broad, and exposure of a 2:1 mixture of triflate **21** and enamide **20** (R = alkyl, aryl) to TBAT (2 equiv) in THF at ambient temperature provided a host of differently substituted isoquinolines **25** in good yields (51–81%). Most notably, the aryne annulation described with 1-methoxy-2,3-didehydrobenzene proceeded with high regioselectivity. This feature of the reaction was harnessed in the masterfully executed 13-step asymmetric total synthesis of quinocarcin (**33**, Scheme 4)—the shortest synthesis of this alkaloid to date.[22]

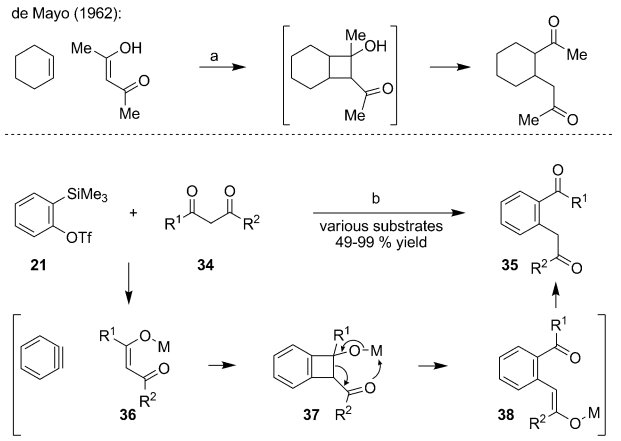
The synthesis commenced with the stereoselective preparation of **28** by a [1,3] dipolar cycloaddition of oxidopyrazinium salt **26** and the acrylamide of Oppolzer's sultam (**27**, Scheme 4). Removal of the auxiliary was followed by acylation of the amide, and the remarkably selective methanolysis of imide **28** using Yb^{III} triflate set the stage for aryne annulation. Whereas the *N*-methyl analogue of **29** provided the desired product in low yields (not shown), exposure of the sterically more encumbered *N*-benzylamine **29** to the conditions previously described resulted in the formation of isoquinoline **31** in 80% yield. The regioselectivity and efficiency of this benzyne annulation with the elaborate substrate **29** are noteworthy. Substrate-directed reduction of the isoquinoline core in a two-step sequence (H_2/Pd and $NaBH_3CN$) was followed by cyclization to give **32** in 55% yield from **31**. After simultaneous removal of the benzyl protecting groups and reductive amination, the methyl ester was subjected to saponification, and the lactam was reduced under dissolving metal conditions to provide (−)-quinocarcin (**33**, 65% yield from **32**). This concise (13 steps) and high-yielding (10% overall) synthesis of quinocarcin convincingly illustrates the power of transformations involving benzyne, and its derivatives, to rapidly build up molecular complexity at an advanced stage of a target-oriented synthesis.

2.3. Ring Insertion Reactions with Arynes

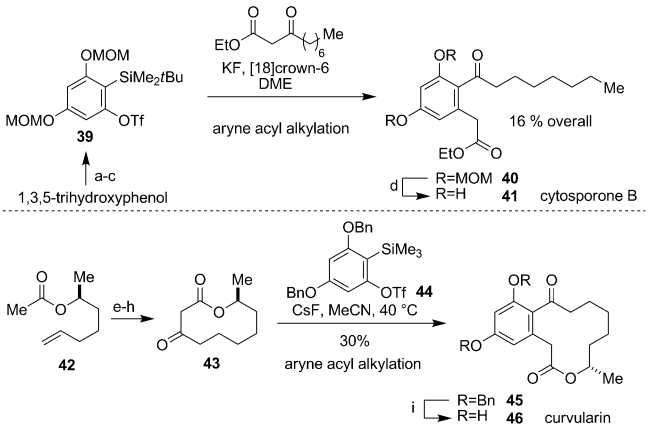
2.3.1. Acyl Alkylation in the Syntheses of Cytosporone B and (−)-Curvularin

In 2005, the research groups of Yoshida/Kunai and Stoltz independently reported that arynes participate in a C–C bond-insertion reaction,[23,24] reminiscent of the de Mayo reaction of cycloalkenes. The de Mayo reaction proceeds by the photoinduced [2+2] cycloaddition of cyclohexene to the enol form of acetylacetone, followed by a retroaldol addition to give 1,5-diketones (Scheme 5).[25] In analogy, the newly described insertion of arynes into the C–C σ bond of 1,3-dicarbonyl compounds (e.g. diketones, β-ketoesters, and malonates) is believed to be initiated by [2+2] cycloaddition of benzyne to enolate **36** and consecutive ring fragmentation to give the corresponding acyl-alkylated products **35**.

The substrate scope of this intriguing cascade reaction has been thoroughly explored by both the Yoshida/Kunai and the Stoltz groups. Notably, this insertion reaction proceeds with excellent regioselectivity if *ortho*-substituted benzynes are employed, as showcased by Yoshida et al. in the synthesis of bioactive octaketide cytosporone B (**41**, Scheme 6).[26] *tert*-Butyldimethylarylsilane **39** as the aryne precursor proved more stable toward fluoride compared to its trimethylsilyl analogue, thus allowing the use of TBDMS-phenol protecting groups in the synthesis of **39**. Aryne insertion into the appropriate β-keto ester occurred regioselectively in the



Scheme 5. Reagents and conditions: a) *hν*, 80 W, 45 h, 78%; b) KF, [18]crown-6, THF, RT or CsF, MeCN, 80°C.



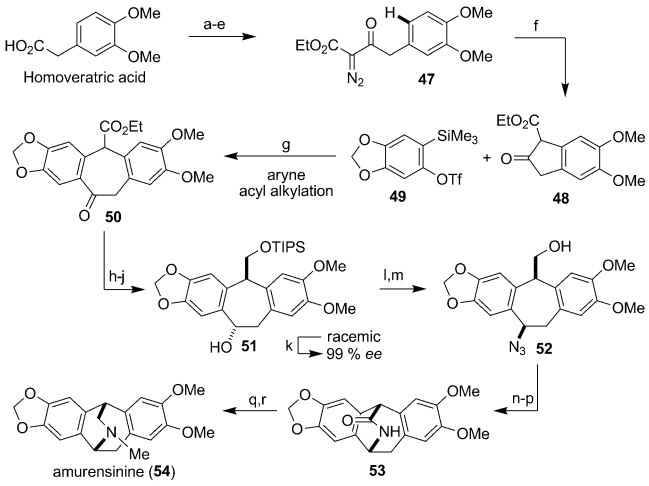
Scheme 6. Reagents and conditions: a) TBDMSOTf, NEt_3, CH_2Cl_2; b) NBS, CH_2Cl_2; c) *n*BuLi then Tf_2O, Et_2O, 74% (over 3 steps); d) TMSBr, CH_2Cl_2, 26% (over 2 steps), 16% overall; e) LDA, acrolein, THF, −78°C, 76%; f) HMDS, 3rd generation Grubbs–Hoveyda cat. (10%), PhH, 57%; g) H_2, Pd/C, EtOH; h) Dess–Martin periodinane, CH_2Cl_2, 92% (2 steps); i) H_2, Pd/C, MeOH, THF, 60%. TBDMSOTf = *tert*-butyldimethylsilyl triflate; NBS = *N*-bromosuccinimide; TMS = $SiMe_3$; HMDS = hexamethyldisilazane; MOM = methoxymethyl; DME = 1,2-dimethoxyethane.

presence of KF and [18]crown-6 to give, after final deprotection, cytosporone B (**41**) in 6 steps and 16% overall yield from trihydroxyphenol.

The Stoltz research group likewise demonstrated the synthetic utility of the acyl-alkylation reaction in a short synthesis of (−)-curvularin (Scheme 6).[27] β-Keto ester **43**, the substrate for benzyne insertion, was accessible from the known acetate **42** in four steps: Alkylation of the acetate in **42** with acrolein set the stage for a ring-closing metathesis mediated by the third generation Grubbs–Hoveyda catalyst. Hydrogenation of the resulting double bond and oxidation of the secondary alcohol provided **43** in 40% yield from **42**. Acyl alkylation using aryl triflate **44** followed by benzyl deprotection provided the polyketide natural product curvularin (**46**).

2.3.2. Synthesis of Amurensinine

With the acyl-alkylation method worked out, Stoltz and co-workers embarked on the synthesis of scalemic amurensinine (**54**, Scheme 7) by using the aryne insertion reaction to convergently construct the carbon scaffold of this pharmacologically relevant alkaloid.[28] The synthesis commenced with the five-step preparation of diazoester **47** from homoveratric acid. Subjecting this diazo compound to $[Rh_2(OAc)_4]$ in dichloroethane generated the transient rhodium carbene. Notably, the subtle interplay of steric and electronic factors in this intermediate dictated formal C–H insertion to regioselectively occur on the arene to give cyclopentanone **48** as the only product observed. Access to β-keto ester **48** set the stage for merging of the two halves of the molecule by acyl alkylation of the aryne generated from silane **49**. Conditions previously devised (CsF, MeCN, 80°C) provided the carbocyclic core of amurensinine **50** in 57% yield.



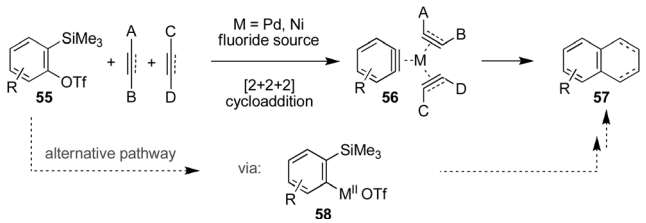
Scheme 7. Reagents and conditions: a) $SOCl_2$, DMF, PhH; b) Meldrum's acid, pyridine, CH_2Cl_2, 0°C to RT; c) HCl (aq); d) EtOH, 75°C, 96% (over 4 steps); e) *p*-ABSA, NEt_3, MeCN, 0°C to RT, 99%; f) $[Rh_2(OAc)_4]$, dichloroethane, 96%; g) CsF, MeCN, 80°C, 57%; h) L-Selectride, THF, −78°C, 97%; i) $LiAlH_4$, THF, 0°C; j) TIPSCl, imidazole, DMF, 86% (over 2 steps); k) [Pd(spartein)Cl_2] (20 mol%), (−)-sparteine (20 mol%), Cs_2CO_3, O_2, 2-methyl-2-butene (20 mol%), $CHCl_3$, 23°C, 82 h; 47%, >99% *ee*; l) $(PhO)_2P(O)N_3$, DBU, PhMe, 0°C; m) TBAF, THF, 62% (over 2 steps); n) Dess–Martin periodinane, CH_2Cl_2, 0°C to RT; o) $NaClO_2$, 2-methyl-2-butene; p) H_2, Pd/C, EtOAc, 49% (over 3 steps); q) $LiAlH_4$, THF, reflux; r) CH_2O, H_2O, $NaBH_3CN$, MeCN, 52% (over 2 steps). *p*-ABSA = *p*-acetamidobenzenesulfonyl azide; TIPS = triisopropylsilyl; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Following this key reaction, reduction of the ketone in **50** with L-selectride installed the secondary alcohol at C12 in the desired *anti* configuration with respect to the carboxy group. At this point the researchers needed to reduce the ester group to prevent dehydration as a side reaction, which otherwise would lead to erosion of the enantiomeric excess later in the synthesis (not shown). Reduction of the ester with $LiAlH_4$ was followed by silyl protection of the primary hydroxy group to give alcohol **51**. Substrate **51** could be enantioenriched to

99% *ee* in 47% yield (50% is the maximum yield, *s* factor >47) by employing Stoltz' oxidative kinetic resolution ([Pd{(−)-spartein}Cl_2]/O_2).[29] Interestingly, the authors note that addition of 2-methyl-2-butene to the reaction mixture proved beneficial, obviating oxidative radical side reactions. The precise role of this additive remained, however, elusive. Installation of an azide at C12 with retention of the configuration was accomplished under Thompson's conditions. Lactam **53** was derived in a four-step sequence, including desilylation and oxidation of the primary alcohol followed by reduction of the azide (30% yield from (−)-**51**). Exhaustive reduction of the amide and reductive alkylation of the resulting amine with formaldehyde provided (+)-amurensinine (**54**) in 52% yield over 2 steps. The synthesis illustrates how consideration of novel aryne reactivity can lead to unprecedented synthetic strategies and enable the concise synthesis of complex molecules. In the present case, the key aryne insertion reaction fulfilled two vital purposes: The carbon scaffold was built up in a convergent manner from two similarly sized building blocks, and at the same time the cyclopentanone ring was expanded to form the central seven-membered ring of amurensinine.

2.4. [2+2+2] Cycloaddition in the Synthesis of Taiwanins C and E

Arynes have been shown to participate in metal-catalyzed [2+2+2] cycloadditions (Scheme 8). This behavior of arynes was first observed by Guitián and co-workers in the Pd^0-catalyzed homotrimerization of arynes, and was quickly further developed into Pd^0/Pd^{II}- and Ni^0/Ni^{II}-mediated cyclotrimerizations of arynes with arynes, alkynes, allenes, nitriles, and alkenes.[30]

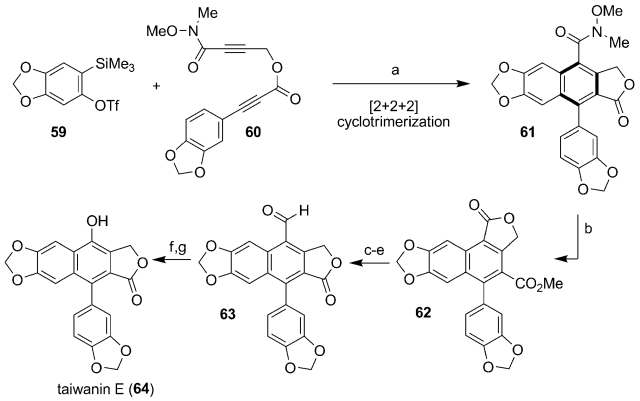


Scheme 8. Mechanistic hypotheses for the [2+2+2] cycloaddition.

Although most publications in this field suggest a reaction mechanism involving arynes, these hypotheses are seldom supported by experimental data, but are instead formulated in agreement with the fact that 1) arynes may be liberated from arylsilanes such as **55** and 2) alkynes participate in [2+2+2] cyclotrimerizations (cf. **56**). In this respect, one caveat must be noted: reaction pathways initiated by oxidative insertion of Pd^0 into the aryl triflate have been uncovered (cf. **58**), and it was suggested that the mechanism of the reaction (i.e. aryne versus organometallic) strongly depends on the palladium source and the substitution pattern of the benzyne precursor.[30c] Hence, caution is warranted, as the reactions may not be proceeding via free benzyne intermediates. In these cases, a straightforward control experiment can bring clarification: Arenes with a regioisomeric substitution pattern, in which the silane and the triflate have changed positions, form the same benzyne but a regioisomeric organometallic species **58**. Thus, the same reaction outcome is obtained if a free aryne is involved, but the reaction will likely give a different product if the reaction proceeds via an organometallic intermediate **58**.[31]

A detailed analysis of the mechanism of these reactions is, however, not the subject of this Minireview and we will refer to the presented reactions as [2+2+2] cyclotrimerizations for the purpose of clarity and consistency, rather than to suggest a specific reaction mechanism.

The application of the aforementioned aryne–alkyne trimerization reaction in natural product synthesis has nicely been demonstrated by Mori and co-workers.[32] In their synthesis of lignan taiwanin E (**64**, Scheme 9), these researchers chose to install the biaryl axis in a counterintuitive way, by employing a [2+2+2] reaction to build up the naphthalene



Scheme 9. Reagents and conditions: a) [Pd_2(dba)$_3$] (5 mol%), P(*o*-tol)$_3$ (40 mol%), CsF (6.0 equiv), MeCN, RT, 4 h, 61%; b) NaH, MeOH, CH_2Cl_2, RT, 78%; c) DIBAL-H, CH_2Cl_2, −78°C, 63%; d) $NaBH_4$, MeOH, 0°C to RT, 95%; e) PCC, MS 4 Å, CH_2Cl_2, 0°C, 89%; f) mCPBA, CH_2Cl_2, RT; g) K_2CO_3, MeOH, RT, 88% (over 2 steps). dba = dibenzylideneacetone; DIBAL-H = *i*Bu_2AlH; PCC = pyridinium chlorochromate; mCPBA = *m*-chloroperbenzoic acid.

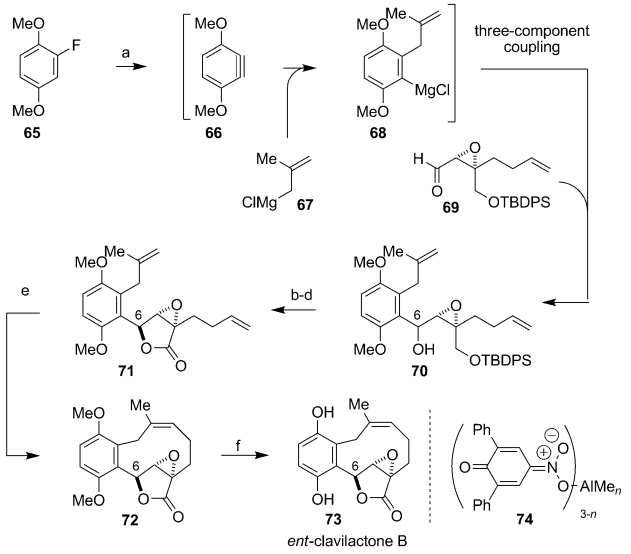
rather than a biaryl coupling of a phenol with a naphthalene. To this end, diyne **60** was allowed to react with aryne precursor **59**. Optimization studies led to the identification of [Pd_2(dba)$_3$]/P(*o*-Tol)$_3$ as the optimal catalytic system and, in the presence of CsF, biaryl **61** was generated in 61% in 4 h at RT. Surprisingly, attempts to reduce the Weinreb amide in **61** to the corresponding aldehyde were thwarted by preferential attack of the hydride on the lactone, thereby resulting in subsequent translactonization (not shown). Thus, the synthetic sequence was revised, and ester **62** was first prepared by exposure of **61** to NaOMe. A three-step reduction/oxidation sequence gave aldehyde **63**, which was converted into taiwanin E (**64**) by Baeyer–Villiger oxidation followed by alkaline hydrolysis of the resulting formate ester. This synthesis illustrates how biaryls can be crafted by cyclotrimerization of an aryne with two alkynes and thus provides intriguing alternative routes to naphthalenes.

2.5. Three- and Four-Component Coupling Reactions

The electrophilic nature of the bent in-plane alkyne π bond renders arynes excellent substrates for carbometalation, as seen in the previous section on the carbopalladation and carbonickelation of arynes. Furthermore, arynes can be subjected to carbomagnesation and carbolithiation, and the organometallic species obtained can then be trapped by carbon electrophiles such as ketones, aldehydes, and CO_2. This section presents examples of the use of three- and four-component coupling reactions in the synthesis of *ent*-clavilactone B (**73**) and dehydroaltenuene B (**83**).

2.5.1. Synthesis of Clavilactone B

Clavilactone B (**73**, Scheme 10) is a fungal metabolite that was isolated in 2000.[33] Besides antimicrobial activity, the clavilactone family of compounds has been shown to represent a new structural class of potent kinase inhibitors and, therefore, piqued the interest of various researchers. Although the relative configuration had been established by X-ray crystallography, the absolute configuration of the clavilactones had not been assigned. The research group of Barrett set out to address this gap by means of an enantioselective total synthesis.[34] These researchers could profit from their expertise in aryne chemistry and devised a synthetic strategy that involved a three-component benzyne coupling as the key step. As the electrophilic coupling partner, aldehyde **69** was prepared in six steps in excellent yield (77%) and enantiomeric excess (97%) from propargyl alcohol. Various benzyne precursors were tested, and fluorobenzene **65** was found to be best suited for the attempted coupling reaction. Lithiation of **65** with *n*BuLi gave a fluoroaryllithium intermediate, which eliminated LiF upon warming from −78 °C to RT with liberation of dimethoxybenzyne (**66**). The aryne was trapped by Grignard reagent **67**. Aldehyde **69** was then added to subsequently obtain a mixture of epimeric alcohols **70** in 65% combined yield. This key reaction thus coupled all the necessary carbon atoms required to build up clavilactone B (**73**).



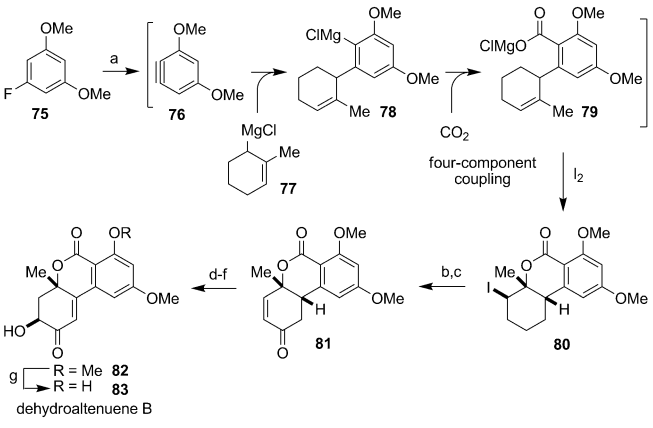
Scheme 10. Reagents and conditions: a) *n*BuLi, THF, **67**, −78 °C to RT, then: **69**, −78 °C to −35 °C, 65% (d.r. = 2:1); b) Bu_4NF, THF, 87%; c) TEMPO (20 mol%), $PhI(OAc)_2$, CH_2Cl_2, 65%; d) **74** (60 mol%), CH_2Cl_2, 80%; e) 2nd generation Grubbs cat. (40 mol%), tetrafluorobenzoquinone (80 mol%), PhMe, 80 °C, 65%; f) CAN, MeCN, H_2O, 74%. TEMPO = tetramethylpiperidine *N*-oxide.

The mixture of epimeric alcohols **70** was subjected to desilylation and oxidation to give lactone **71** as an epimeric mixture at C6 (56% over 2 steps). At this point, a novel aluminum Lewis acid **74** was identified which induced isomerization at the stereogenic C6 center, presumably via the benzylic cation, to convert the mixture of C6 epimers of **71** into pure **71** in 80% yield.

Diene **71** was now set up for a final ring-closing metathesis (RCM). Previous experiments had shown that **71** is a rather challenging substrate for RCM, since dimerization of the less-hindered olefin occurs readily. Thus, the strategy included rendering the reaction of this olefin reversible in order to obtain useful yields of the desired macrocycle. The optimized conditions involve the slow addition of the second generation Grubbs catalyst and tetrafluorobenzoquinone to the reaction mixture, with concomitant removal of ethylene, thereby forming **72** in 65% yield. Comparison of the optical rotation of **72** obtained through de novo synthesis and by derivatization of the natural product indicated that the enantiomer of the natural product had been prepared, thus unraveling the absolute configuration of clavilactone B to be the enantiomer of **73**. Demethylation of **72** led to the first asymmetric total synthesis of *ent*-clavilactone B (**73**).

2.5.2. Synthesis of Dehydroaltenuene B

After their successful structural determination of clavilactone B (**73**), the Barrett research group further elaborated the aryne multicomponent coupling reaction and showcased its applicability to the synthesis of another interesting natural product—dehydroaltenuene B (**83**, Scheme 11).[35] Dehy-



Scheme 11. Reagents and conditions: a) *n*BuLi, −78 °C, then: **77**, to RT, then: CO_2, −78 °C to RT, then I_2, 0 °C to RT, 56%; b) DBU, THF, 65 °C, 95%; c) $[Rh_2(cap)_4]$ (10 mol%), *t*BuOOH, K_2CO_3, CH_2Cl_2, RT, 77%; d) $(PhSe(O))_2O$, CSA, 71%; e) $(Ph_3PCuH)_6$, 0 °C to RT, 82%; f) LiHMDS, −78 °C, then Davis' oxaziridine; g) BCl_3, CH_2Cl_2, 0 °C, 81% (over 2 steps). cap = caprolactam; CSA = camphersulfonic acid; LiHMDS = lithium hexamethyldisilazide.

droaltenuene B (**83**) was isolated in 2006 along with its hydroxy epimer dehydroaltenuene A as well as their ketone derivatives, in which the enone is saturated, termed dihydroaltenuenes A and B.[36] Synthetic access to these marine natural products would enable closer studies of their antibacterial activity as well as assignment of the absolute configuration of these structures, which until then had not been established. To this end, Barrett and co-workers set out to establish a concise route to the dehydroaltenuenes by using a four-component aryne coupling reaction. It was found that fluorodimethoxybenzene **75** was a suitable precursor for dimethoxybenzyne **76**, which was generated upon deprotonation of **75** with *n*BuLi. Upon warming the reaction mixture to RT, and in the presence of Grignard reagent **77**, phenylmagnesium **78** was formed regioselectively and trapped with CO_2 to give carboxylate **79**. The selectivity for nucleophilic attack at the aryne can be rationalized by the effect of the nearby methoxy group. The Grignard reagent attacks the site that affords a carbanion *ortho* to the methoxy substituent, where it is stabilized inductively and through chelation. The reaction mixture obtained was finally treated with iodine to trigger a substrate-induced diastereoselective iodolactonization to obtain **80** in 56% yield from **75**.

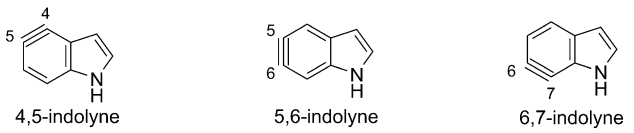
The four-component coupling delineated above establishes the entire carbon framework of the natural product in one synthetic operation, leaving the researchers with the adjustment of the oxidation state of the cyclohexane ring. To this end, HI elimination was induced by the action of DBU on iodide **80** to install unsaturation, which allowed for subsequent allylic oxidation under Doyle's conditions to obtain enone **81** in 73% yield over two steps. Oxidation of **81** to the corresponding dienone with benzeneseleninic anhydride was followed by reduction of the less sterically hindered enone by Stryker's reagent and hydroxylation using the Davis oxaziridine to obtain methyldehydroaltenuene B **82**. O-Demethylation with BCl_3 provided racemic dehydroaltenuene in 47% yield from **81**, thereby completing the first synthesis of this antibacterial natural product in a total of seven steps from **75**. Rendering this synthetic route enantioselective would require the asymmetric allylation of an aryne, thus providing opportunities for further innovation in the field of aryne chemistry.

3. Indolynes

3.1. Background

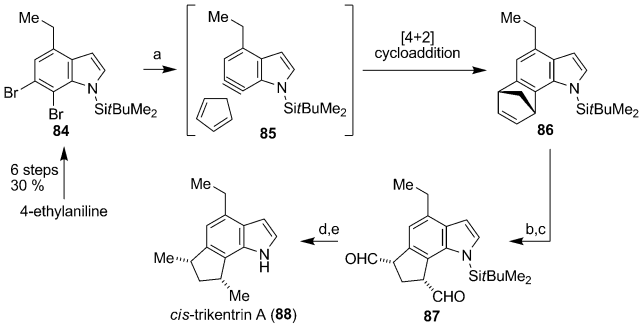
Benzynes undergo a myriad of synthetically useful transformations, as showcased in the previous section. A large number of bioactive natural products contain an indole core, and a strategic question consequently arises whether these indole alkaloids could be assembled from indolyne intermediates, which were anticipated to participate in a host of reactions similar to benzynes. This strategy is particularly interesting since it would allow the use of an inherently electron-rich indole building block as the electrophilic reaction partner.

The existence of indolynes was suggested by Igolen and co-workers in the 1960s.[37] In a number of publications these researchers documented the electrophilic character of indolynes generated by treatment of bromoindoles with amide bases. For example, a mixture of 4- and 5-aminoindole was obtained by treatment of 5-bromoindole with KNH_2. However, the generally modest yields (< 50%) prevented further synthetic application of indolynes. This research field remained dormant for 40 years and has only recently undergone a renaissance. Key to the advances is the new methods developed for the generation of indolynes. However, indolyne reactivity is to date far less understood than that of benzynes, in particular with respect to the regioselectivity of cycloadditions and attack by nucleophiles.



3.2. Indolynes in [4+2] Cycloadditions—Synthesis of cis-Trikentrin A

In 2007, Buszek and co-workers documented that 4,5-, 5,6- and 6,7-indolynes are accessible from the corresponding dihaloindoles (Cl, Br) by halogen–lithium exchange with *t*BuLi, followed by elimination to give the didehydroindole.[38] This reaction sequence allowed rapid access to the indole alkaloid *cis*-trikentrin A (**88**, Scheme 12). Indole **84** was synthesized by a Bartoli indole synthesis from 4-ethylaniline in 6 steps and 30% yield. Treatment of **84** with *n*BuLi in the presence of cyclopentadiene initiated indolyne formation, which was followed by [4+2] cycloaddition of the two reaction partners to give adduct **86** in 77% yield. The authors note that the use of toluene as a solvent was crucial to prevent deprotonation of cyclopentadiene by the organometallic species, and that silylation of the indole nitrogen atom was essential. The double bond in **86** was oxidatively cleaved by using the method of Lemieux and Johnson (OsO_4, $NaIO_4$) to obtain dialdehyde **87** (87%). The synthesis of *cis*-trikentrin A (**88**) was completed by conversion of **87** into its dithioacetal



Scheme 12. Reagents and conditions: a) cyclopentadiene, *n*BuLi, PhMe, −78 °C to RT, 77%; b) OsO_4, NMO, THF, H_2O, 88%; c) $NaIO_4$, THF, H_2O, 99%; d) EtSH, BF_3OEt_2, −78 °C to RT, 91%; e) Raney-Ni, EtOH, reflux, 85%. NMO = *N*-methylmorpholine-*N*-oxide.

with concomitant desilylation, followed by desulfurization by Raney nickel to give the target compound in 74% yield.

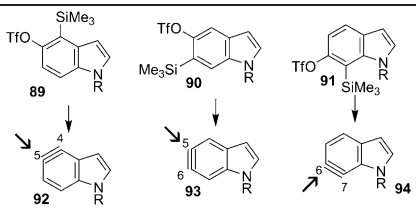
Recent studies by the groups of Buszek and Garg showed that indolynes readily react in a number of [2+2], [3+2], and [4+2] cycloadditions with, for example, enol ethers, organic azides, and pyroles, respectively.[39,40] Although these reports suggest that this highly reactive aryne intermediate can find similar widespread application to its parent benzyne in synthetic organic chemistry, the regioselectivity in these addition reactions (with unsymmetrical substrates) is modest. Furthermore, the corresponding controlling factors are to date not yet well understood.

3.3. Nucleophilic Reactions of Indolynes—Synthesis of Indolactam V

Garg and co-workers have established a research program with the aim of developing the use of indolynes in organic synthesis. The work that has appeared to date attests to the fact that indolynes may be readily accessed under mild conditions by using Kobayashi's strategy to liberate the aryne from an *ortho*-trimethylsilyl triflate precursor upon treatment with fluoride (Table 1).[40,41] These conditions even allowed access to NH-indolynes, thus obviating the necessity to protect the indole nitrogen atom. In collaboration with Houk, Garg and co-workers recently used this method to study nucleophilic attack onto indolynes.[41] Quantum chemical calculations revealed a significant distortion of the aryne carbon skeleton, which results in a predicted preferred attack of nucleophiles at the carbon atom with the largest internal C-C-C angle (see black arrows). For example, nucleophilic attack at C5 of 4,5-indolyne (**92**) requires less geometrical rearrangement of the aryne en route to the calculated transition-state structure as does attack at C4. Furthermore, distortion of the indolyne carbon scaffold results in an unfavorably reduced C-C-C angle at C3a. This angle strain is reduced upon nucleophilic attack at C5, whereas it is exacerbated on attack at C4. Calculation of the geometries of 5,6- and 6,7-indolyne (**93** and **94**) gave similar results, and predicted nucleophilic attack to occur primarily at C5 and C6, respectively, namely at the carbon atom with the largest internal C-C-C angle. These theoretical studies have been confirmed experimentally. Thereby, the desired indolyne was formed by the action of fluoride on the corresponding trimethylsilyl triflate precursors (**89**–**91**) and trapped with *p*-methylphenol, aniline, and KCN. For 4,5-indolyne (**92**), modest to good selectivity for the generation of the C5 adduct was obtained (3:1 to 12.5:1). Interestingly, in the case of *p*-methylphenol and aniline, the nitrogen protecting group had a dramatic effect on the observed regioselectivity. It was found that the 5,6-indolyne (**93**) exhibits less pronounced preference for attack at C5, with selectivity not exceeding 3:1. Furthermore, the N-protecting group had only a marginal influence on the reaction outcome. In sharp contrast, 6,7-indolynes (**94**) yield the C6 adduct essentially exclusively, irrespective of the nitrogen substituent, thus rendering this strategy highly valuable for the regioselective nucleophilic functionalization of the indole nucleus.

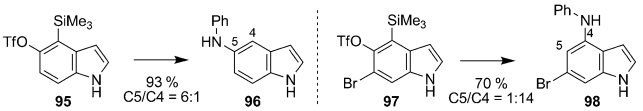
Having observed that nucleophiles add to indolynes preferentially at C5 and C6, Garg and co-workers next investigated how to overcome this inherent regioselectivity to selectively functionalize indolynes at C4.[42] To this end, the two indoles **95** and **97** were synthesized with the objective of studying the influence of a bromine substitutent on the adjacent aryne triple bond (Scheme 13). Interestingly, these studies showed that regioselectivity was entirely reversed by the effect of the halide. For example, whereas the reaction of **95** with CsF in MeCN in the presence of aniline gave the C5 adduct **96** with a selectivity of 6:1 (93% yield), bromoindole **97** gave amine **98** with a selectivity of 14:1 for attack at C4 (70% yield).

Table 1: Preference for nucleophilic attack on indolynes.[a]



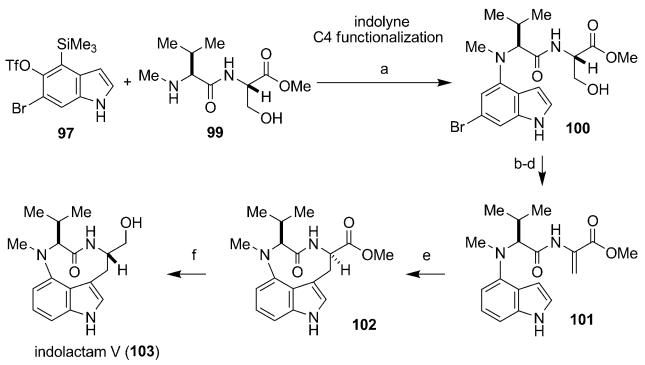
Nucleophile	R		Ratio	
p-methylphenol	Me	3:1	2:1	only C6 attack
	H	5:1	2:1	10.7:1
	Boc	8.2:1	1.1:1	only C6 attack
aniline	Me	12.5:1	3:1	only C6 attack
	H	6.4:1	2.9:1	13.8:1
	Boc	8.3:1	1.5:1	only C6 attack
KCN	Me	3.3:1	1.7:1	only C6 attack
	H	3.4:1	1.8:1	7.6:1
	Boc	3.5:1	1.6:1	only C6 attack

[a] Reaction conditions: excess nucleophile (1.5–5 equiv), CsF (3 equiv), MeCN, 50–80°C.



Scheme 13. Reagents and conditions: CsF, MeCN, aniline, 50°C.

The findings described above paved the way for the synthesis of indolactam V (**103**, Scheme 14) by C4-functionalization of indolyne.[42] Thus, unprotected indole **97** was treated with dipeptide **99** and CsF in MeCN, and adduct **100** was obtained in 62% yield. The efficiency of this reaction is remarkable in terms of the high chemoselectivity of this intermolecular reaction, in which both partners have multiple competing reactive sites. The authors note that, much to their surprise, this intermolecular approach was successful, whereas prior attempts to close the macrocycle in an intramolecular fashion, on an indolyne lacking the halide substituent, were met with failure. This C–N bond formation was followed by reductive removal of the bromide and dehydration to furnish enoate **101** (69% over 3 steps). $ZrCl_4$-mediated alkylation of the indole at C3 furnished macrocycle **102**, which, being an



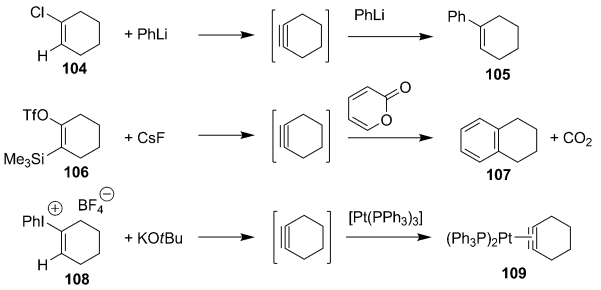
Scheme 14. Reagents and conditions: a) CsF, MeCN, 0 °C to RT, 62%; b) H_2, Pd/C, NEt_3, MeOH; c) Ac_2O, AcOH, RT; d) K_2CO_3, DMF, 65 °C, 69% (over 3 steps); e) $ZrCl_4$, CH_2Cl_2, 34 °C, 56%; f) Ref. [43].

intermediate in Nakatsuka's synthesis, could be converted into indolactam V (**103**) in two steps.[43]

4. Cyclohexyne

4.1. Background

In sharp constrast to aryne chemistry, which has evolved into a powerful tool for synthetic chemistry, cyclohexyne has until now not been employed in organic synthesis. This can mainly be attributed to the fact that generation of this cyclic alkyne in synthetically useful yields has proven difficult. Scardiglia and Roberts first considered cyclohexyne as a fleeting intermediate formed from the elimination of HCl from chlorocyclohexene **104** by PhLi (Scheme 15).[44] Following its liberation, cyclohexyne then reacted in a carbolithiation



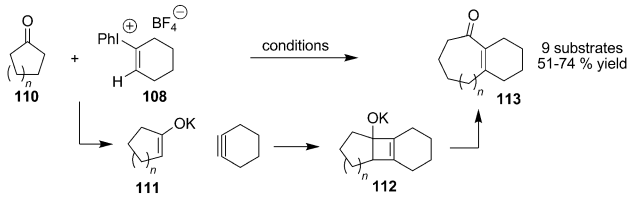
Scheme 15. Cyclohexyne generation by elimination from substituted cyclohexenes.

reaction to give **105** after workup. Wittig and co-workers as well as the research group of Caubère later showed that generation of cyclohexyne by base-induced elimination from chlorohexene leads to competitive formation of 1,2-cyclohexadiene, namely cycloallene.[45] As a remedy to this problem, Guitián and co-workers adapted Kobayashi's method for aryne generation to the synthesis of cyclohexyne.[46] Thereby, triflate **106** liberates cyclohexyne upon treatment with CsF at room temperature. More recently, the research group of Fujita reported that cyclohexyne could be formed by the action of KOtBu on iodonium salt **108** at 0 °C and trapped, for example, as platinum complex **109**.[47] Interestingly, no competitive formation of cycloallene or benzyne was observed.

It must be noted that the methods for cyclohexyne generation presented here are only a selection of the studies that have been done in this field. Conceptually different approaches to cyclohexyne have been described based on the formation of vicinal dicarbenes or on generation of exocyclic vinylidenes, which undergo rearrangement to cyclohexyne.[48] These methods have been reviewed previously and a detailed account of this approach is beyond the scope of this Minireview.[4,49]

4.2. Ring Insertion Reactions En Route to Sandresolide A

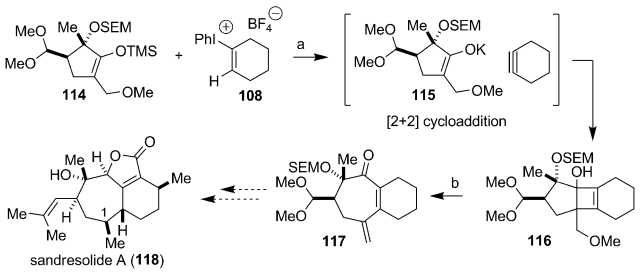
Carreira and co-workers recently reported the first application of cyclohexyne in the synthesis of a complex molecule.[50] In this study, *n*-cyclic ketones **110** were treated with $KOCEt_3$ in THF in the presence of Fujita's cyclohexyne precursor **108**, and [$n+2.6.0$]bicyclic enones **113** were obtained (Scheme 16). The use of the more basic $KOCEt_3$ as compared to KOtBu enabled the cycloinsertion to occur on



Scheme 16. Reagents and conditions: $KOCEt_3$, THF, −78 °C to RT.

a variety of simple cyclic ketones as well as steroids and terpenes in synthetically useful yields of 51–74%. The fact that cyclobutenols could be isolated and identified as reaction intermediates enabled a mechanism to be proposed for this cascade reaction. The potassium alkoxide is believed to liberate cyclohexyne from iodonium salt **108** and to convert the ketone into its enolate **111**. These two species undergo a formal [2+2] reaction to give cyclobutenolate **112**, which undergoes cleavage of the cyclobutene ring to give the observed enone products **113** after protonolytic workup.

This intriguing ring insertion reaction gives rapid access to bicyclic scaffolds with medium-sized rings and was, thus, anticipated to be a useful tool for the synthesis of various terpene natural products. However, application of this cyclohexyne cycloinsertion reaction in a complex molecule synthesis would require the reaction conditions to be compatible with more elaborate substrates. Sandresolide A (**118**, Scheme 17), for example, has a highly substituted bicyclic carbon core and, thus, offered a testing ground for the cyclohexyne cycloinsertion reaction with a more complex substrate. In particular, the sandresolide scaffold bears a methyl substituent at C1, which could be installed in the cycloinsertion reaction by using the appropriately substituted TMS-enol ether **114**. Notably, the use of a stoichimetric

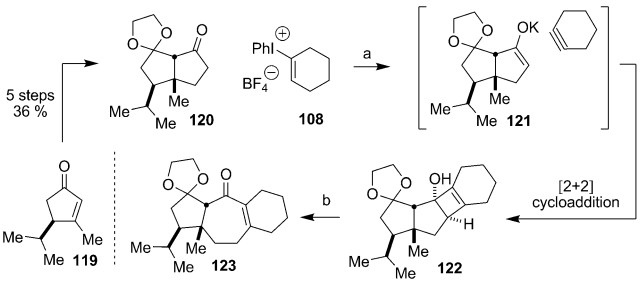


Scheme 17. Reagents and conditions: a) **108** (2.4 equiv), KO*t*Bu (3.0 equiv), H_2O (1.2 equiv), THF, −78 °C to RT; b) KHMDS (1.1 equiv), [18]crown-6 (0.5 equiv), THF, RT. KHMDS = potassium hexamethyldisilazide, SEM = 2-(trimethylsilyl)ethoxymethyl.

amount of water along with KO*t*Bu allowed generation of the free enolate from TMS-enol ether **114** without inducing elimination of the β-methoxy group, and cyclobutenol **116** was isolated in 83 % yield. The presence of the methoxy group in **116** proved crucial for opening of the cyclobutene ring, enabling a fragmentation pathway for ring cleavage. Whereas a similar substrate lacking the methoxy group did not undergo ring opening under basic conditions, **116** yielded dienone **117** in 51 % yield.

4.3. Syntheses of Guanacastepenes O and N

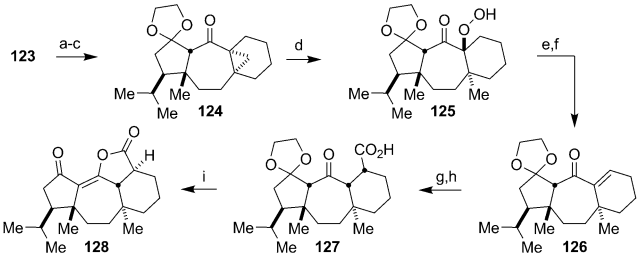
Based on their previous findings, Gampe and Carreira developed a strategy for the synthesis of the guanacastepenes that involved a cyclohexyne cycloinsertion into pentalenone **120** as the key reaction (Scheme 18).[51] This ring insertion would address the major synthetic challenge, namely the construction of the tricyclic carbon scaffold incorporating



Scheme 18. Reagents and conditions: **108**, $KOCEt_3$, THF, −78 °C to RT, **122**: 74 %, **120**: 13 %; b) $[Fe_2(CO)_9]$, PhH, 90 °C then DBU, 51 %.

a five-, seven-, and six-membered ring, by insertion of the six-membered ring into a bicyclic system, thereby expanding the five- to the required central seven-membered ring. The synthesis commenced with known enone **119**, which was converted into pentalenone **120** in 5 steps and 36 % yield. Treatment of **120** with cyclohexyne precursor **108** and $KOCEt_3$ generated cyclobutenol **122** as a single diastereomer in 74 % yield. To avoid side reactions, cyclobutenol **122** was not ring openend under basic conditions, but instead subjected to iron-promoted electrocyclic ring opening. Enone **123** was obtained in 51 % yield, and thus the tricyclic core of the guanacastepenes was accessed in seven steps from cyclopentenone **119**.

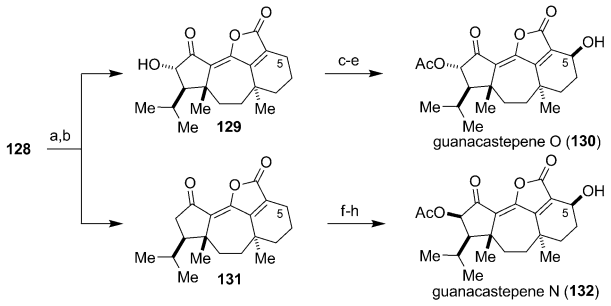
The next task in the synthetic route was the installation of the second quaternary center. To this end, a three-step procedure was implemented, comprising diastereoselective 1,2-reduction of enone **123**, directed cyclopropanation of the resulting allylic alcohol, and oxidation, to give cyclopropyl ketone **124** (61 % over 3 steps, Scheme 19). Cleavage of the cyclopropane was induced with Li/NH_3, and it was found that



Scheme 19. Reagents and conditions: a) DIBAL-H, *n*BuLi, −78 °C, 30 min, d.r. > 95:5; b) $ZnEt_2$, TFA, CH_2I_2, CH_2Cl_2, 0 °C, 15 min, 61 % (over 2 steps); c) PDC, Ac_2O, CH_2Cl_2, RT, 99 %; d) Li/NH_3, THF, then SiO_2, CH_2Cl_2, O_2; e) Me_2S, acetone, RT, 79 % (over 2 steps); f) $SOCl_2$, pyridine, RT, 95 %; g) $Me_2AlCCTMS$, Et_2O, RT, then NaOMe, MeOH, 81 %; h) $RuCl_3$, oxone, $NaHCO_3$, H_2O, MeCN, EtOAc, RT, 55 % (1 × recycling); i) HCl (0.1 M), THF, 57 °C, then $(COCl)_2$, pyridine, CH_2Cl_2, 0 °C, 15 min, 79 %. DIBAL-H = *i*Bu_2AlH, TFA = F_3CCO_2H.

the primarily obtained enol underwent facile, SiO_2-promoted oxidation in air to yield hydroperoxide **125**. Reduction of **125** followed by dehydration provided enone **126** (75 % over 2 steps). The missing carbon atom was introduced by 1,4-addition of TMS-acetylene to enone **126** followed by oxidative cleavage of the internal alkyne—using RuO_4—to give acid **127** (45 % over 2 steps), which was converted into lactone **128** under acidic conditions.

Lactone **128** was located at the branching point of the stereodivergent synthesis of both guanacastepenes N and O (Scheme 20). Exposure of **128** to TBSOTf generated the corresponding bis(TBS)-silylenol ether, which was treated



Scheme 20. Reagents and conditions: a) *t*$BuMe_2SiOTf$, NEt_3, CH_2Cl_2; b) OsO_4, NMO, $MeSO_2NH_2$, acetone, HO*t*Bu, H_2O, 0 °C, over 2 steps: **131**: 40 %; **129**: 29 %, d.r. = 9:1; c) Ac_2O, NEt_3, DMAP, CH_2Cl_2, RT, 87 %; d) NBS, $(PhCOO)_2$, CCl_4, 80 °C, 76 %; e) Bu_3SnH, toluene, air, then PPh_3, 72 %; f) $Mn(OAc)_3$, benzene, MS 3 Å, 80 °C, 68 %, d.r. = 4:1; g) NBS, $(PhCOO)_2$, CCl_4, 80 °C, 1 h, 58 %; h) Ref. [52].

with OsO_4 to obtain α-hydroxyketone **129** in good stereoselectivity (d.r. = 9:1) as well as dehydrogenated lactone **131**. The former was acylated and radical allylic hydroxylation at C5 completed the first total synthesis of guanacastepene O (**130**). Treatment of lactone **131** with $Mn(OAc)_3$ directly installed the acetoxy group with epimeric configuration (d.r. = 4:1) to allow access to guanacastepene N (**132**).

This synthesis includes the first example of the use of cyclohexyne as a building block in natural product synthesis and, thus, represents a milestone in the development of the chemistry of angle-strained cycloalkynes. It was shown how the inherent reactivity of cyclohexyne can be cleverly harnessed to effect a cycloinsertion reaction that is beyond the realm of classic synthetic strategies.

5. Summary and Outlook

Over the past seven decades the field of aryne and angle-strained cycloalkyne chemistry has constantly developed, and these reactive intermediates are no longer chemical curiosities. This Minireview highlights a number of natural product syntheses that have been disclosed in the past decade, in which these highly reactive molecules were used to effect bond formations that are otherwise difficult to implement. Exciting new reactivity of benzynes has been uncovered that allows rapid access to a range of natural products. Furthermore, even highly substituted benzynes can be generated and subjected to reactions with advanced synthetic intermediates. In contrast, the reactivity of indolynes has only recently been studied. However, seminal work by Buszek and Garg suggests that indolyne chemistry can be further advanced and will heavily influence future synthetic strategies toward indole alkaloids. The first application of an angle-strained cycloalkyne in natural product synthesis was recently reported by Carreira and co-workers. In this synthesis of guanacastepenes O and N, cyclohexyne undergoes an intriguing cycloinsertion reaction, thus highlighting the synthetic potential of angle-strained cycloalkynes. It will be exciting to witness the future development of the chemistry of angle-strained cycloalkynes, in particular with regard to the use of substituted cyclohexynes and cyclopentynes.

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