Tetrahedron

Development and applications of highly selective palladium-catalyzed monocoupling reactions of (cyclo)alkenes and 1,3-alkadienes bearing two or three electrophilic sites and bis(enol triflates) with terminal alkynes

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ABSTRACT

This review with 572 references illustrates the development of highly selective Pd/Cu-catalyzed and Cu-free Pd-catalyzed monoalkynylation reactions of (cyclo)alkenes and 1,3-butadienes bearing two or three identical or different electrophilic sites and bis(enol triflates) with terminal alkynes, highlighting the use of these reactions as key steps of the syntheses of core structures and models of enediyne antitumor antibiotics, pharmacologically active compounds, and bioactive natural substances including insect pheromone components, and fungal and plant metabolites. A focus has also been set on efficient and powerful strategies involving the formation of substituted acetylene derivatives by one-pot site-selective Pd-catalyzed consecutive alkynylation reactions of di(pseudo)halogenated olefinic substrates with two different terminal alkynes. Finally, where appropriate, the reasons for the observed stereo-, site- and/or chemoselectivitites of the illustrated monoalkynylation reactions have been mentioned and discussed.

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Abbreviations: Ac, acetyl; Ar, aryl; Bn, benzyl; Boc, *tert*-butoxycarbonyl; *n*-Bu, *n*-butyl; *t*-Bu, *tert*-butyl; Cp, cyclopentadienyl; DABCO, 1,4-diazabicyclo[2.2.2]octane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DEAD, diethyl azodicarboxylate; DIBALH, diisobutylaluminum hydride; DMA, *N,N*-dimetylacetamide; DMAP, 4-dimethylaminopyridine; DMF, *N,N*-dimethylformamide; DME, dimethoxyethane; dppf, 1,1'-bis(diphenylphosphino)ferrocene; dppp, 1,3-bis(diphenylphosphino)propane; EDCI, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride; Et, ethyl; Fm, 9-fluorenemethyl; HMPA, hexamethylphosphoramide; LDA, lithium diisopropylamide; LiHMDS, lithium bis(trimethylsilyl)amide; Me, methyl; MOM, methoxymethyl; NIS, *N*-iodosuccinimide; NBS, *N*-bromosuccinimide; *o*-NBS, *ortho*-nitrobenzenesulfonyl; Piv, pivaloyl; Ph, phenyl; *i*-Pr, *iso*-propyl; *n*-Pr, *n*-propyl; Red-Al, sodium bis(2-methoxyethoxy)aluminum hydride; rt, room temperature; TBAs, tetrabutylammonium hydrogen sulfate; TBDMS, *tert*-butyldimethylsilyl; TES, triethylsilyl; Tf, trifluoromethylsulfonyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; THP, tetrahydropyranyl; TIPS, triisopropylsilyl; *p*-Tol, *p*-tolyl; Ts, *p*-toluenesulfonyl; Xantphos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene; Z(2-Cl), *N*-(2-chlorobenzyloxycarbonyloxy).

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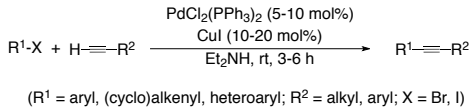
1. Introduction

Among the myriad of transition metal-catalyzed reactions, the Pd-catalyzed C(sp^2)–C(sp) bond-forming reactions from terminal alkynes and aryl and alkenyl halides or pseudohalides have emerged as a highly fascinating methodology of primary importance in synthetic organic chemistry. In fact, these cross-coupling reactions provide an effective route for preparing arylacetylenes and conjugated enynes which are precursors for natural compounds, pharmaceuticals, agrochemicals, and materials with specialized electronic and optical properties.[1]

These direct alkynylation reactions were introduced in 1975 by Cassar[2a] who reported the synthesis of aryl- and alkenyl-substituted acetylene derivatives by $Pd(PPh_3)_4$-catalyzed reaction of aryl and alkenyl halides with 1-alkynes in DMF at 50 °C in the presence of MeONa as base. Simultaneously and independently, Dieck and Heck[2b] showed that 1-alkynes are converted into 1,2-disubstituted acetylenes by treatment with aryl, heteroaryl and alkenyl bromides and iodides at 100 °C in the presence of Et_3N or piperidine as base and a catalytic amount of $Pd(OAc)_2(PPh_3)_2$. A few months later Sonogashira, Tohda and Hagihara[3a] demonstrated that the cross-coupling of 1-alkynes with iodoarenes, bromoalkenes or bromopyridines could be performed at room temperature in Et_2NH in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI (Scheme 1).



(R^1 = aryl, (cyclo)alkenyl, heteroaryl; R^2 = alkyl, aryl; X = Br, I)

Scheme 1. Sonogashira reaction.

This protocol,[3a] in which CuI is thought to accelerate the transfer of a 1-alkynyl group to an R^1-Pd-X·Ln complex through an alkynylcopper species,[3b–d] has become known as the Sonogashira reaction[4] and has found wide application, especially in the preparation of intermediates for natural products, bioactive molecules and materials.

There is still great interest in this reaction, due to its technical simplicity, high yields, ability to tolerate a wide variety of functional groups, and the fact that it does not involve the use of preformed and expensive organometallic reagents, as demonstrated by the impressive number of

studies on the development of catalyst systems more efficient and reactive than that formed by combining $PdCl_2(PPh_3)_2$ and CuI[5] and by the efforts devoted to develop modifications to the original protocol. These modifications include: (i) reactions carried out under phase-transfer conditions;[6] (ii) copper-free Pd-catalyzed couplings under conditions different from those of the Cassar-Heck alkynylations;[7] (iii) copper- and amine-free Pd-catalyzed alkynylation reactions;[8] (iv) copper- and ligand-free Pd-catalyzed alkynylations;[9] (v) copper- and solvent-free Sonogashira couplings;[10] (vi) copper-, amine-, and solvent-free Pd-catalyzed couplings;[11] (vii) copper-catalyzed Pd-free Castro-Stephens-type reactions,[12] and (viii) reactions carried out using Pd catalysts immobilized on various support materials.[13]

However, despite the great attention paid to this process and its applications, as demonstrated by the fact that 5340 references can be found in the SciFinder data base for the topic "Sonogashira" for the period 1975–September 2012, no comprehensive review summarizing and discussing the updated literature data on selective Sonogashira-type monocoupling reactions of substrates with two or more identical or different electrophilic sites on their sp^2-hybridized carbon atoms has been published to date. The motivation for writing this review with 572 references, which covers the literature up to the end of September 2012, is to fill a part of this gap by illustrating highly selective Pd/Cu-catalyzed and Cu-free Pd-catalyzed monoalkynylation reactions of (cyclo)alkenes and 1,3-butadienes bearing two or three identical or different electrophilic sites and bis(enol triflates) with terminal alkynes. However, Pd-catalyzed selective monocoupling reactions of 1-alkynes with (hetero)aryl halides or pseudohalides with two identical or different electrophilic sites will not be covered. Moreover, Pd-catalyzed monocoupling reactions of 1-alkynes with non-conjugated diene systems bearing an electrophilic site on each carbon-carbon double bond have also been considered to be beyond the scope of this review.

In addition to describing and commenting on the aforementioned monoalkynylation reactions of (cyclo)alkenes and 1,3-dienes with two or three identical or different electrophilic sites and bis(enol triflates), emphasis has been placed on the use of Pd-catalyzed monoalkynylations of (cyclo)alkenes and 1,3-butadienes bearing two or three identical or different electrophilic sites and bis(enol triflates) as key steps of the syntheses of core structures and models of enediyne antitumor antibiotics, pharmacologically active compounds, and bioactive naturally occurring compounds including insect sex pheromone components, and fungal and plant metabolites. Moreover, the review has been focused on the formation of disubstituted acetylenic derivatives by one-pot site-selective Pd-catalyzed consecutive alkynylation reactions of di(pseudo)halogenated olefinic substrates with two different terminal alkynes. Where appropriate, the reasons for the observed stereo-, site- and/or chemoselectivities of the reported Sonogashira-type monoalkynylation reactions have been mentioned and discussed.

For the sake of clarity, the scientific literature concerning the topics covered in this review has been subdivided into three sections (interposed between the introduction and conclusions): (i) monoalkynylation reactions of 1,2-dihalogenated ethenes bearing identical or different halogen atoms; (ii) monoalkynylation reactions of 1,1-dihalogenated-1-alkenes bearing identical or different halogen atoms; and (iii) monoalkynylation reactions of stereodefined bis(enol triflates). In each of these sections, significant applications of the monoalkynylation reactions have been reported and discussed.

2. Monoalkynylation reactions of 1,2-di- and polyhalogenated ethenes and dihalogenated 1,3-dienes

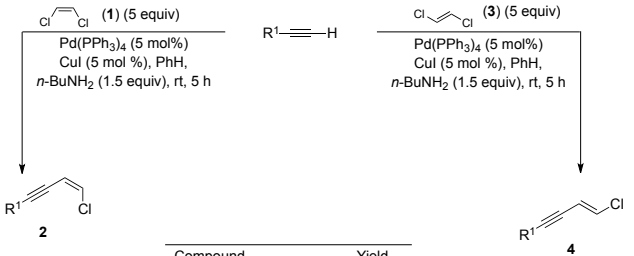
Among the various strategies that have been designed and employed to form stereoselectively C(sp)–C(sp^2) bonds of stereodefined conjugated enynes, dienynes and enediynes via Pd-catalyzed monoalkynylation reactions of stereodefined 1,2-dihalogeno-1-alkenes,[14] the Sonogashira protocol and its modifications are undoubtedly the most useful and extensively used.

This section, which has been divided into four subsections, concerns Sonogashira-type monoalkynylation reactions of 1,2-dihalogenated ethenes and dihalogenated conjugated dienes. The first of these subsections has been devoted to reviewing and commenting on the Sonogashira-type reactions of (*Z*)- and (*E*)-1,2-dichloroethene, the second subsection discusses Sonogashira-type reactions of stereoisomeric mixtures of 1,2-dibromoethenes and (*E*)-1,4-diiodo-1,3-butadienes, the third subsection concerns monoalkynylation reactions of stereodefined 1-bromo-2-chloro-, 1-bromo-2-iodo-, 1-bromo-2-trifluoromethanesulfonyloxy-, 1-chloro-2-iodo-, and 1-fluoro-2-iodo-1-alkenes, and (1*Z*,3*E*)-1-chloro-3-iodo-1,3-butadienes, and the fourth subsection summarizes the monoalkynylation reactions of trihalogenated ethene derivatives bearing two different halogen atoms. Synthetic applications of the cross-coupling products, which were obtained from the Pd-catalyzed reactions described in the above-mentioned subsections, have also been reported.

2.1 Monolkynylation reactions of (*E*)- and (*Z*)-1,2-dichloroethene

In 1981, Ratovelomanana and Linstrumelle reported that the reaction of 1-alkynes with 5 equiv of (*Z*)-1,2-dichloroethene (**1**) in benzene at room temperature for 5 h in the presence of 5 mol% $Pd(PPh_3)_4$, 5 mol% CuI and 1.5

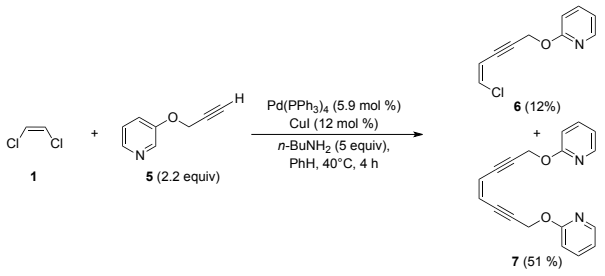
equiv of *n*-$BuNH_2$ provided stereospecifically (*Z*)-1-chloro-1-en-3-ynes **2a-d** in high yields (Scheme 2).[15] They also found that the reaction of (*E*)-1,2-dichloroethene (**3**) with 1-alkynes under experimental conditions very similar to those used to prepare compounds **2** gave stereospecifically and in high yields (*E*)-1-chloro-1-en-3-ynes **4a-d** (Scheme 2).[15]



Compound **2** or **4**	R^1	Yield (%)
2a	*n*-C_5H_{11}	95
4a	*n*-C_5H_{11}	98
2b	CH_2OTHP	95
4b	CH_2OTHP	95
2c	CH_2OAc	72
4c	CH_2OAc	65
2d	CH_2SMe	95
4d	CH_2SMe	100

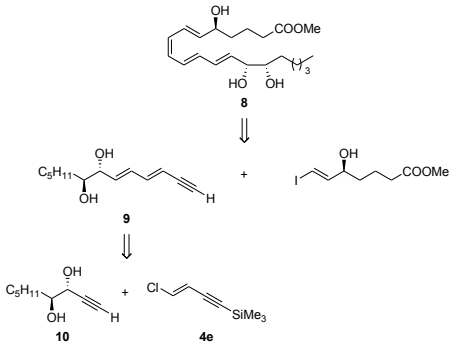
Scheme 2. Stereospecific synthesis of chloroenynes **2** and **4**.

However, more recently, the reaction between 2.2 equiv of 3-(2-prop-2-ynyloxy)pyridine (**5**) with 1 equiv of **1** in benzene at 40 °C, in the presence of 5.9 mol% $Pd(PPh_3)_4$, 12 mol% CuI and 5 equiv of *n*-$BuNH_2$, was found to provide (*Z*)-3-(5-chloropent-4-en-2-ynyloxy)pyridine (**6**) in low yield.[16] The main product of this Sonogashira-type reaction was, in fact, the bisalkynylation derivative **7** (Scheme 3).[16]



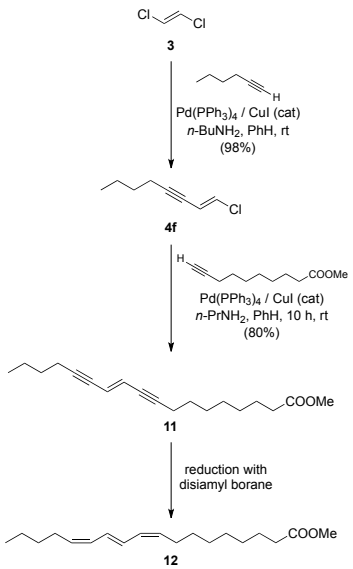
Scheme 3. Stereospecific synthesis of compounds **6** and **7**.

In 1993, the Linstrumelle modification of the original protocol of the Sonogashira reaction was employed to prepare (*E*)-1-chloro-4-trimethylsilyl-1-en-3-yne (**4e**)[17] in 82% yield, which was used as a building block in a stereocontrolled total synthesis of the methyl ester **8** of lipoxin LXB4.[18] The convergent synthesis of this metabolite of arachidonic acid, which was isolated by Samuelson in 1984,[19] was achieved on the basis of the retrosynthetic analysis depicted in Scheme 4. The homochiral diol **9** was prepared in 75% yield by the reaction of 1-alkyne **10** with **4e** in THF in the presence of 7 mol% $PdCl_2(PhCN)_2$, 10 mol% CuI and 20 equiv of piperidine, *i.e.* using a protocol that allows the synthesis of conjugated enynes in high yields from vinyl chlorides and 1-alkynes.[18]



Scheme 4. Retrosynthesis of compound **8**.

Ratovelomanana and Linstrumelle also performed the synthesis of methyl ester **12** of (9*Z*,11*E*,13*Z*)-9,11,13-octadecatrienoic acid (punicic acid), a polyunsaturated fatty acid isolated from the pomegranate,[20] via a three-step reaction sequence (Scheme 5) in which the (*E*)-1-chloro-1-ene-3-yne **4f**, which was obtained in 98% yield by $Pd(PPh_3)_4$/CuI-catalyzed reaction of **3** with 1-hexyne, was a key intermediate.[21]



Scheme 5. Synthesis of methyl ester **12** of punicic acid.

Compound **11**, the direct precursor to **12**, was synthesized in 80% yield by $Pd(PPh_3)_4$/CuI-catalyzed reaction of **4f** with methyl 9-decynoate, which was carried out according to a procedure previously employed for the alkynylation of (*E*)-1-chloro-1-butene (**13**) with 9-decyn-1-yl acetate (**14**) (Figure 1).[21]

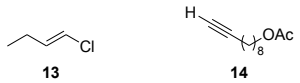


Figure 1. Structures of compounds **13** and **14**.

Finally, reduction of the two triple bonds of **11** with disiamylborane led to stereoisomerically pure **12** in 60% overall yield.[21]

In 1985, an alkynylation sequence similar to that illustrated in Scheme 5 was employed for a three-step synthesis of macrolide **17** in 60.5% overall yield from (*Z*)-1,2-dichloroethene (**1**), methyl 4-pentynoate (**15**) and 3-butyn-1-ol (**16**) (Figure 2).[23]

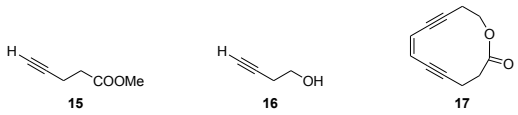
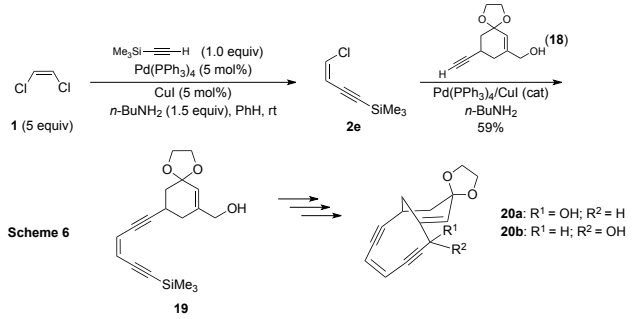


Figure 2. Structures of compounds **15–17**.

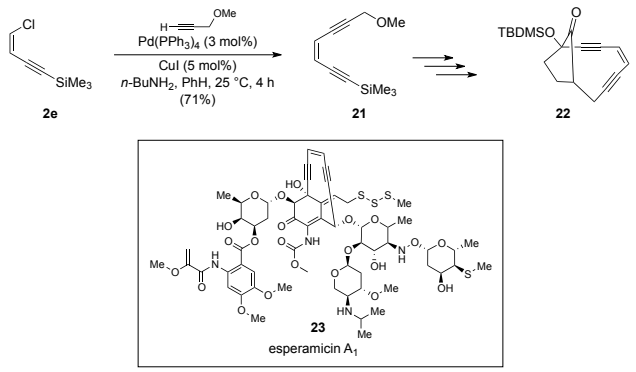
Three years later, (*Z*)-1-chloro-4-trimethylsilyl-1-buten-3-yne (**2e**), which was prepared by coupling of **1** with trimethylsilylacetylene,[15] was reacted with 1-alkyne **18** in the presence of *n*-$BuNH_2$ and catalytic amounts of $Pd(PPh_3)_4$ and CuI to give (*Z*)-1-trimethylsilyl-3-ene-1,5-diyne **19** in 59% yield (Scheme 6).[24]



Scheme 6. Synthesis of compound **19**, a precursor to epimeric carbinols **20a** and **20b**.

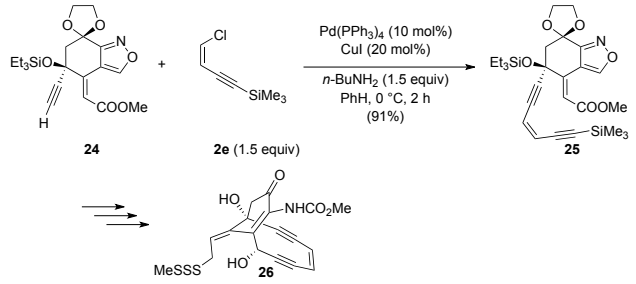
Compound **19** was then employed as a precursor to the epimeric carbinols **20a** and **20b**[24] comprising a deoxyaglycone model for calicheamicins, a class of enediyne antibiotics derived from the bacterium *Micromonospora echinospora*.[25]

Compound **2e** and other (*Z*)-1-chloro-1-en-3-ynes **2**, which were synthesized from (*Z*)-1,2-dichloroethene (**1**) (Scheme 2), were also used in the synthesis of simplified analogues of naturally occurring enediyne anticancer antibiotics and intermediates of the core structure of natural enediynes.[26] Thus, in 1989, Kadow and coworkers[27] assembled enediyne **21** by stereospecific $Pd(PPh_3)_4$/CuI-catalyzed reaction of **2e** with methoxymethylacetylene. Compound **21** was then used to prepare the stable bicycloenediyne **22** (Scheme 7) possessing the core structure of esperamicin A_1 (**23**), an antitumor enediyne antibiotic isolated from *Actinomadura verrucosospora*.[28]



Scheme 7. Synthesis of bicycloenediyne **22**.

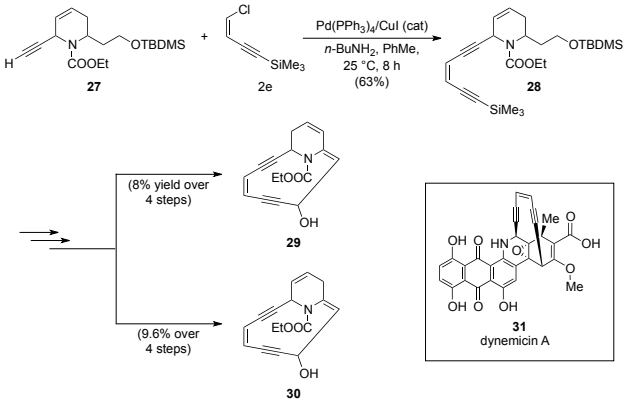
Four years later, the $Pd(PPh_3)_4$/CuI-catalyzed reaction between 1.5 equiv of **2e** and the highly crystalline alkyne **24** was used as a key step of the first enantioselective total synthesis of (-)-calicheamicinone (**26**), the naturally occurring antipode of the calicheamicin aglycone (Scheme 8).[29]



Scheme 8. Synthesis of enediyne **25**, a precursor to compound **26**.

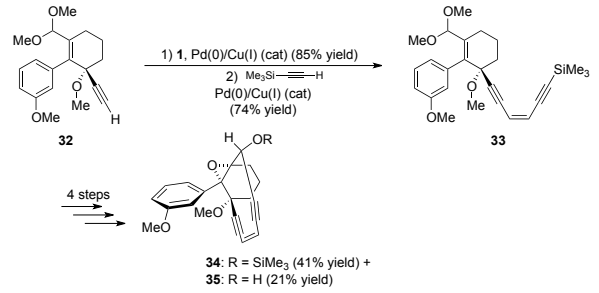
As shown in Scheme 8, the alkynylation of **2e** was carried out at 0 °C in the presence of 1.5 equiv of *n*-$BuNH_2$ to give chemoselectively and stereospecifically enediyne **25** in 91% yield.[29]

In 1994, the highly unstable model compounds **29** and **30** related to dynemicin A (**31**), an antitumor antibiotic isolated from *Micromonospora chersina*[30,31] and *M. globosa* MG 331-hF6[32] that is capable of cleaving double-stranded DNA in the presence of a reducing factor such as NADPH or glutathione, were synthesized using enediyne **28** as a precursor (Scheme 9).[33] Compound **28** was chemoselectively and stereospecifically synthesized in 63% yield by $Pd(PPh_3)_4$/CuI-catalyzed cross coupling of 1-alkyne **27** with **2e** in toluene at 25 °C in the presence of *n*-$BuNH_2$ as base (Scheme 9).[33]



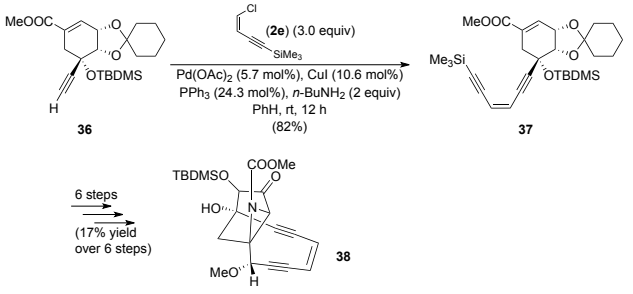
Scheme 9. Synthesis of enediyne **28**, a precursor to compounds **29** and **30**.

In 1995, the dynemicin analogues **34** and **35** that lack the nitrogen atom were synthesized from enediyne **33** which was prepared in 62.9% overall yield by sequential Pd/Cu-catalyzed alkynylation of (*Z*)-1,2-dichlorethene with alkyne **32** and trimethylsilylacetylene (Scheme 10).[34]



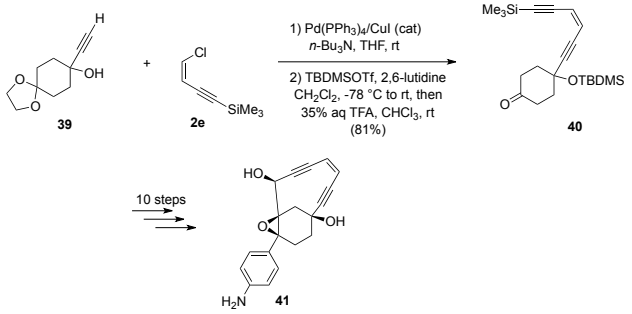
Scheme 10. Synthesis of enediyne **33**, a precursor to dynemycin analogues **34** and **35**.

Again in 1995, (+)-(3*S*,4S,5*S*)-5-*O*-(*t*-butyldimethylsilyl)-3,4-*O*-cyclohexylidene-1-carbomethoxy-5-[6-(trimethylsilyl)-3-hexen-1,5-diynyl]-1-cyclohexene-3,4,5-triol (**37**), which is a precursor to aziridine **38** possessing the bicyclic core of the enediyne antibiotic esperamicin A_1 (**23**), was prepared in 82% yield by $Pd(PPh_3)_4$/CuI-catalyzed reaction of chloroenyne **2e** with 1-alkyne **36** in benzene at room temperature in the presence of 2 equiv of *n*-$BuNH_2$ and 24.3 mol% PPh_3 (Scheme 11).[35]



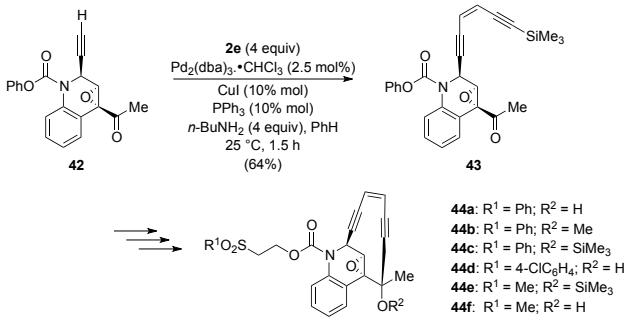
Scheme 11. Synthesis of enediyne **37**, a precursor to aziridine **38**.

Compound **41**, a further esperamicin core analog possessing an epoxide trigger similar to that found in dynemicin, was subsequently synthesized, as outlined in Scheme 12,[36] starting from acyclic (*Z*)-enediyne **40** which was prepared in 81% yield by $Pd(PPh_3)_4$/CuI-catalyzed reaction of the known 1-alkyne **39**[37] with **2e** followed by deprotection of the tertiary alcohol. Surprisingly, compound **41** proved to be relatively stable.[36]



Scheme 12. Synthesis of enediyne **40**, a precursor to the esperamicin analogue **41**.

In 1997, (*Z*)-enediyne **43** was synthesized in 64% yield by $Pd_2(dba)_3$/CuI-catalyzed coupling of alkyne **42** with a large molar excess of chloroenyne **2e** in benzene at 25 °C in the presence of *n*-$BuNH_2$ and PPh_3 (Scheme 13).[38]



Scheme 13. Synthesis of enediyne **43**, a precursor to the bioactive cyclic enediynes **44a-f**.

Compound **43** was then used as an intermediate in the synthesis of the cyclic enediyne compounds **44a-f** (Scheme 13) related to dynemicin. Remarkably, compounds **44a-f**, which are equipped with a 2-(arylsulfonyl)ethoxycarbonyl group or the 2-(methylsulfonyl)ethoxycarbonyl group as a triggering device, showed both cytotoxicity against various tumor cell lines and potent DNA-cleaving activity.[38]

The procedure used for the synthesis of (*Z*)-enediyne **43** was also employed to prepare analogues of this compound that included enediynes **45**,[39] **46**[40] and **47**[40] (Figure 3), which were used as starting materials in the synthesis of a series of simple enediyne analogues of dynemycin A.[39,40]

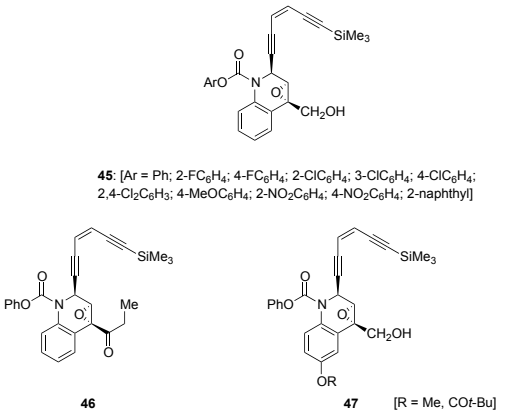
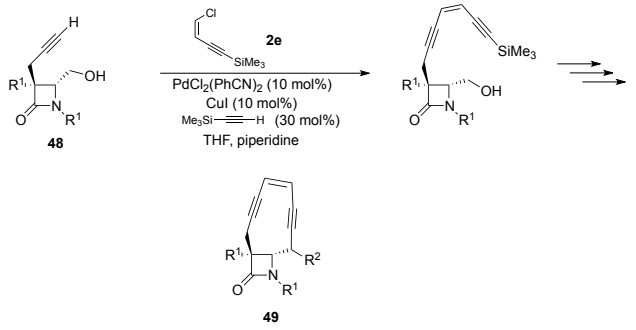


Figure 3. Structures of compounds **45–47**.

In 1995 and in subsequent years, Banfi and Guanti synthesized a series of 10-membered cyclic enediynes of general formula **49**, *trans*-fused with *N*-protected and *N*-unprotected β-lactams, which were named lactenediynes, via reaction schemes involving as a key step the reaction of (*Z*)-chloroenyne **2e** with 3-(prop-2-ynyl)azetidin-2-ones **48** in a mixture of THF and piperidine at room temperature in the presence of catalytic amounts of $PdCl_2(PhCN)_2$, CuI and trimethylsilylacetylene (Scheme 14).[41–45]



Scheme 14. Synthesis of 10-membered cyclic enediynes **49**.

Moreover, a protocol very similar to that employed to prepare compounds **49** was used to prepare lactenediynes **51** from **2e** and 1-alkyne **50** (Figure 4).[46]

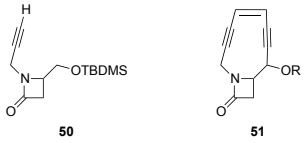
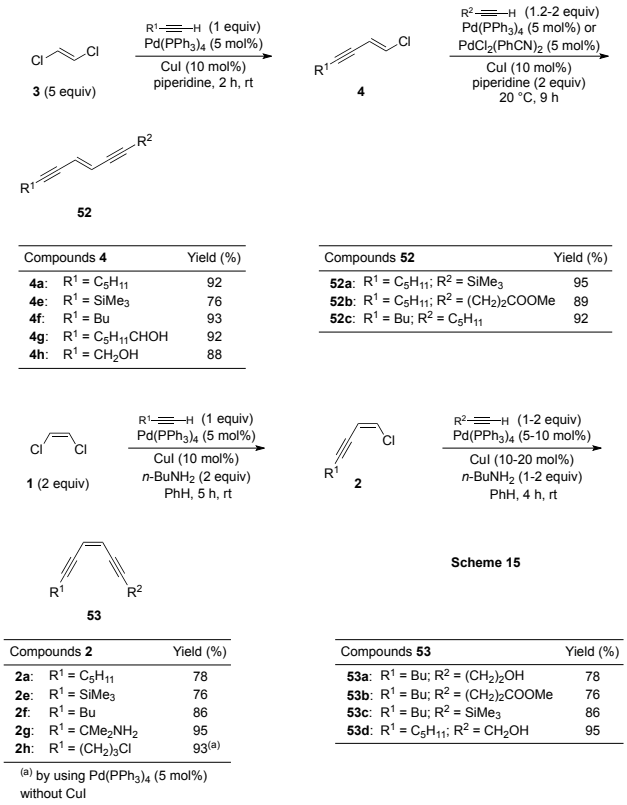


Figure 4. Structures of compounds **50** and **51**.

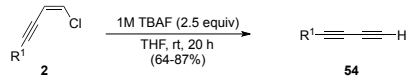
In 1994, Chemin and Linstrumelle reported several examples of Pd/Cu-catalyzed sequential alkynylation reactions of (*Z*)- and (*E*)-1,2-dichloroethene that provided chloroenynes and then enediynes[47] and described that both the nature of the catalyst and the amine were critical for the success of the couplings.



Scheme 15. Synthesis of chloroenynes **4** and **2** and their conversion into enediynes **52** and **53**, respectively.

In particular, (*E*)-1-chloro-1-ene-3-ynes **4** were stereospecifically prepared in high yields by the reaction of 1-alkynes with 5 equiv of (*E*)-1,2-dichloroethene (**3**) in benzene at room temperature in the presence of 5 mol% $Pd(PPh_3)_4$, 10 mol% CuI and 2 equiv of piperidine (Scheme 15).[47] Compounds **4** were then converted stereospecifically in high yields into (*E*)-enediynes **52** by treatment with 1.2–2.0 equiv of 1-alkynes in benzene at 20 °C in the presence of 5 mol% $Pd(PPh_3)_4$ or $PdCl_2(PhCN)_2$, 10 mol% CuI and 2 equiv of piperidine. Noteworthy is that the use of *n*-$BuNH_2$ instead of piperidine proved to be preferable in the synthesis of (*Z*)-1-chloro-1-ene-3-ynes **2** from (*Z*)-1,2-dichloroethene (**1**) and 1-alkynes. It was also found that the molar ratio between **1** and 1-alkynes could be lowered from 5 to 2 and that a further reaction of compounds **2** with 1-alkynes under experimental conditions very similar to those employed for the monoalkynylation of **1** led stereospecifically to (*Z*)-enediynes **53** in excellent yields (Scheme 15).[47]

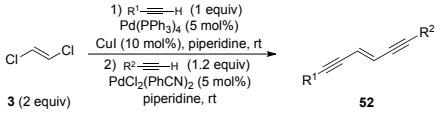
A further demonstration of the synthetic usefulness of compounds **2** was given through their conversion to 1,3-diynes **54** by treatment with TBAF in THF at room temperature (Scheme 16).[48]



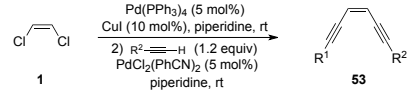
[R^1 = C_5H_{11}; Ph; $(CH_2)_2OH$; CH(OH)Et; $CH(OEt)_2$; CH_2NEt_2; CH_2COOMe; CH_2SEt]

Scheme 16. Synthesis of 1,3-diynes **54** from (*Z*)-12-chloro-1-en-3-ynes **2**.

Stereoisomerically pure unsymmetrically substituted (*E*)- and (*Z*)-enediynes of general formula **52** and **53,** respectively, were also prepared in good yields by a one-pot procedure involving two sequential cross-coupling reactions of alkynes with dichlorethenes **3** and **1**, respectively, in which the monoalkynylation reactions were carried out using a $Pd(PPh_3)_4$/CuI catalyst system and piperidine as the solvent and the alkynylation of the resulting cross-coupling products was performed by the addition of a catalytic amount of $PdCl_2(PhCN)_2$ to the crude reaction mixtures (Scheme 17).[49]



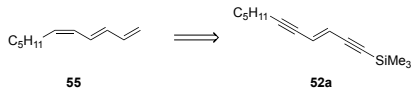
Compounds **52**	Yield (%)
52a: $R^1 = C_5H_{11}$; $R^2 = SiMe_3$	75
52b: $R^1 = C_5H_{11}$; $R^2 = (CH_2)_2OH$	68
52c: $R^1 = C_5H_{11}CH(OH)$; $R^2 = (CH_2)_2OH$	71
52d: R^1 = Ph; R^2 = Ph	62



Compounds **53**	Yield (%)
53a: $R^1 = (CH_2)_4OH$; $R^2 = C_5H_{11}$	78
53b: $R^1 = C_5H_{11}$; $R^2 = SiMe_3$	73
53c: $R^1 = C_5H_{11}CHOH$; $R^2 = CH_2OH$	72
53d: $R^1 = (CH_2)_2OH$; $R^2 = CH_2OH$	62
53e: $R^1 = CMe_2NH_2$; $R^2 = C_5H_{11}$	71
53f: $R^1 = CMe_2NH_2$; $R^2 = C_5H_{11}CHOH$	64

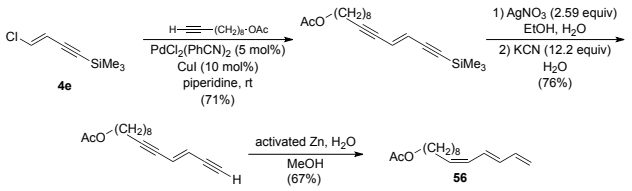
Scheme 17. One-pot synthesis of enediynes **52** and **53**.

In 1995, compound **52a** was used as a precursor to (3*E*,5*Z*)-1,3,5-undecatriene (**55**)[50] (Scheme 18), a compound isolated from the essential oil of galbanum.[51]



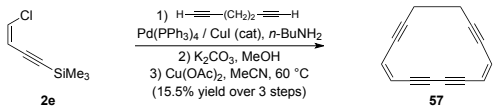
Scheme 18. Retrosynthesis of triene **55**.

In addition, (*E*)-1-chloro-4-trimethylsilyl-1-butene-3-yne (**4e**) was employed as a starting material in a three-step synthesis of (9*Z*,11*E*)-9,11,13-tetradecadien-1-yl acetate (**56**) (Scheme 19),[50] a sex pheromone component of *Stenoma cecropia*,[52] a serious defoliator of oil palm trees in South America.[53]



Scheme 19. Synthesis of (9*Z*,11*E*)-9,11,13-tetradecadien-1-yl acetate (**56**).

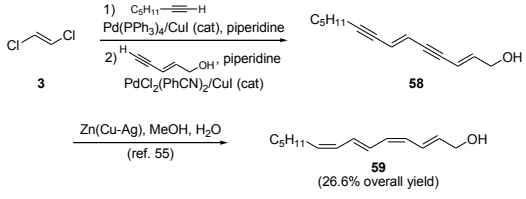
A year earlier, (*Z,Z*)-cyclodeca-3,9-diene-1,5,7,11-tetrayne (**57**) was synthesized from compound **2e** in 15.5% overall yield via a short reaction sequence (Scheme 20)[54] in which **2e** was coupled to 1,5-hexadiyne under standard Pd/Cu catalysis.[24]



Scheme 20. Synthesis of (*Z,Z*)-cyclodeca-1,5,7,11-tetrayne-3,9-diene (**57**).

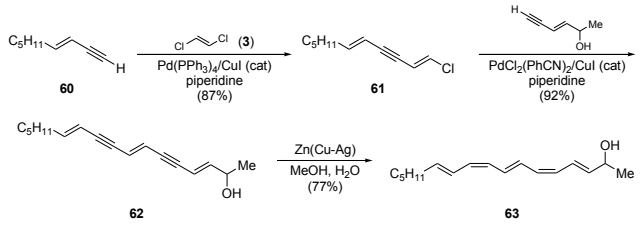
The resulting bis-enediyne was deprotected with K_2CO_3 in MeOH to give the corresponding bis-terminal diyne which was immediately added to a solution of $Cu(OAc)_2$ in MeCN at 60 °C to give compound **57** as a shock-sensitive dark solid (Scheme 20).[54]

Again in 1995, sequential stereospecific alkynylation reactions of (*E*)-1,2-dichloroethene were employed as key steps of the synthesis of stereodefined polyenes, including tetraenes, pentaenes, and heptaenes.[55] Thus, (2*E*,4*Z*,6*E*,8*Z*)-2,4,6,8-tetradecadien-1-ol (**59**) was synthesized in 26.6% overall yield by sequential alkynylation of **3** with 1-heptyne and (*E*)-2-penten-4-yne followed by selective reduction[56] of the triple bonds of the resulting coupling product **58** (Scheme 21).[55]



Scheme 21. Synthesis of (2*E*,4*Z*,6*E*,8*Z*)-2,4,6,8-tetradecadien-1-ol (**59**).

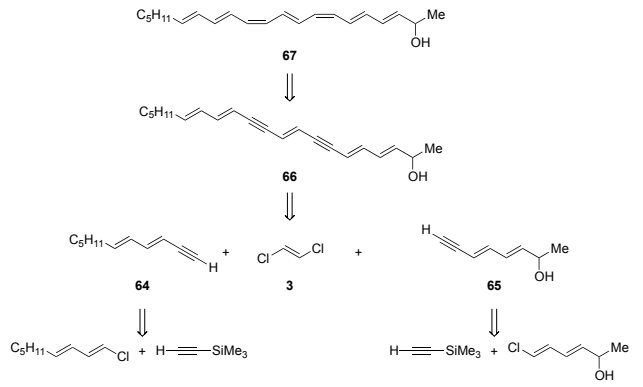
The stereoisomerically pure (3*E*,5*Z*,7*E*,9*Z*,11*E*)-pentaene **64** was prepared in a similar way (Scheme 22).[55]



Scheme 22. Synthesis of pentaene **63**.

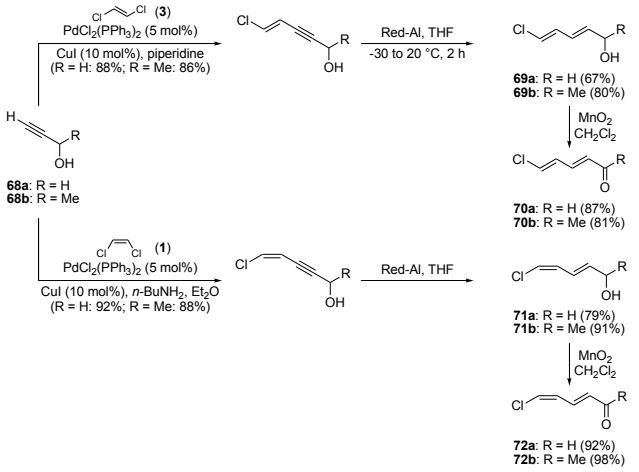
Specifically, the $Pd(PPh_3)_4$/CuI-catalyzed monoalkynylation of **3** with enyne **60** gave chlorodiene **61** in 87% yield. This compound was reacted with (*E*)-3-hexen-5-yn-2-ol in piperidine in the presence of catalytic quantities of $PdCl_2(PhCN)_2$ and CuI, affording the trienediyne **62** in 92% yield, which was reduced to **63** in 77% yield (Scheme 22).[55]

On the other hand, heptaene **67** was chemoselectively and stereospecifically synthesized on the basis of the retrosynthetic analysis outlined in Scheme 23.[55] A key step of this synthesis, which was performed without any protection-deprotection sequence of the alcohol functions, was the preparation of compound **66** by sequential alkynylation of **3** with dieneynes **64** and **65**.



Scheme 23. Retrosynthesis of heptaene **67**.

In 1996, the $PdCl_2(PPh_3)_2$/CuI-catalyzed reactions of **3** with propargyl alcohols **68a** and **68b** in piperidine were employed as key steps of the stereoselective synthesis of chlorodienols **69a** and **69b**, respectively (Scheme 24).[57]



Scheme 24. Synthesis of compounds **70a**, **70b**, **72a**, and **72b**.

Manganese dioxide oxidation of these compounds then led to (*E,E*)-chlorodienal **70a** and (*E,E*)-chlorodienone **70b**, respectively (Scheme 24).[57] On the other hand, (1*Z*,3*E*)-1-chloro-5-hydroxy-1,3-dienols **71a** and **71b** were synthesized by $PdCl_2(PPh_3)_2$/CuI-catalyzed monoalkynylation of (*Z*)-1,2-dichloroethene (**1**) with propargyl alcohols **69a** and **69b**, respectively, in Et_2O in the presence of *n*-$BuNH_2$ as the base, followed by selective reduction of the resulting (*Z*)-1-chloro-1-en-3-ynes with Red-Al. Manganese dioxide oxidation of **71a** and **71b** eventually led to dienals **72a** and **72b**, respectively (Scheme 24).[57]

A similar protocol was employed to prepare chlorodienynols **74a** and **74b** from **1** and enynols **73a** and **73b**, respectively, as well as chlorodienols **75a** and **75b** by coupling of **3** with **73a** and **73b**, respectively (Figure 5).[57] Compounds **74a** and **74b** were then used as precursors to chlorotrienal **76a** and chlorotrienone **76b**, respectively, via a four-step reaction sequence involving their reduction by Red-Al® into trienols, a rapid Pd(II)-catalyzed rearrangement of the corresponding acetates, and hydrolysis of the resulting acetoxytrienes followed by MnO_2 oxidation.[57] Compounds **77a** and **77b** (Figure 5) were similarly prepared from **75a** and **75b**, respectively.[57]

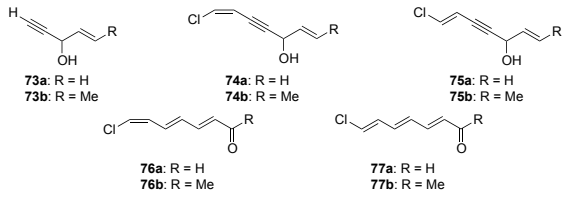
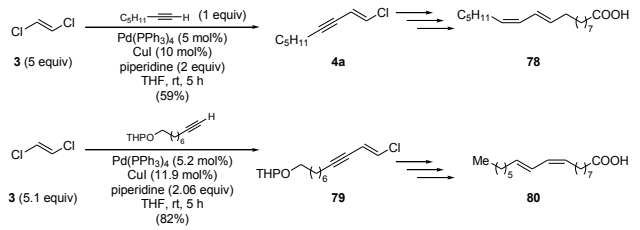


Figure 5. Structures of compounds **73a,b**, **74a,b**, **75a,b**, **76a,b**, and **77a,b**.

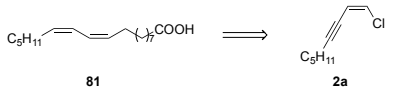
In 2001, (*E*)-1-chloro-1-nonen-3-yne (**4a**), which was prepared in 59% yield by treatment of 1-heptyne with 5 equiv of **3** in THF in the presence of catalytic amounts of

$Pd(PPh_3)_4$ and CuI and 2 equiv of piperidine, was used as an intermediate in the synthesis of (10*E*,12*Z*)-[1-^{14}C]-octadeca-10,12-dienoic acid (**78**) (Scheme 25).[58]



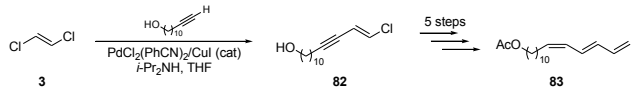
Scheme 25. Synthesis of dienoic acids **78** and **80**.

Moreover, (*E*)-1-chloro-1-en-3-yne **79**, which was obtained in 82% yield by $Pd(PPh_3)_4$/CuI-catalyzed reaction of **3** with 2-non-8-ynyloxy-tetrahydropyran in THF at room temperature using piperidine as base, was employed as the starting material in a convergent synthesis of (9*Z*,11*E*)-[1-^{14}C]-octadeca-9,11-dienoic acid (**80**) (Scheme 25).[58] On the other hand, (*Z*)-1-chloro-1-nonen-3-yne (**2a**), which was prepared in 80% yield by $Pd(PPh_3)_4$/CuI-catalyzed reaction of **1** with 1-heptyne in THF at room temperature using piperidine (2 equiv) as base, was employed as a precursor to (10*Z*,12*Z*)-[1-^{14}C]-octadeca-10,12-dienoic acid (**81**) (Scheme 26).[58]



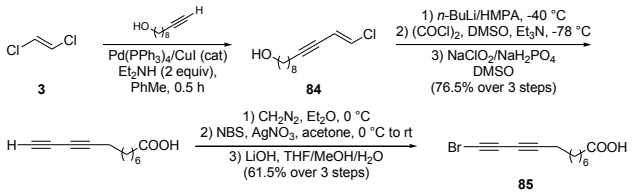
Scheme 26. Retrosynthesis of compound **81**.

In 2004, (11*Z*,13*E*)-11,13,15-hexadecatrien-1-yl acetate (**83**), a sex pheromone component of oak processionary moth, *Thaumotopoea processionaria,* was synthesized via a seven-step reaction sequence in which (*E*)-1-chloro-5-hydroxy-1-tetradecen-3-yne (**82**), a key intermediate, was prepared by $PdCl_2(PPh_3)_2$/CuI-catalyzed reaction of **3** with 11-dodecyn-1-ol in the presence of *i*-Pr_2NH as base (Scheme 27).[59] Unfortunately, the experimental conditions of the process were not reported.



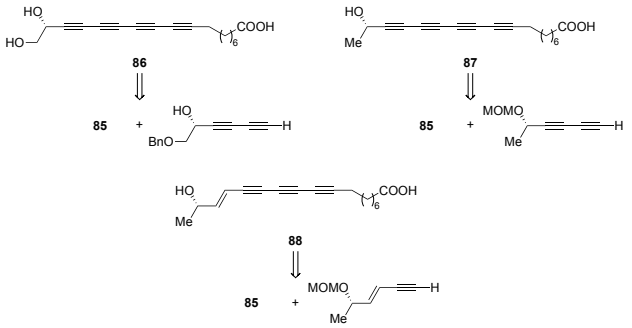
Scheme 27. Synthesis of the sex pheromone component **83** from **3**.

In 2006, (*E*)-1-chloro-1-en-3-yne **84** was synthesized in 80% yield by the reaction of equimolar amounts of **3** and 10-hydroxy-1-decyne in toluene in the presence of catalytic quantitites of $Pd(PPh_3)_4$ and CuI and 2 equiv of Et_2NH (Scheme 28).[60] Compound **84** was then converted into bromodiyne **85** in 47% overall yield via a six-step reaction sequence (Scheme 28).[60] Finally, compound **85** was employed as a building block in the total synthesis of three polyacetylenic natural products, (*S*)-18-hydroxyminquartynoic acid (**86**), (*S*)-minquartynoic acid (**87**), and (*E*)-15,16-dihydrominquartynoic acid (**88**), which was accomplished on the basis of the retrosynthetic analysis outlined in Scheme 29.[60] Compounds **86–88** were isolated from a $CHCl_3$ extract of the twigs of *Ochanostachys amantea* from Southeast Asia[61] and compound **87** was also isolated from the stembark of *Minquartia guianensis*.[62]



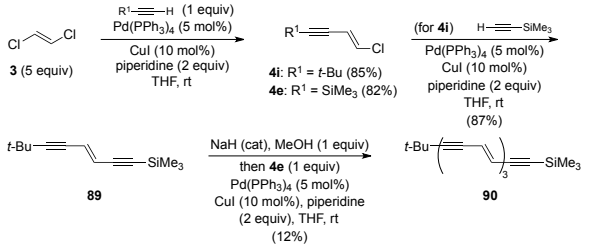
Scheme 28. Synthesis of bromodiyne **85**.

Cadiot-Chodkiewicz cross-coupling reactions[63] were used as key steps for the construction of the tetraene units of **86** and **87** and the triyne unit of **88**.[60]



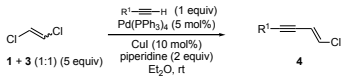
Scheme 29. Retrosynthesis of the naturally occurring polyynes **86–88**.

In 2003, a route involving sequential Pd/Cu-catalyzed alkynylation reactions of (*E*)-1,2-dichloroethene (**3**) was employed to prepare oligoenyne **90** (Scheme 30).[64] Specifically, the reaction between 5 equiv of **3** with 1 equiv of *t*-butylacetylene in THF in the presence of 2 equiv of piperidine, 5 mol% $Pd(PPh_3)_4$ and 10 mol% CuI gave (*E*)-1-chloro-1-en-3-yne **4i** in 85% yield. An analogous reaction between **3** and trimethylsilylacetylene produced compound **4e** in 82% yield. Compound **4i** was then converted into (*E*)-enediyne **89** in 87% yield by coupling with trimethylsilylacetylene in the presence of piperidine and a $Pd(PPh_3)_4$/CuI catalyst system. Finally, removal of the trimethylsilyl group in **89** and further $Pd(PPh_3)_4$/CuI-catalyzed reaction of the resulting desilylated compound with **4e** gave compound **90** in 12% yield (Scheme 30).[64]



Scheme 30. Synthesis of oligoenyne **90**.

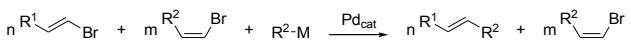
A year earlier, Alami and coworkers had investigated the $Pd(PPh_3)_4$/CuI-catalyzed monoalkynylation of a 1:1 mixture of (*Z*)- and (*E*)-1,2-dichloroethene and found that, when 5 equiv of (*Z*)/(*E*)-1,2-dichloroethene were reacted with 1-alkynes in Et_2O at room temperature in the presence of 5 mol% $Pd(PPh_3)_4$, 10 mol% CuI and 2 equiv of piperidine, (*E*)-1-chloro-1-en-3-ynes **4** were obtained in high yields and with high stereoisomeric purity, except in the case of phenylacetylene (Scheme 31).[65] They also observed that a change of the amine had no significant effect on the reaction.



	R^1	Yield (%)	*E*/*Z*
4a	*n*-C_5H_{11}	90	98/2
4i	Ph	80	90/10
4j	$(CH_2)_8OH$	85	97/3
4k	CH_2OH	90	98/2
4g	$C_5H_{11}CHOH$	70	95/5
4l	CH_2NMe_2	75	95/5
4m	$CH_2CH(C_5H_{11})OH$	71	98/2
4n	$(CH_2)_2OH$	88	95/5
4o	CHPhOH	78	95/5

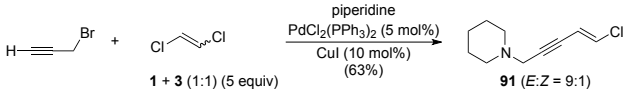
Scheme 31. Stereoselective synthesis of (*E*)-chloroenynes **4**.

These results clearly demonstrated that (*E*)-1,2-dichloroethene (**3**) is remarkably more reactive than its *Z*-stereoisomer. On the other hand, similar trends in selectivity had already been observed in Pd-catalyzed cross-coupling reactions of (*E*)- and (*Z*)-1-bromo-1-alkenes, where the (*E*)-stereoisomers were found to undergo preferentially intermolecular Pd-catalyzed cross-coupling reactions with organometallic compounds to give (*E*)-configured cross-coupling products having high stereoisomeric purity (Scheme 32).[66]



Scheme 32. Stereoselective cross-coupling reactions involving (*E*)/(*Z*)-1-bromo-1-alkenes.

More recently, Alami and coworkers have reported a catalytic domino three-component process involving the reaction of 1 equiv of propargyl bromide with 5 equiv of a 1:1 mixture of compounds **1** and **3** in piperidine at 80 °C in the presence of 5 mol% $PdCl_2(PPh_3)_2$ and 10 mol% CuI.[67] The reaction gave selectively a 9:1 mixture of the (*E*)- and (*Z*)-stereoisomers of compound **91** in 63% yield (Scheme 33).[67]

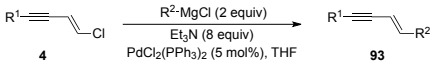


Scheme 33. Stereoselective synthesis of compound **91**.

Alami and coworkers also investigated some synthetic applications of (*E*)-1-chloro-1-en-3-ynes **4** involving Pd-catalyzed reactions and, in this context, they found that treatment of (*E*)-1-chloro-4-phenyl-1-buten-3-yne (**4i**) with propargyl bromide in piperidine in the presence of 5 mol% $PdCl_2(PPh_3)_2$ and 10 mol% CuI provided (*E*)-enediyne **92** (Figure 6) in 76% yield.[67]

Figure 6. Structures of compounds **4i** and **92**.

Moreover, they showed that the reaction of chloroenynes **4** with Grignard reagents in the presence of $PdCl_2(PhCN)_2$ and Et_3N gave stereoisomerically pure cross-coupling products **93** in modest-to-excellent yields (Scheme 34).[68,69]

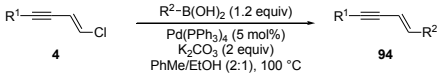


93	R^1	R^2	Yield (%)
a	C_5H_{11}	4-MeC_6H_4	95
b	C_5H_{11}	(*Z*)-Me-CH=CH	90
c	C_5H_{11}	CH_2=CH	71
d	C_5H_{11}	CH_2=CMe	62
e	C_5H_{11}	C_8H_{17}	15
f	$SiMe_3$	Ph	70
g	Ph	Ph	93
h	$C_5H_{11}CH(OTBDMS)$	Ph	76
i	$(CH)_3Cl$	Ph	77
j	$(CH)_3COOEt$	Ph	51
k	4-$MeOC_6H_4$-CH=CH	Ph	81

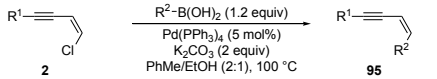
Scheme 34. Stereoselective synthesis of enynes **93**.

A stereocontrolled process involving the Pd-catalyzed Suzuki-type reaction between (*E*)- or (*Z*)-1-chloro-1-en-3-ynes and boronic acids was also recently developed.[70] The procedure (Scheme 35) proved to be general and allowed good access to several functionalized (*E*)- and (*Z*)-1-en-3-ynes **94** and **95**, respectively, in good-to-excellent yields with excellent stereoselectivities.[70]

Moreover, high yields of conjugated enynes **94** and **95** bearing a functional group were obtained with complete stereoselectivity when chloroenynes **4** and **2**, respectively, were reacted under Pd catalysis with a molar excess of the organozincate reagents generated *in situ* by the reaction of alkyl and aryl Grignard compounds with less-than-molar amounts of $ZnCl_2$ (Scheme 36).[71]

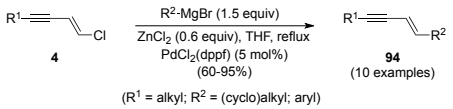


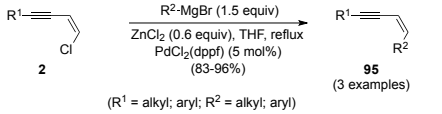
94	R^1	R^2	Yield (%)	*E*/*Z*
a	2-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	94	100/0
b	Ph	4-MeOC$_6$H$_4$	79	100/0
c	C$_5$H$_{11}$	4-MeOC$_6$H$_4$	81	100/0
d	2-MeOC$_6$H$_4$	2-MeOC$_6$H$_4$	85	98/2
e	2-MeOC$_6$H$_4$	3,4 -H$_2$C(O)(O)C$_6$H$_3$	88	98/2
f	2-MeOC$_6$H$_4$	2-naphthyl	81	97/3
g	2-MeOC$_6$H$_4$	4-ClC$_6$H$_4$	86	100/0
h	2-MeOC$_6$H$_4$	4-AcC$_6$H$_4$	84	97/3
i	2-MeOC$_6$H$_4$	4-CHOC$_6$H$_4$	71	91/9
j	2-MeOC$_6$H$_4$	3-NO$_2$C$_6$H$_4$	71	95/5
k	2-MeOC$_6$H$_4$	3-thienyl	93	100/0
l	2-MeOC$_6$H$_4$	(*E*)-1-pentenyl	78	95/5



95	R^1	R^2	Yield (%)	*E*/*Z*
a	2-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	76	0/100
b	2-EtOOCC$_6$H$_4$	4-MeOC$_6$H$_4$	83	3/97
c	C$_5$H$_{11}$	4-MeOC$_6$H$_4$	83	0/100

Scheme 35. Synthesis of enynes **94** and **95** from chloroenynes **4** and **2**, respectively, by Suzuki-type reactions.

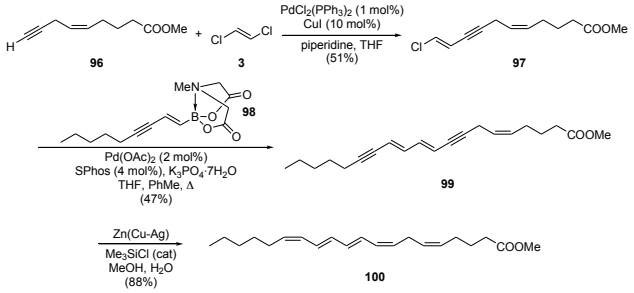




Scheme 36. Synthesis of enynes **94** and **95** from chloroenynes **4** and **2**, respectively, by Pd-catalyzed reactions with organozincate reagents.

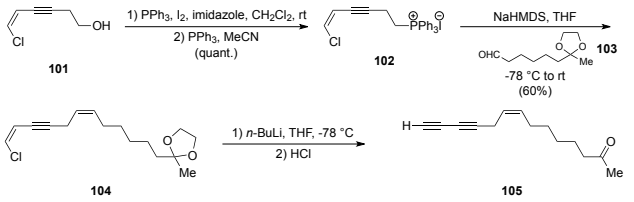
Recently, the methyl ester **100** of bosseopentaenoic acid [(5*Z*,8*Z*,10*E*,12*E*,14*Z*)-5,8,19,12,14-eicosapentaenoic acid], a compound isolated from the red marine alga *Lithothamnion corallioides*,[72] was synthesized via a route involving, as the first step, the $PdCl_2(PPh_3)_2$/CuI-catalyzed monoalkynylation of (*E*)-1,2-dichloroethene (**3**) with 1-alkyne **96** in piperidine (Scheme 37).[73] A $Pd(OAc)_2$/S-Phos-catalyzed Suzuki-Miyaura reaction of the resulting cross-coupling product **97** with the protected boronate ester **98** using Burke's conditions[74] yielded trienediyne **99** in 47% yield. Finally, stereoselective reduction of the triple bonds of **100**, which was achieved with Zn(Cu/Ag)[56,75] in aqueous MeOH in the presence of a catalytic quantity of Me_3SiCl, gave compound **101** in 88% yield (Scheme 37).[73]

Another natural compound, (*Z*)-tetradeca-8-en-11,13-diyn-2-one (**105**), a ketone isolated from *Echinacea pallida* which exhibits a range of biological activitites,[76] was recently synthesized using (*Z*)-1-chloro-6-hydroxy-1-hexen-3-yne (**101**) as precursor (Scheme 38).[77]



Scheme 37. Synthesis of the methyl ester **100** of bosseopentaenoic acid.

Compound **101**, which was prepared in one step from **1** and 3-butyn-1-ol according to the procedure of Kende and Smith,[24] was converted in two steps into the phosphonium salt **102**. Compound **102** underwent a *cis*-selective Wittig reaction with aldehyde **103** to give chlorodiene **104** in 60% yield. Finally, treatment of **104** with *n*-BuLi in THF at -78 °C followed by removal of the ketal protecting group with HCl provided ketone **105** in 24% overall yield (Scheme 38).[77]



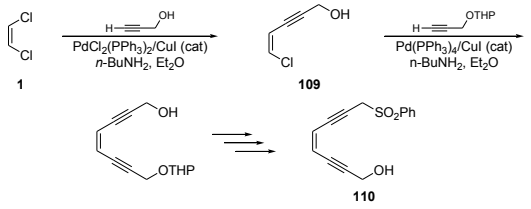
Scheme 38. Synthesis of naturally occurring ketone **105**.

Excellent site selectivity was unexpectedly observed by McGaffin and de Meijere in the $Pd(PPh_3)_4$/CuI-catalyzed reaction of 2-ethoxy-1-ethynylcyclopropane (**106**) with an equimolar amount of (*Z*)-1,2-dichloroethene (**1**) in a 14:1 mixture of benzene and *i*-Pr_2NH at 20 °C.[78] In fact, the cross-coupling reaction (Scheme 39) provided (Z)-1-chloro-1-en-3-yne **107** in 34% yield accompanied by 40% yield of the homocoupled bisacetylene **108**, without any detectable amount of the bisalkynylation derivative of **1**.[78] According to a previous report,[79] the formation of compound **108** was believed to be catalyzed by traces of oxygen.

Scheme 39. Site-selective synthesis of compound **108**.

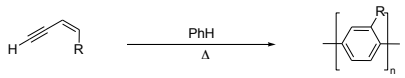
In 1996, (Z)-enediyne **110** was synthesized through a five-step reaction sequence involving the $PdCl_2(PPh_3)_2$/CuI-catalyzed monoalkynylation of **1** with propargyl alcohol in Et_2O in the presence of *n*-$BuNH_2$ as the base and the subsequent $Pd(PPh_3)_4$/CuI-catalyzed cross coupling of the resulting stereoisomerically pure (*Z*)-1-chloro-1-en-3-yne

109 with THP-protected propargyl alcohol in Et_2O in the presence of *n*-$BuNH_2$ (Scheme 40).[80] Unfortunately, the experimental details of the reactions summarized in Scheme 40 were not reported. It also deserves to be mentioned that (*Z*)-enediyne **110** was found to exhibit DNA-cleaving properties at 37 °C in pH 8.0 as well as potent cytotoxicity against human carcinoma cells.[80]



Scheme 40. Synthesis of (*Z*)-enediyne **110**.

In 1997, (Z)-3-en-1,5-diynes **111**, which were prepared according to the procedure reported in reference 46 by sequential alkynylation of **1** with trimethylsilylacetylene and a different 1-alkyne and subsequent desilylation, were converted into the corresponding poly(*p*-phenylene)s **112** by thermolysis in benzene (Scheme 41).[81] No exogenous chemical catalysts or reagents were required for the process.

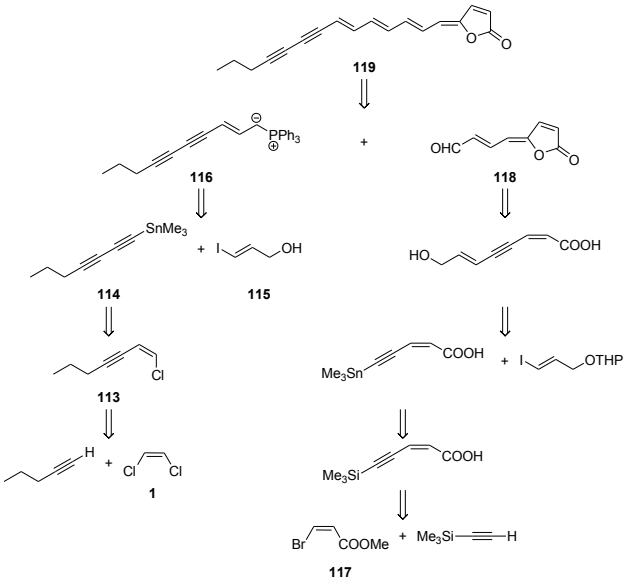


[R = *n*-C_6H_{13}; Ph; 4-C_6H_4-Ph; 2-C_6H_4-Ph; 4-C_6H_4-*t*-Bu; 1-naphthyl; 9-anthryl]

Scheme 41. Synthesis of poly(*p*-phenylene)s **112**.

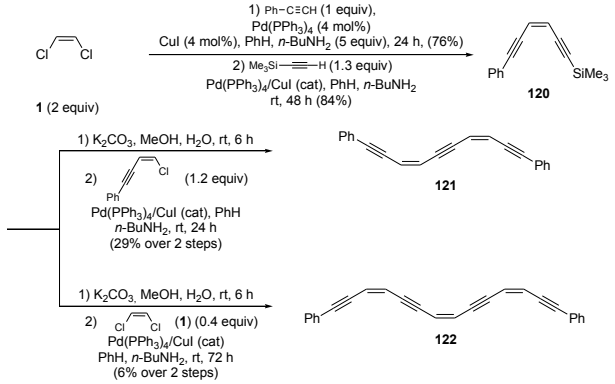
In 2000, dihydroxerulin (**119**), a noncytotoxic inhibitor of the biosynthesis of cholesterol which was isolated from cultures of *Xerula melanotricha,*[82] was stereoselectively synthesized according to the retrosynthetic analysis outlined in Scheme 42.[83,84] A key step of this approach was the Wittig reaction between aldehyde **118** and the phosphonium ylide **116**. Compound **118** was prepared through a reaction sequence in which the first step was a $PdCl_2(PPh_3)_2$/CuI-catalyzed Sonogashira reaction of methyl (*Z*)-3-bromopropenoate (**117**) with trimethylsilylacetylene in acetonitrile in the presence of Et_3N as base. On the other hand, compound **116** was conveniently obtained via a short reaction sequence involving the synthesis of (*Z*)-chloroenyne **113** in 90% yield from **1** and 1-pentyne and a Stille reaction between (*E*)-3-iodo-2-propen-1-ol (**115**) and diynyltrimethylstannane **114** prepared from **113**.[83]

In 2001, a strategy based on the Sonogashira $Pd(PPh_3)_4$/CuI-catalyzed C(sp)–C(sp^2) coupling of 1-alkynes with (*Z*)-chlorovinyl chlorides was employed for the construction of *cis*-dioligoacetylenes.[85]



Scheme 42. Synthesis of dihydroxerulin (**119**).

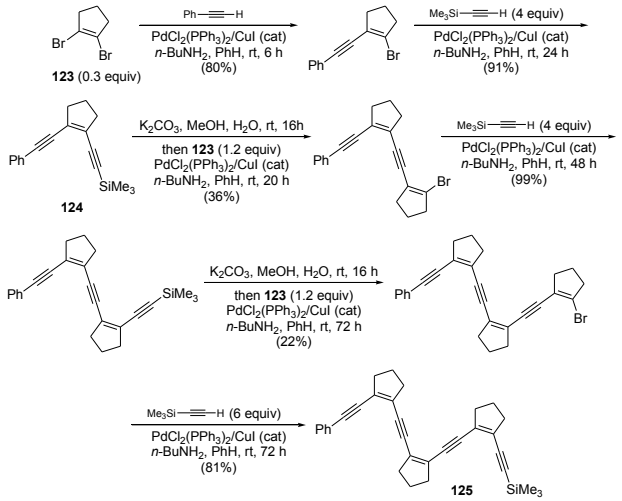
Thus, (*Z*)-1-trimethylsilyl-6-phenyl-3-hexen-1,5-diyne (**120**) was prepared in 63.8% yield by sequential $Pd(PPh_3)_4$/CuI-catalyzed alkynylation of **1** with phenylacetylene and trimethylsilylacetylene in benzene at room temperature in the presence of *n*-$BuNH_2$ as base (Scheme 43).



Scheme 43. Synthesis of *cis*-oligoenynes **121** and **122**.

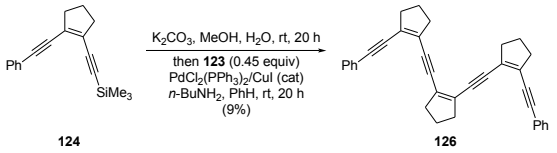
Compound **120** was then employed to prepare *cis*-oligoenynes **121** and **122**. Specifically, the $Pd(PPh_3)_4$/CuI-catalyzed cross coupling between 1.2 equiv of (*Z*)-1-chloro-4-phenyl-1-buten-3-yne and the desilylation derivative of **120** gave compound **121** in modest yield (Scheme 43). On the other hand, compound **122** was obtained in 6% overall yield by desilylation of **120** followed by a cross coupling reaction between the resulting 3-en-1,5-diyne with 0.4 equiv of **1** in benzene at room temperature in the presence of *n*-$BuNH_2$ and catalytic amounts of $Pd(PPh_3)_4$ and CuI (Scheme 43). It should be noted that **122** was found to undergo *cis/trans* stereomutation in solution,[85] but this stereomutation could be avoided by incorporation of its ene

moiety into ring systems, as in the case of compounds **125** and **126** (Schemes 44 and 45).[85] Scheme 44 illustrates the multistep stereocontrolled synthesis of configurationally stable **125**, starting from phenylacetylene and 1,2-dibromocyclopentene (**123**).[85]



Scheme 44. Synthesis of configurationally stable *cis*-oligoenyne **125**.

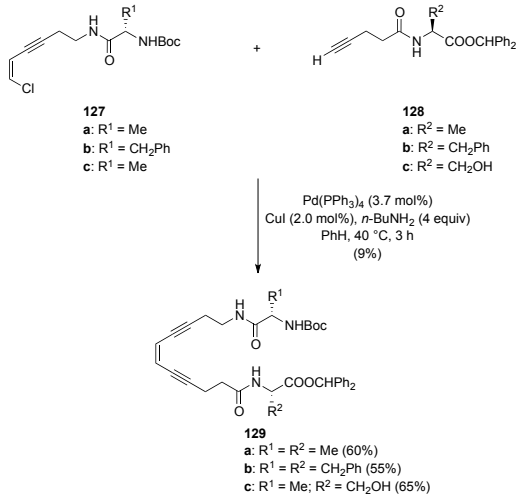
A key intermediate of this synthesis was enediyne **124**, which was also employed to prepare compound **126** (Scheme 45) in 9% yield.[85]



Scheme 45. Synthesis of configurationally stable *cis*-oligoenyne **126**.

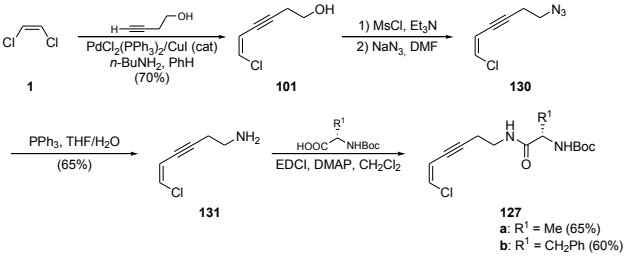
In 2002, (*Z*)-enediynyl tripeptides **129a-c** in fully protected form were synthesized without racemization by $Pd(PPh_3)_4$/CuI-catalyzed reaction of (*Z*)-1-chloro-1-en-3-ynes **127a-c** with acetylenic amides **128a-c** in benzene at 40 °C in the presence of *n*-$BuNH_2$ (Scheme 46).[86]

Compound **131**, a precursor to compounds **127a,b**, had been previously synthesized according to the reaction sequence illustrated in Scheme 47 which began with the $PdCl_2(PPh_3)_2$/CuI-catalyzed monoalkynylation of **1** with 3-butyn-1-ol.[87] The resulting (*Z*)-1-chloro-1-en-3-yne **101** was converted into azide **130** via mesylation followed by treatment with NaN_3. Subsequent reduction with PPh_3 in THF/H_2O gave amine **131** in 65% yield.[87]



Scheme 46. Synthesis of compounds **129a-c**.

Finally, compound **131** was coupled to the required *N*-*t*-Boc-amino acids in the presence of EDCI[88] to produce compounds **127a** and **127b** in 65% and 60% yield, respectively (Scheme 47).[86]



Scheme 47. Synthesis of of compounds **127a,b**.

Interestingly, (*Z*)-chloroenyne **101** proved also to be a useful intermediate in the synthesis of 1-(*p*-tosyl)-1-azacyclodec-5-en-3,7-diyne (**132**),[89] an *N*-substituted 10-membered monocyclic enediyne, which was found to undergo Bergman cyclization[90] at 23 °C with a half life of 72 h.[89]

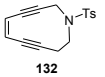
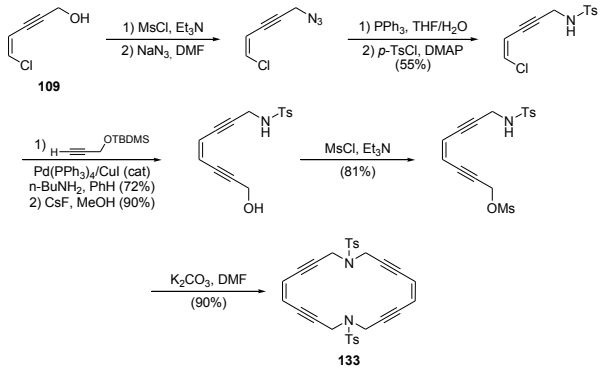


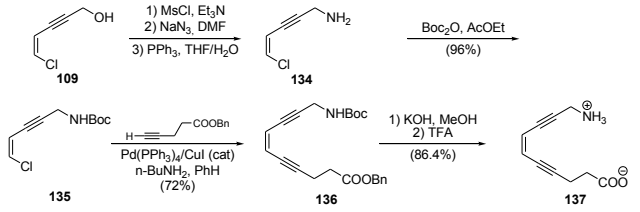
Figure 7. Structure of compound **132**.

Moreover, in 2000, compound **133**, a macrocyclic 18-membered bis(diazaenediyne), was efficiently synthesized from (*Z*)-1-chloro-5-hydroxy-1-penten-3-yne (**109**)[80] via the eight-step reaction sequence illustrated in Scheme 48.[89a]



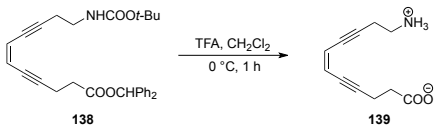
Scheme 48. Synthesis of macrocyclic compound **133**.

Compound **109** was also employed as the starting material in the synthesis of enediynyl amino acid **137** (Scheme 49).[91] Specifically, **109** was converted in three steps into amine **134**, which was immediately protected as the Boc derivative **135**. A $Pd(PPh_3)_4$/CuI-catalyzed reaction between **137** and benzyl 4-pentynoate gave the protected enediynyl amino acid **136** in 72% yield. Removal of the benzyl ester of **136** by stirring in an alkaline MeOH solution followed by final deprotection with trifluoroacetic acid gave **137** in 86.4% yield (Scheme 49).[91]



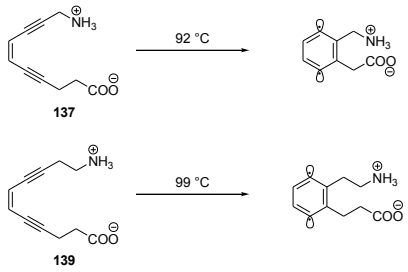
Scheme 49. Synthesis of amino acid **137**.

Amino acid **139**, a higher homologue of **137**, was synthesized by treatment of enediyne **138** with trifluoroacetic acid in CH_2Cl_2 at 0 °C (Scheme 50).[86]



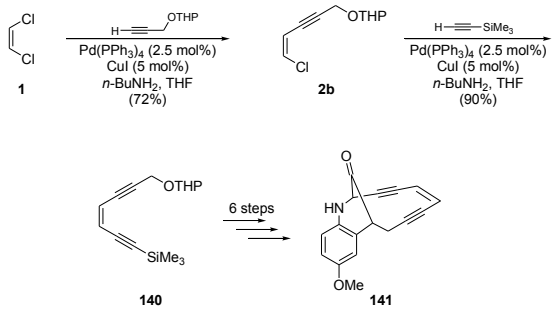
Scheme 50. Synthesis of amino acid **139** from compound **138**.

A comparison between the thermal stability of **137** and that of **139** towards Bergman cyclization allowed a demonstration for the first time of the effect of H-bonds and electrostatic interactions in lowering the activation energy of the Bergman cyclization (Scheme 51).[91]



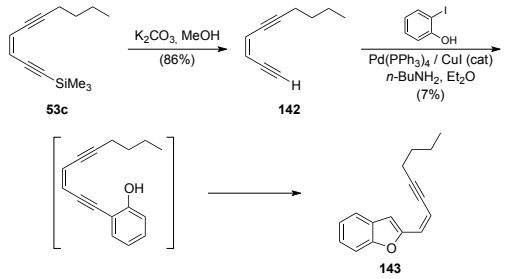
Scheme 51. Thermal stability of **137** and **139** towards Bergman cyclization.

In 1997, as a part of another study on enediyne antitumor agents, the 3-keto-10-azabicyclo[7.3.1]enediyne core structure **141** of dynemicin A (**31**) was synthesized, starting from (*Z*)-1,2-dichloroethene (**1**) (Scheme 52) via a reaction sequence involving the preparation of stereoisomerically pure **2b** by highly selective monoalkynylation of **1** with THP propargyl ether, followed by the conversion of **2b** into (*Z*)-3-en-1,5-diyne **140** by $Pd(PPh_3)_4$/CuI-catalyzed reaction with trimethylsilylacetylene. Finally, a six-step reaction sequence allowed the isolation of compound **141**, which was found to exhibit modest *in vitro* and *in vivo* antitumor activity.[92]



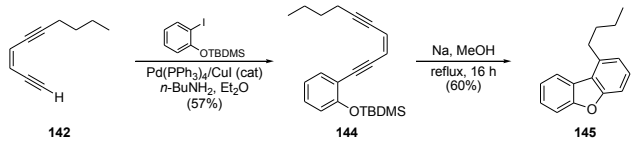
Scheme 52. Synthesis of enediyne **141**.

More recently, (*Z*)-enynylbenzofuran **142** was synthesized in two steps from (*Z*)-enediyne **52c** (Scheme 53),[93] which was prepared in 36.2% overall yield by sequential Pd/Cu-catalyzed alkynylation of **1** with 1-hexyne and trimethylsilylacetylene, according to the procedure of Chemin and Linstrumelle.[46] Desilylation of **52c** with K_2CO_3 in MeOH gave compound **142**, which was coupled with 2-iodophenol in Et_2O in the presence of *n*-$BuNH_2$ and catalytic quantities of $Pd(PPh_3)_4$ and CuI to give **143** in 7% yield (Scheme 53).[93] The formation of the benzofuran ring presumably involved a cyclization process, catalyzed by the acidic phenol group, of the Sonogashira-type coupling derivative obtained from **142** and 2-iodophenol.[93]



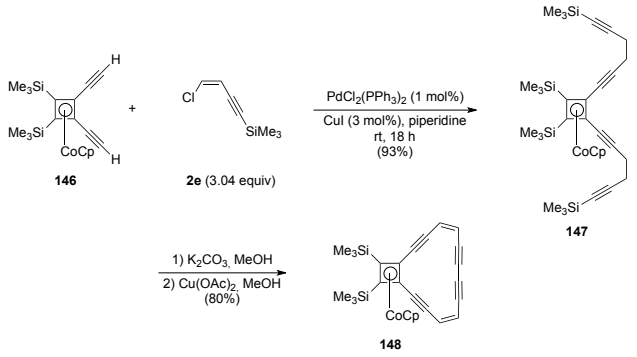
Scheme 53. Synthesis of compound **143**.

5-Butylbenzofuran (**145**) was instead obtained in 34.2% overall yield by a two-step reaction sequence in which the first step was the $Pd(PPh_3)_4$/CuI-catalyzed reaction of (*Z*)-3-decen-1,5-diyne (**142**) with the *t*-butyldimethylsilyl ether of 2-iodophenol, which provided enediyne **144** in 57% yield (Scheme 54).[93] Anionic cycloaromatization of **144** with sodium methoxide in MeOH under reflux then gave compound **145** in 60% yield (Scheme 54).[93]



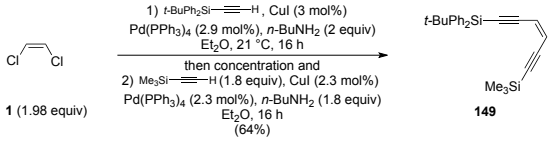
Scheme 54. Synthesis of 5-butylbenzofuran (**145**).

In 2001, dehydro[14]annulene **148** was synthesized by $PdCl_2(PPh_3)_2$/CuI-catalyzed bis-coupling of Vollhardt's cyclobutadiene **146** to (*Z*)-chloroenyne **2e** in piperidine.[94a] The reaction gave tetrayne **147** in 93% yield. Removal of the C(sp)-silyl groups from **147** followed by ring closure with $Cu(OAc)_2$ in acetonitrile utilizing a procedure by Vögtle[94b] then furnished **148** in 80% yield after chromatography. (Scheme 55).[94a]



Scheme 55. Synthesis of dehydro[14]annulene **148**.

Some years before, (*Z*)-1-trimethylsilyl-6-*t*-butyldiphenylsilylhex-3-en-1,5-diyne (**149**) was obtained in 64% yield by sequential $Pd(PPh_3)_4$/CuI-catalyzed alkynylation of **1** with *t*-butyldiphenylsilylacetylene and trimethylsilylacetylene in Et_2O at 21°C in the presence of *n*-$BuNH_2$ (Scheme 56).[95,96]



Scheme 56. Synthesis of 3-en-1,5-diyne **149**.

Enediyne **150** (Figure 8) was similarly prepared from **1**, triisopropylsilylacetylene and trimethylsilylacetylene.[95,96] Compounds **149** and **150** were then used as building blocks in the preparation of enediyne **151** (Figure 8),[95–97] a substance that mimics the enediyne antibiotics, esperamicin and calicheamicin. Moreover, compound **152** (Figure 8), which was obtained in high yield by desilylation of **150** with K_2CO_3 in a mixture of MeOH and benzene at room temperature,[96] was employed as a building block in the synthesis of the bicyclo[7.3.1]trideca-4,9-dien-2,6-diyne **153**[98] and racemic calicheamicinone (**154**) (Figure 8).[99] Compound **153** is a calicheamicin-taxoid mimic that possesses the Taxotere® side chain and an enediyne core. On the other hand, compound **154** is the racemic form of the aglycon of calicheamicin γ_1, an antitumor antibiotic isolated from fermentations of *Micromonospora echinospora* sp.[100]

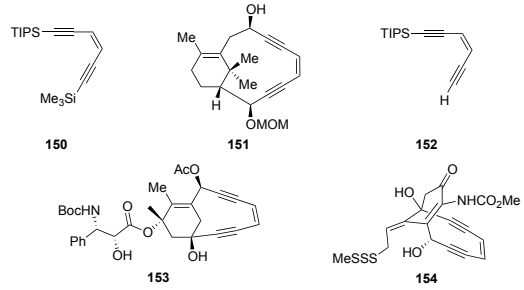
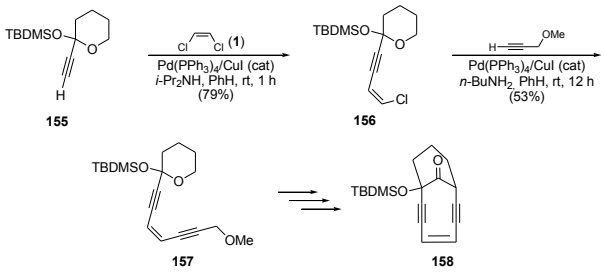


Figure 8. Structures of compounds **150–154**.

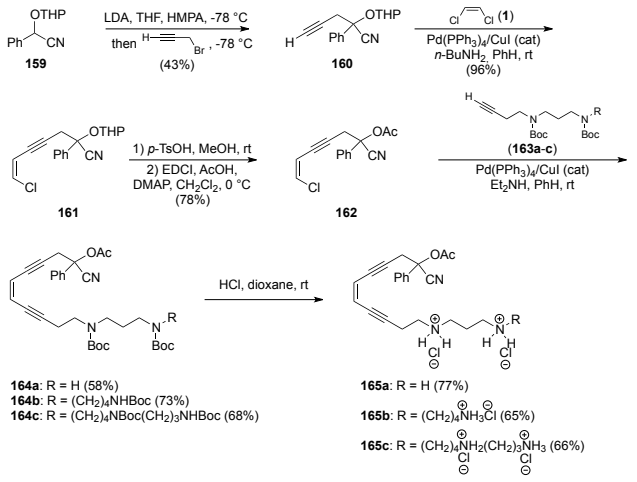
In 1989, bicyclo[7.3.1]enediyne **158**, possessing the core structure of the esperamicin-calicheamicin class of antitumor antibiotics, was synthesized in 9% overall yield via an 8-step reaction sequence[101] in which the key intermediate **157** was prepared by $Pd(PPh_3)_4$/CuI-catalyzed sequential alkynylation of **1** with 1-alkyne **155** and methyl propargyl ether (Scheme 57).[88] The selective $Pd(PPh_3)_4$/CuI-catalyzed monoalkynylation reaction of **1** with **155** was carried out at room temperature in benzene in the presence of *i*-Pr_2NH as base. The resulting compound **156**, which was obtained in 79% yield, was then reacted with methyl propargyl ether in benzene at room temperature in the presence of *n*-$BuNH_2$ and catalytic quantities of $Pd(PPh_3)_4$ and CuI to give **157** in 53% yield (Scheme 57).[101]



Scheme 57. Synthesis of bicyclic enediyne **158**.

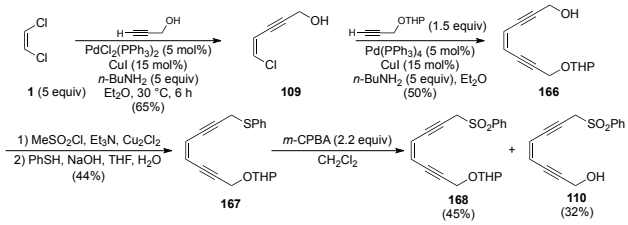
Remarkably, bicyclic enediyne **158** proved to be stable at room temperature.[101]

More recently, the polyamine-enediyne conjugates **165a–c** were synthesized using (*Z*)-1-chloro-1-en-3-yne **161** as a key intermediate, which was prepared in excellent yield by $Pd(PPh_3)_4$/CuI-catalyzed monoalkynylation of **1** with 1-alkyne **160** obtained from the THP *O*-protected cyanohydrin **159** (Scheme 58).[102] Deprotection of **164** with *p*-TsOH in methanol and acetylation of the resulting alcohol gave **162**, which was coupled with polyamine-alkynes **163a–c** in benzene in the presence of Et_2NH and catalytic quantities of $Pd(PPh_3)_4$ and CuI to give enediynes **164a–c**. Finally, treatment of these compounds with HCl in dioxane yielded the required compounds **165a–c**, which were found to exhibit potent DNA-damaging activity under physiological conditions.[102]



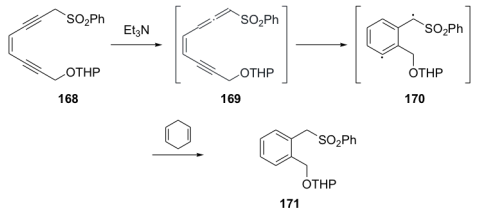
Scheme 58. Synthesis of the polyamine-enediyne conjugates **165a–c**.

In 1994, Wu and coworkers synthesized the unsymmetrically 1,8-functionalized (*Z*)-4-hexen-2,6-diyne **168** via $Pd(PPh_3)_4$/CuI-catalyzed reaction of (*Z*)-1-chloro-1-en-3-yne **109** with tetrahydropyranyl propargyl ether (Scheme 59).[103] The resulting compound **166** was then converted into the corresponding mesylate, which was reacted with thiophenol under alkaline conditions to give the sulfide **167**. Finally, oxidation of **167** with *m*-chloroperbenzoic acid (mCPBA) provided **168** in 45% yield along with 32% of the deprotected compound **110** (Scheme 59).[103]



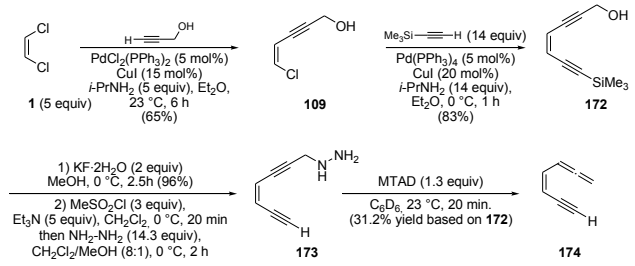
Scheme 59. Synthesis of the unsymmetrically 1,8-functionalized (*Z*)-4-hexen-2,6-diyne **168**.

Interestingly, the reaction of a degassed solution of **168** with 5 equiv of Et_3N in the presence of 1,4-cyclohexadiene at 30 °C for 10 h provided the *O*-disubstituted benzene derivative **171** (Scheme 60).[103] This result strongly suggested that the formation of **171** involved a base-catalyzed isomerization of **168** to the (*Z*)-enyne-allene-sulfone **169** and the subsequent Myers cyclization[104] of this compound to give the biradical intermediate **170** (Scheme 60).[103]



Scheme 60. Synthesis of compound **171** from enediyne **168**.

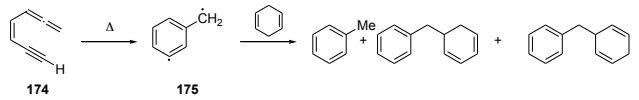
In a very interesting paper, Myers and coworkers had previously reported the synthesis of (*Z*)-1,2,4-heptatrien-6-yne (**174**) via a stereospecific route which began with the Pd/Cu-catalyzed sequential one-pot alkynylation of **1** with propargyl alcohol and trimethylsilylacetylene (Scheme 61).[105]



Scheme 61. Synthesis of (*Z*)-1,2,4-heptatrien-6-yne (**174**).

Desilylation of the resulting dialkynylated derivative **172** followed by mesylation of the hydroxyl group and subsequent treatment with a large molar excess of hydrazine in methanol at 0 °C gave compound **173**. Finally,

treatment of this crude compound with 4-methyl-1,2,4-triazoline-3,5-dione (MTAD) under anaerobic conditions produced compound **174** containing the (Z)-allene-ene-yne functional group, which was found to undergo a mild thermal reaction to form aromatic compounds in the presence of 1,4-cyclohexadiene.[105] The initial step in the formation of the aromatic compounds was supposed to be an electrocyclization reaction forming α,3-dehydrotoluene (**175**) (Scheme 62), which might function as a DNA-damaging agent.[105]



Scheme 62. Thermal conversion of compound **174** into aromatic compounds.

In 2010, (*Z*)-enediyne **172**, which was prepared in 72.3% yield by Myers' route,[105] was employed as an intermediate in the synthesis of compound **176**, a building block in a synthesis of the labile *cis-cis-trans* unit of fosfotriecin (**177**) (Figure 9).[106] This secondary metabolite, isolated from *Streptomyces pulvuraceus*,[107] was shown to be active against leukemia, lung cancer, breast cancer, and ovarian cancer[108a,b] and to be a strong inhibitor of type 2A and a weak inhibitor of type 1 serine/threonine protein phosphatase.[108c]

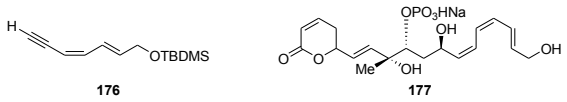
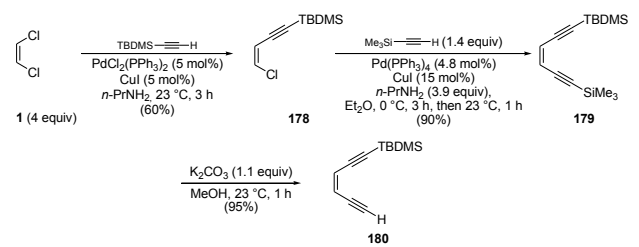


Figure 9. Structures of compounds **176** and **177**.

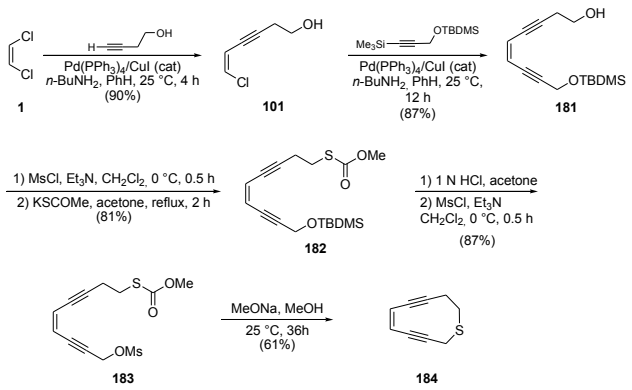
Some years earlier, Myers and coworkers, in the context of an enantioselective synthesis of (+)-dynemicin A (**31**) and its analogues, carried out the synthesis of enediyne **180** in 51.3% overall yield by sequential Pd/Cu-catalyzed monocoupling reactions of **1** with *t*-butyldimethylsilylacetylene and trimethylsilylacetylene and subsequent cleavage of the trimethylsilyl-protected group of the resulting dialkynylated derivative **179** (Scheme 63).[109] As in the case of other Pd/Cu-catalyzed sequential Sonogashira reactions of **1**,[103,105] the monoalkynylation reaction of this substrate was conveniently performed using air-stable and inexpensive $PdCl_2(PPh_3)_2$ as the Pd derivative.[109]



Scheme 63. Synthesis of enediyne **180**.

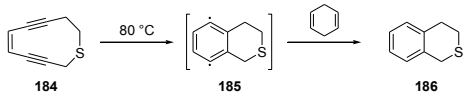
However, the alkynylation of the resulting coupling compound **178** was carried out in the presence of catalytic quantities of $Pd(PPh_3)_4$ and CuI.[109]

Pd/Cu-catalyzed sequential alkynylation reactions of (*Z*)-1,2-dichloroethene (**1**) were also used by Shibuya and coworkers for the synthesis of the 10-membered heterocyclic enediyne **184** (Scheme 64).[110] Monocoupling of **1** with 3-butyn-1-ol in benzene at 25 °C in the presence of *n*-$BuNH_2$ and catalytic quantitites of $Pd(PPh_3)_4$ and CuI gave (*Z*)-vinyl chloride **101** in 90% yield. A second coupling of **101** with *t*-butyldimethylsilyl propargyl ether under analogous reaction conditions provided enediyne **181** in 87% yield. Mesylation of **181** followed by nucleophilic substitution with potassium thioacetate gave thioacetate **182** in 81% yield, which by desilylation and subsequent mesylation of the resulting alcohol provided compound **183** in 87% yield. Finally, simultaneous slow addition of solutions of **183** and sodium methoxide in MeOH via a syringe pump into a large amount of MeOH at room temperature gave the enediyne **184** in 61% yield (Scheme 64).[110]



Scheme 64. Synthesis of the 10-membered heterocyclic enediyne **184**.

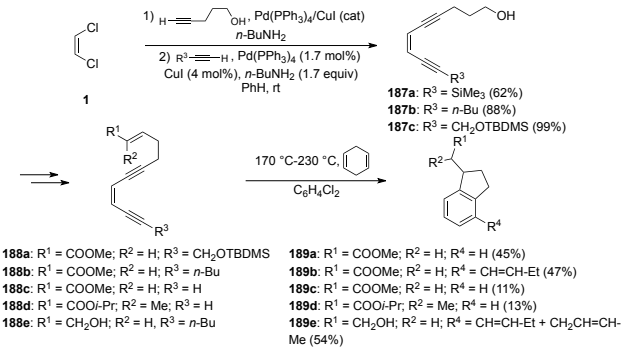
Compound **184** was then converted into isothiochromanone (**186**) in 58% yield by heating in benzene (2 mM solution) in the presence of 1,4-cyclohexadiene at 80 °C.[110] As shown in Scheme 65, the reaction very likely involved the formation of intermediate **185** via the Bergman reaction.[90]



Scheme 65. Synthesis of isothiochromanone (**186**).

In 1993, Grissom and coworkers synthesized unsymmetrical enediynes **187a–c** by sequential alkynylation of **1** (Scheme 66).[111] Thus, 4-pentyn-1-ol was

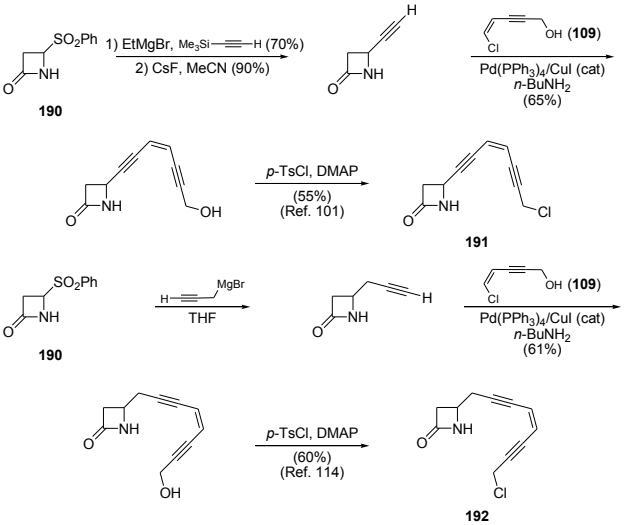
coupled to **1** under standard conditions[22] to yield the required monocoupling product in 95% yield. The second coupling was achieved under the same conditions with the required 1-alkynes to yield enediynes **187a–c** in 62, 88 and 99% yields, respectively, which were used as precursors to enediynes **188a–e** with one olefinic tether. It was then found that thermolysis of compounds **188a–e** at 170–245 °C in the presence of 1,4-cyclohexadiene gave 2,3-dihydroindenes **189a–e** in moderate isolated yields (Scheme 66).[111]



Scheme 66. Synthesis of 2,3-dihydroindenes **189a–e**.

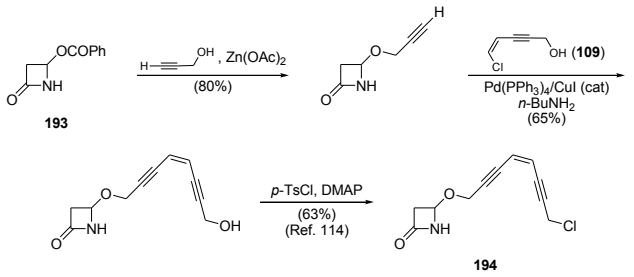
Remarkably, the cyclization reactions of the nonaromatic enediynes **188a–e** proceeded at lower temperature than those of the corresponding aromatic enediynes.[112]

Monocyclic enediynes **191**, **192** and **194** possessing a β-lactam functionality were synthesized by Basak and Khamrai using stereospecific $Pd(PPh_3)_4$/CuI-catalyzed alkynylation reactions of (*Z*)-1-chloro-5-hydroxy-1-penten-3-yne (**109**) as key steps (Schemes 67 and 68).[113] The reaction sequences employed to prepare compounds **191** and **192** from 4-phenylsulfonylazetidinone (**190**)[114] are outlined in Scheme 67. Interestingly, compounds **191** and **192** proved to exhibit significant activity against ampicillin-resistant *E. coli*.[113]



Scheme 67. Synthesis of compounds **191** and **192**.

On the other hand, enediyne **194** was synthesized from 4-benzoylazetidinone (**193**)[116] by the three-step reaction sequence shown in Scheme 68.[113]



Scheme 68. Synthesis of enediyne **194**.

It should be noted that attempted $Pd(PPh_3)_4$/CuI-catalyzed alkynylation reactions of **109** with terminal alkynes possessing a β-lactam functionality in the presence of an excess of Et_3N instead of *n*-$BuNH_2$ failed to produce any of the desired product.[113]

In 1996, chloroenyne **109** was also employed as electrophilic partner in a $Pd(PPh_3)_4$/CuI-catalyzed reaction with alkyne **195** in Et_2O in the presence of *n*-$BuNH_2$ as base, which provided enediyne **196** (Figure 10) in 40% yield.[117]

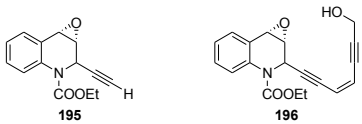
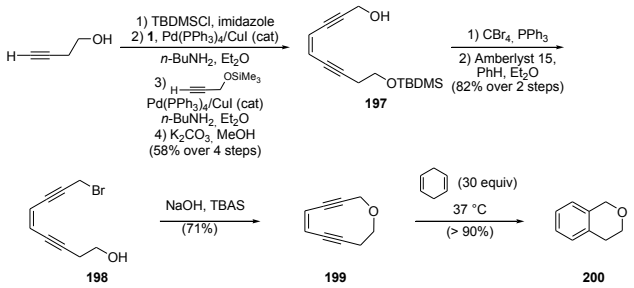


Figure 10. Structures of compounds **195** and **196**.

In 1996, Jones and coworkers performed a six-step synthesis of enediyne **198** involving the sequential $Pd(PPh_3)_4$/CuI-catalyzed reaction of dichloroethene **1** with homopropargyl alcohol and trimethylsilyl *O*-protected propargyl alcohol (Scheme 69).[118]

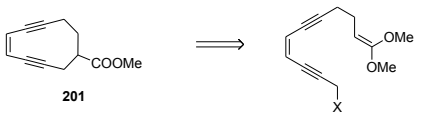


Scheme 69. Synthesis of isochromone **200**.

The resulting cross-coupling product was reacted with K_2CO_3 in MeOH to give compound **197**, which was reacted

with CBr_4 and PPh_3 and subsequently with Amberlyst 15 in benzene and Et_2O providing **198** in 82% yield from **197**. Finally, a Williamson-type ring closure of **198** furnished compound **199** in 71% yield, which was incubated with a large excess of 1,4-cyclohexadiene at 37 °C to give a nearly quantitative yield of isochromone (**200**) via a Bergman cyclization reaction (Scheme 69).[118]

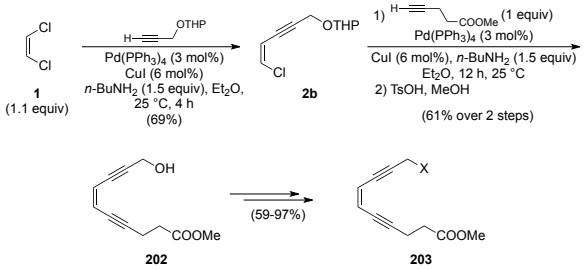
Four years later, Jones and coworkers attempted to prepare the monocyclic enediyne **201** according to the exocyclic enolate ring-closure strategy outlined in Scheme 70.[119]



201

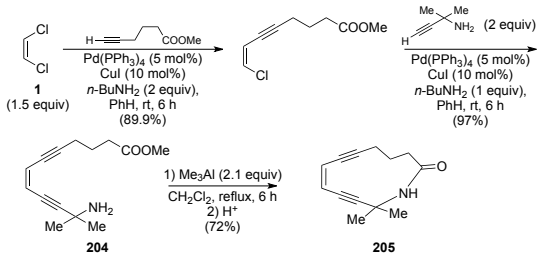
Scheme 70. Exocyclic enolate ring-closure strategy.

The synthesis of the requisite acyclic enediyne substrates **203** was achieved by the reaction sequence illustrated in Scheme 71. Specifically, they prepared compound **2b** in 69% yield by selective monocoupling of **1** with THP *O*-protected propargyl alcohol according to a modification of the procedure of Ratovelomanana and Linstrumelle[15] in which 1.1 equiv instead of 5 equiv of **1** were used.[119] The $Pd(PPh_3)_4$/CuI-catalyzed reaction of **2b** with an equimolar amount of methyl 5-hexynoate in Et_2O in the presence of *n*-$BuNH_2$ followed by deprotection of the THP-protected hydroxyl group of the resulting compound furnished (*Z*)-enediyne **202** in 61% yield. Compound **202** was then converted into a variety of functional-group analogues of general formula **203** (Scheme 71), but attempts to obtain monocyclic enediyne **201** by intramolecular cyclization of compounds **203** failed.[119]



Scheme 71. Synthesis of compounds **203**.

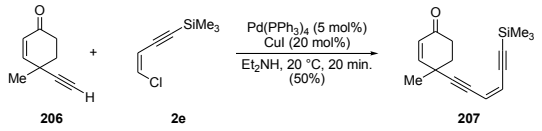
In 1995, (*Z*)-enediyne **204** was prepared in high yield by highly selective sequential $Pd(PPh_3)_4$/CuI-catalyzed reactions of **1** with methyl 5-hexynoate and 1,1-dimethyl-2-propynylamine (Scheme 72).[120]



Scheme 72. Synthesis of the stable enediyne lactam **205**.

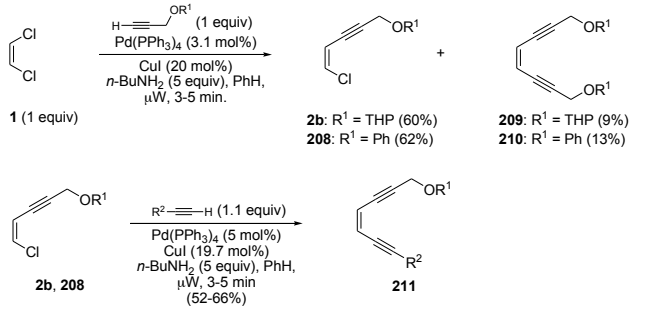
Ring closure of compound **204** by treatment with trimethylalane in refluxing CH_2Cl_2 provided after acidification the stable enediyne lactam **205** in 72% yield (Scheme 72).[120]

In many of the examples reported in this subsection, it has been shown that several Pd/Cu-catalyzed reactions of (*Z*)-1-chloro-1-en-3-ynes with terminal alkynes were successfully carried out using *n*-$BuNH_2$ as the solvent or base. However, the $Pd(PPh_3)_4$/CuI-catalyzed cross coupling of (*Z*)-chloroenyne **2e** with 4-ethynyl-4-methylcyclohex-2-en-1-one (**206**), which was performed in the context of a study on arene diradical formation in calicheamicin-esperamicin analogues, was instead carried out using Et_2NH as the base and the solvent (Scheme 73).[121] Nevertheless, the result of the reaction was not entirely satisfactory, since the coupling provided 91% pure compound **207** in 50% yield.[121]



Scheme 73. Synthesis of compound **207**.

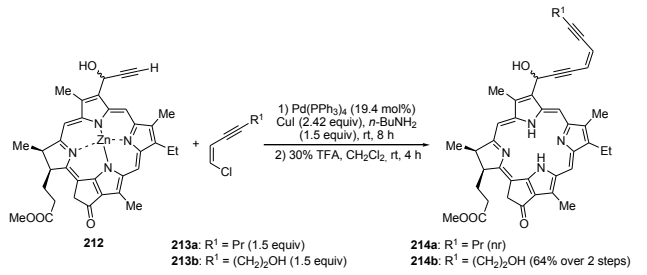
Instead, as regards the Pd/Cu-catalyzed monoalkynylation reactions of **1** with terminal alkynes, it should be noted that, in many of the examples discussed so far, the required (*Z*)-1-chloro-1-en-3-ynes were obtained in high yields using molar ratios between **1** and 1-alkynes that were higher than 1 and performing the Sonogashira reactions at room temperature. Nevertheless, (*Z*)-1-chloro-1-en-3-ynes **2b** and **208** were recently obtained in satisfactory yields by the reaction of 1 equiv of **1** with 1 equiv of THP *O*-protected propargyl alcohol and 3-phenoxy-1-propyne, respectively, in the presence of 5 equiv of *n*-$BuNH_2$, 3.1 mol% $Pd(PPh_3)_4$, and 20 mol% CuI in benzene under microwave irradiation for 3-5 min (Scheme 74).[122,123]



Scheme 74. Synthesis of compounds **2b**, **208** and **211**.

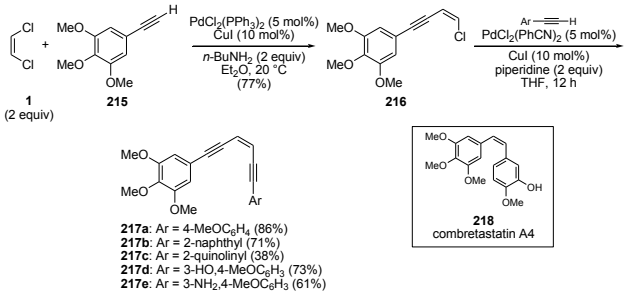
Compounds **2b** and **208** were in fact obtained in 60 and 62% yield, respectively, but the reactions also furnished significant amounts of the symmetrically substituted (*Z*)-3-en-1,5-diynes **209** and **210**, respectively (Scheme 74).[122] It was also shown that very short reaction times were necessary to prepare unsymmetrically substituted enediynes of general formula **211** in satisfactory yields by $Pd(PPh_3)_4$/CuI-catalyzed alkynylation of **2b** and **208** under microwave irradiation (Scheme 74).[122]

In 2004, two conjugated (*Z*)-enediyne-carrying chlorophyll derivatives, **214a** and **214b** were synthesized by $Pd(PPh_3)_4$/CuI-catalyzed coupling of the zinc-chlorin **212** with (Z)-chloroenynes **213a** and **213b**, respectively, followed by removal of zinc from the resulting cross-coupling products by treatment with TFA in CH_2Cl_2 (Scheme 75).[124]



Scheme 75. Synthesis of compounds **214a** and **214b**.

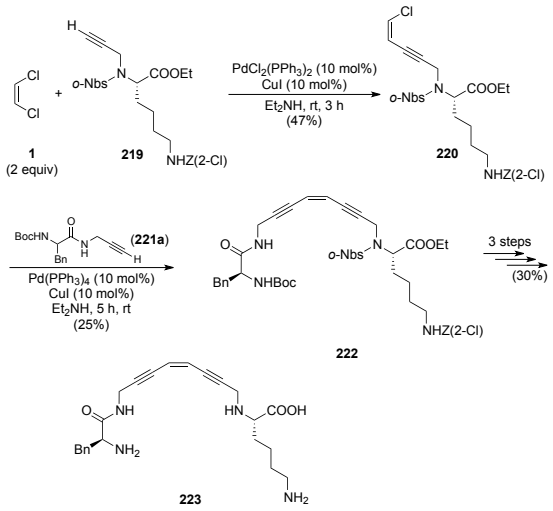
A year later, Provot, Alami and coworkers achieved the synthesis of unsymmetrically substituted (*Z*)-enediynes **217a–e**,[125] which can be considered analogues of combretastin A4 (**218**), a compound isolated from the South African willow *Combretum caffrum*,[126] which exhibits strong antitubulin activity by binding to the colchicine binding site of tubulin,[127] shows potent cytotoxicity against a variety of human cancer cells,[128] and has demonstrated powerful antiangiogenesis properties.[129]



Scheme 76. Synthesis of (*Z*)-enediynes **217a-e**.

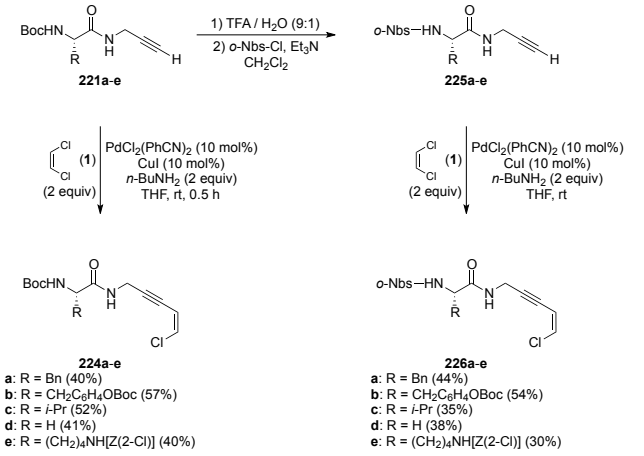
The two-step synthesis of compounds **217a–e** began with a $PdCl_2(PPh_3)_2$/CuI-catalyzed reaction of 3,4,5-trimethoxyphenylacetylene (**215**) with 2 equiv of **1** in Et_2O at 20 °C in the presence of 2 equiv of *n*-$BuNH_2$ (Scheme 76).[125] The reaction produced (*Z*)-chloroenyne **216** in 77% yield, which was reacted with the required (hetero)arylacetylenes using $PdCl_2(PhCN)_2$ associated with CuI as the catalyst and piperidine as base.[125] The cross couplings gave (Z)-enediynes **217a–e** in 38–86% yield (Scheme 76).[125,130]

In 2007, the enediyne-bridged amino acid **223** was synthesized via a low-yielding route in which the first step was the reaction of alkyne **219** with 2 equiv of **1** in Et_2NH at room temperature in the presence of 10 mol% $PdCl_2(PPh_3)_2$ and 10 mol% CuI, which provided the (Z)-chloroenyne derivative of lysine **220** in 47% yield (Scheme 77).[131] The $Pd(PPh_3)_4$/CuI-catalyzed cross coupling of **220** with 1-alkyne **221a** (see also Scheme 78) in Et_2NH at room temperature furnished (*Z*)-enediyne **222** in 25% yield. Finally, a three-step reaction sequence allowed the conversion of **222** into compound **223** in 30% yield (Scheme 77).[131]



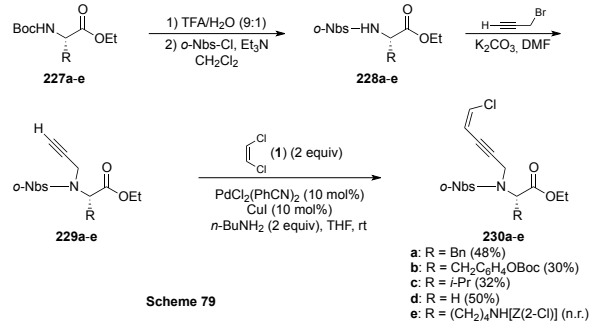
Scheme 77. Synthesis of the enediyne-bridged amino acid **223**.

In 2008, Jeric and coworkers focused their attention on the synthesis of (*Z*)-chloroenyne-substituted amino acids suitable for the construction of enediyne-related peptide derivatives.[132] Two groups of chloroenyne-modified amino acids, **224a-e** and **226a-e** were synthesized as illustrated in Scheme 78. Specifically, compounds **224a-e** were prepared in satisfactory yields by the coupling of alkynes **221a-e** with 2 equiv of **1** in THF at room temperature in the presence of 2 equiv of *n*-$BuNH_2$, 10 mol% $PdCl_2(PhCN)_2$ and 10 mol% CuI. A similar protocol was used in the synthesis of compounds **226a-e** from **1** and alkynes **225a–e**, which were prepared by deprotection of the Boc group of compounds **221a-e** under acidic conditions followed by the introduction of the *o*-Nbs group. The yields of **226a-e** were found to be lower than those of compounds **224a-e**.[132]



Scheme 78. Synthesis of compounds **224a-e** and **226a-e**.

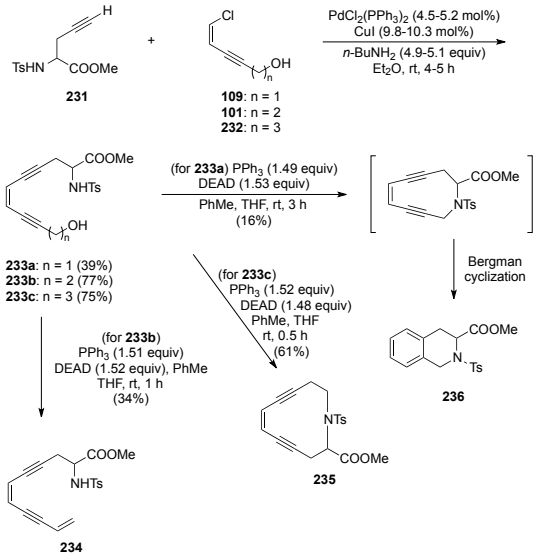
A third group of (*Z*)-chloroenyne-modified amino acids **230a–e** was prepared from the ethyl esters of N-Boc-protected amino acids **227a–e**, which were converted into compounds **228a–e** possessing the amino group activated through the *o*-Nbs moiety (Scheme 79).[132]



Scheme 79. Synthesis of (*Z*)-chloroenyne-modified amino acids **230a–e**.

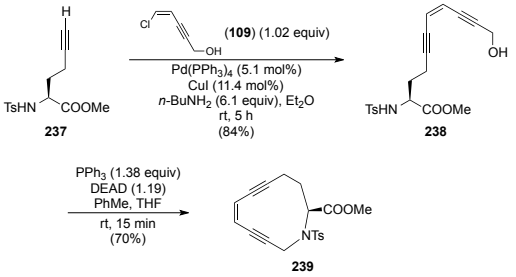
Compounds **228a–e** were converted into alkynes **229a–e** by treatment with propargyl bromide in DMF in the presence of K_2CO_3. Finally, the $PdCl_2(PhCN)_2$/CuI-catalyzed Sonogashira-type reaction of **229a–e** with **1** gave compounds **230a–e** in modest-to-satisfactory yields (Scheme 79).[132]

In 2009, (*Z*)-enediynols **233a**, **233b** and **233c** were synthesized in 39, 77 and 75% yield, respectively, by the $PdCl_2(PPh_3)_2$/CuI-catalyzed reaction of the propargylglycine derivative **231** with (*Z*)-haloenynols **109**, **101** and **232**, respectively (Scheme 80).[133] It was then found that subjecting of **233b** to Mitsunobu conditions[134] led to the elimination product **234** in 34% yield, while **233c** under these conditions was transformed into the 12-membered heterocycle derivative **235** in 61% yield. However, no enediyne could be isolated when **233a** was reacted in experimental conditions similar to those employed to prepare **234** and **235**. In this case, the tetrahydroisoquinoline derivative **236** was obtained in 16% yield (Scheme 80).[133]



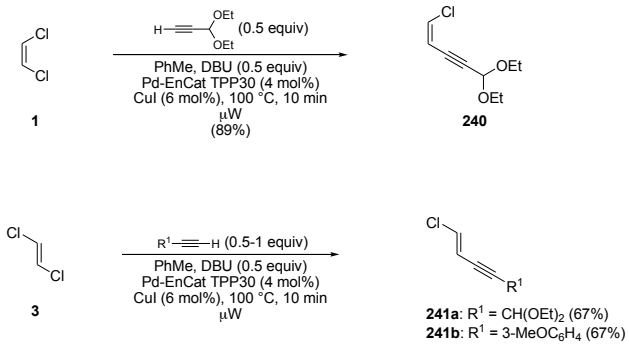
Scheme 80. Synthesis of compounds **234–236**.

It was also found that the homochiral 11-membered cyclic enediyne **239** was obtained in 70% yield by cyclization, under high-dilution Mitsunobu conditions, of acyclic (*Z*)-enediyne **238**, which was prepared in 84% yield by coupling of alkyne **237** with (Z)-chloroenyne **109** in Et_2O at room temperature in the presence of *n*-$BuNH_2$ and a combination of $Pd(PPh_3)_4$ and CuI as catalyst (Scheme 81).[133]



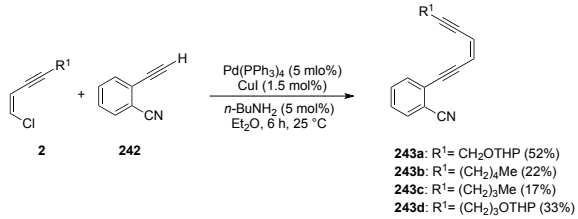
Scheme 81. Synthesis of the 11-membered cyclic enediyne **239**.

In 2009, the group of Ley successfully employed the commercially available easily-handled encapsulated Pd species Pd-EnCat TPP30 as a catalyst component of the microwave-mediated reaction of **1** with 0.5 equiv of 3,3-diethoxy-1-propyne, which was carried out in toluene, in the presence of 6 mol% CuI and 0.5 equiv of DBU (Scheme 82).[135] The resulting chloroenyne **240** was obtained in 89% yield. A similar procedure was then employed for the stereospecific synthesis of the (*E*)-configured compounds **241a** and **241b** in 67% yield from (*E*)-1,2-dichloroethene (**3**) and 0.5 equiv of 3,3-diethoxy-1-propyne and 1 equiv of 3-methoxyphenylacetylene, respectively (Scheme 82).[135] Remarkably, Pd-EnCat TPP30, containing co-encapsulated PPh_3 ligand, could be recovered and recycled by simple filtration of the reaction mixtures.[135]



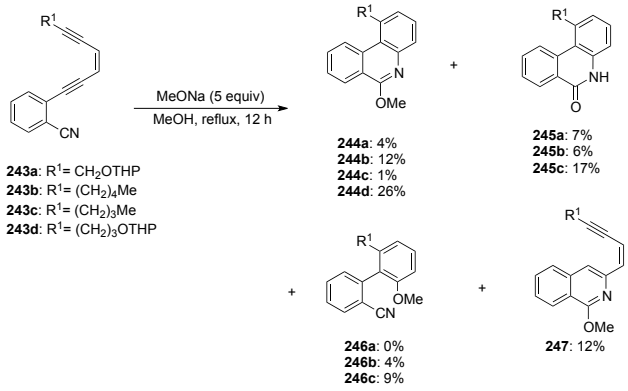
Scheme 82. Synthesis of compounds **240**, **241a** and **241b**.

An extensive use of (*Z*)-1-chloro-1-en-3-ynes was made by Wu and coworkers in the synthesis of unsymmetrically substituted acyclic (*Z*)-3-en-1,5-diynes (used) as precursors to heterocycles.[93,136–140] As previously mentioned (Scheme 53), enediyne **52a** was employed as a starting material in the synthesis of the 2-substituted benzofuran **143**.[93] Moreover, 2-(6-substituted-3-hexen-1,5-diynyl)benzonitriles **243a–d** were prepared in 17–52% yields by treatment of 2 equiv of 2-ethynylbenzonitrile (**242**) with 1 equiv of the required (*Z*)-1-chloro-1-en-3-ynes **2** in Et_2O containing 5 mol% $Pd(PPh_3)_4$, 15 mol% CuI, and 5 equiv of *n*-$BuNH_2$ (Scheme 83).[136] As shown in Scheme 84, compounds **243a–d** were found to undergo cycloaromatization by treatment with sodium methoxide in refluxing MeOH.[136]



Scheme 83. Synthesis of 2-(6-substituted-3-hexen-1,5-diynyl)benzonitriles **243a–d.**

Specifically, treatment of **243a** with 5 equiv of sodium methoxide in refluxing MeOH for 6 h gave phenanthridine **244a** in 4% yield along with phenathridinone **245a** in 7% yield. The reaction of **243b** with sodium methoxide under the same reaction conditions gave **244b** in 12% yield, **245b** in 6% yield, and the biphenyl derivative **246b** in 4% yield (Scheme 84). Similarly, cycloaromatization of **243c** provided biphenyl **246c** in 9% yield along with compounds **244c** and **245c** in 1 and 17% yield, respectively. Under the same reaction conditions, **243d** gave phenanthridine **244d** in 26% yield and isoquinoline **247** in 12% yield (Scheme 84).[136]

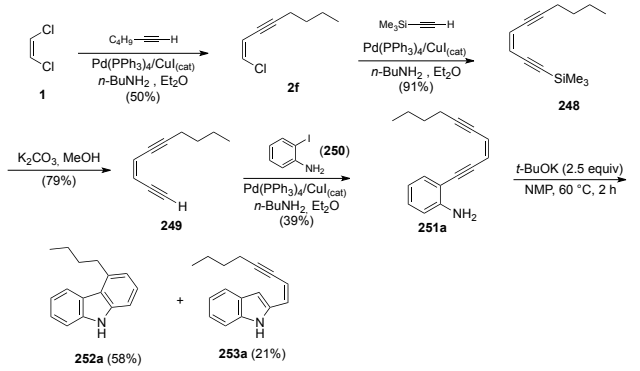


Scheme 84. Cycloaromatization of compounds **243a–d**.

A plausible mechanism for the formation of compounds **244**, **245** and **247**, involving methoxide addition to the cyano group of compounds **243**, was proposed. The anionic cycloaromatization of (*Z*)-enediynes **243** and the product formation in this mechanism were suggested to be dependent upon the regiochemistry of the nucleophilic addition reaction.[136]

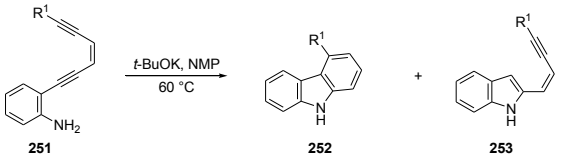
In 2004, Wu and coworkers synthesized 4-butyl-9*H*-carbazole (**252a**) in 58% yield by treatment of 2-(6-butyl-3(Z)-hexen-1,5-diynyl)aniline (**251a**) with *t*-BuOK in NMP at 60 °C for 2 h (Scheme 85).[137] The synthesis of compound **251a** from **1** was accomplished according to a reaction sequence that involved the efficient conversion of **1** into

unsymmetrically substituted (*Z*)-3-en-1,5-diyne **248** by sequential $Pd(PPh_3)_4$/CuI-catalyzed alkynylation reactions. The reaction of **248** with K_2CO_3 in MeOH provided compound **249** in 79% yield, which was coupled with 2-iodoaniline (**250**) in Et_2O in the presence of *n*-$BuNH_2$ and a catalyst system consisting of a mixture of $Pd(PPh_3)_4$ and CuI to give **251a** in 39% yield.[137] Noteworthy, the intramolecular anionic cyclization of **251a** gave **252a** along with the indole derivative **253a** in 21% yield.



Scheme 85. Synthesis of compounds **252a** and **253a**.

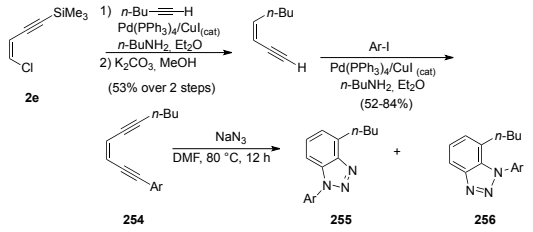
Various (Z)-2-(6-substituted 3-hexen-1,5-diynyl)anilines **251** were then prepared using the procedure employed for the synthesis of **251a**. Treatment of compounds **251** with *t*-BuOK resulted in the formation of carbazoles **252** in 36–60% yields along with indoles **253** in 21–40% yield (Scheme 86).[136]



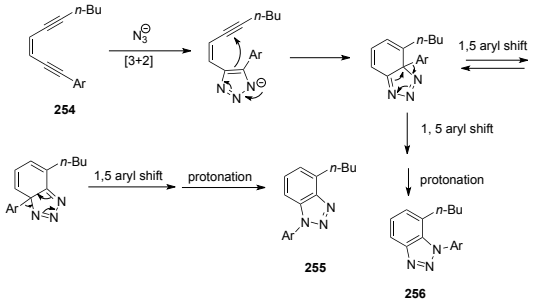
Scheme 86. Intramolecular anionic cyclization of enediynes **255**.

In 2005, several 1-aryl-1*H*-benzotriazoles were prepared in high yields from (*Z*)-3-en-1,5-diynes **254**, which were synthesized from (*Z*)-1-chloro-4-trimethylsilyl-1-buten-3-yne (**2e**) as outlined in Scheme 87.[138] Treatment of compounds **254** with sodium azide in DMF at 80 °C for 12 h provided 1-aryl-4-butyl-1*H*-benzo[*d*][1,2,3]-triazoles **255** in 54-70% yields along with 7-butyl-1-aryl-1*H*-benzo[*d*][1,2,3]-triazoles **256** in 18–20% yields. Interestingly, when DMSO was employed as the solvent instead of DMF, compounds **255** were obtained in 24–64% yields and the yields of compounds **256** ranged from 43 to 67%.[138]

A mechanism for the formation of compounds **255** and **256** was proposed (Scheme 88),[138] involving a 1,3-dipolar cycloaddition reaction of the azide anion to enediynes **254** followed by anionic cyclization and subsequent sigmatropic rearrangement of the resulting compounds.[138]

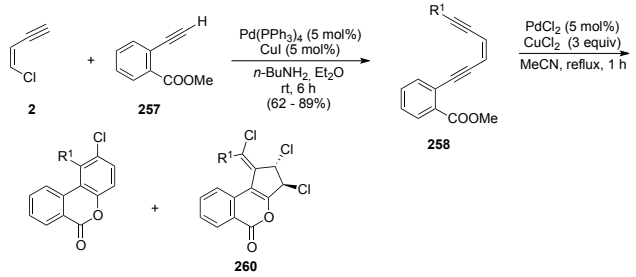


Scheme 87. Synthesis of triazoles **255** and **256**.



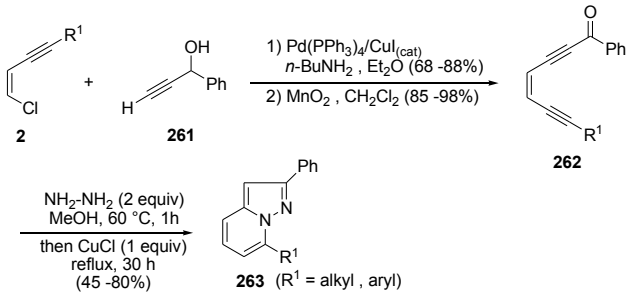
Scheme 88. Proposed mechanism for the formation of compounds **255** and **256**.

In 2008, several (Z)-2-(6-substituted-3-hexen-1,5-diynyl)benzoates **258** were prepared in 62–89% yields by the reaction of (*Z*)-1-chloro-1-en-3-ynes **2** with methyl 2-ethynylbenzoate (**257**) in Et_2O at room temperature for 6 h in the presence of *n*-$BuNH_2$ as base, 5 mol% $Pd(PPh_3)_4$ and 5 mol% CuI (Scheme 89).[139] Compounds **258** were then reacted with 3 equiv of $CuCl_2$ and 5 mol% $PdCl_2$ in refluxing acetonitrile to give dibenzo[*b,d*]pyran-6-ones **259** in modest-to-good yields. However, the one-step tandem cyclization reaction of enediynes **258** bearing an electron-donating group on the aryl ring in the 6-position of the enediyne system gave compounds **259** as the major products along with the minor trichloro derivatives **260** (Scheme 89).[139]



Scheme 89. Synthesis of compounds **259** and **260**.

More recently, several (*Z*)-enediynones **262** were synthesized in high yields by Sonogashira coupling of chloroenynes **2** with propargyl alcohol **261** followed by oxidation of the resulting cross-coupling products with MnO_2 (Scheme 90).[140] Compounds **262** were then treated with 2 equiv of hydrazine in acetonitrile at 60 °C for 1 h and subsequently with 1 equiv of CuCl to provide 2,7-disubstituted pyrazolo[1,5-*a*]pyridines **263** in good yields (Scheme 90). Noteworthy is that the cascade cyclization reaction leading to compounds **263** was able to tolerate many functional groups.[140,141]

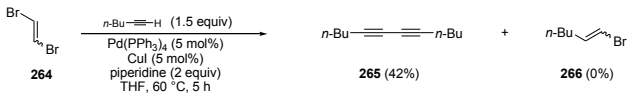


Scheme 90. Synthesis of pyrazolo[1,5-*a*]pyridines **263**.

It is also worth mentioning that the copper-catalyzed cyclization of the enediynone **262** in which R^1 = *t*-butyl gave the expected pyrazolo[1,5-*a*]pyridine in 13% yield along with 72% yield of an (η^2-alkyne)copper complex, which was apparently the intermediate to the final cyclization derivative.[140]

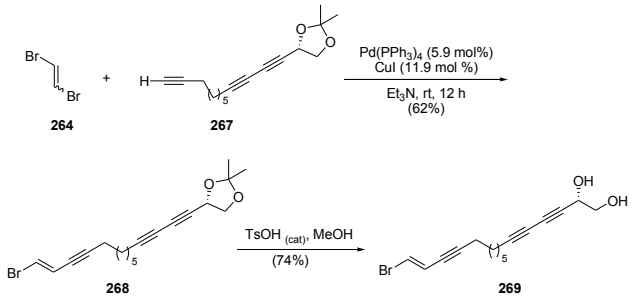
2.2 Monoalkynylation reactions of stereodefined and (*E*)/(*Z*)-1,2-dibromo-1-alkenes and (*E, E*)-1,4-diiodo-1,3-butadiene

In 2004, Organ and coworkers investigated the Sonogashira reaction of a 1:1 mixture of (*Z*)- and (*E*)-1,2-dibromoethene (**264**) and found that the reaction of 1.5 equiv of 1-hexyne with 1 equiv of **264** in THF at 60 °C in the presence of 2 equiv of piperidine, 5 mol% $Pd(PPh_3)_4$ and 5 mol% CuI gave diyne **265** in 42% yield (Scheme 91).[142] Surprisingly, the monocoupling product **266** was not detected.[142] On the contrary, the formation of **265** was not a surprise since homocoupling products of 1-alkynes are common side products of Pd/Cu-catalyzed Sonogashira reactions.[4b]



Scheme 91. Synthesis of diyne **265** by Pd/Cu-catalyzed reaction of 1-hexyne with (*E*)/(*Z*)-1,2-dibromoethene (**264**).

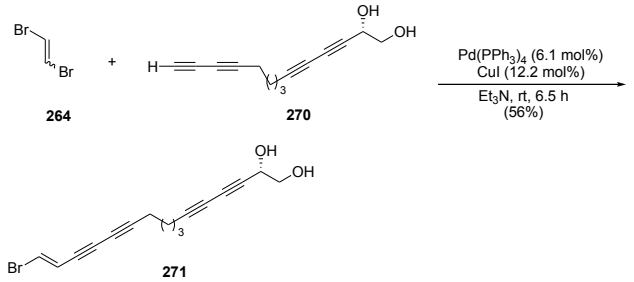
Again in 2004, and in contrast to these results, Gung and coworkers achieved successful stereoselective Sonogashira-type monoalkynylation reactions of a stereoisomeric mixture of 1,2-dibromoethene with terminal alkynes.[143] In particular, they found that the reaction of 1,2-isopropylidenetetradeca-3,5,13-triyne (**267**) with 4 equiv of a stereoisomeric mixture of 1,2-dibromoethene in Et_3N at room temperature for 12 h in the presence of 5 mol% $Pd(PPh_3)_4$ and 11.9 mol% CuI gave 98% stereoisomerically pure (*E*)-1-bromo-1-en-3-yne **268** in 62% yield (Scheme 92).



Scheme 92. Synthesis of compounds **268** and (+)-diplyne A (**269**).

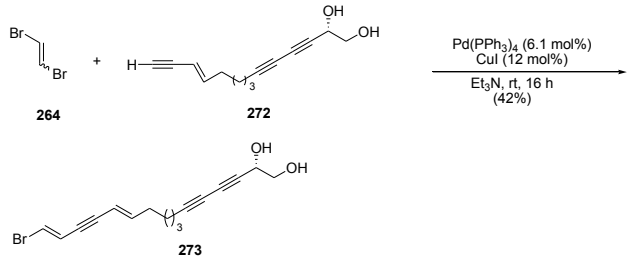
Removal of the acetonide protecting group from **268** using a catalytic amount of TsOH in MeOH gave (+)-diplyne A (**269**) (Scheme 92).[143] The enantiomer of **269**, which was isolated from the crude extract of the Philippine sponge *Diplastrella* sp., was found to inhibit the activity of the HIV-1 integrase,[144] a 32-kDa protein produced from the C-terminal portion of the Pol gene product, which is an attractive target for new anti-HIV drugs.

Gung and coworkers also reported that the reaction of tetradeca-3,5,11,13-tetrayn-1,2-diol (**270**) with (*E*)/(*Z*)-1,2-dibromoethene (**264**) under experimental conditions very similar to those employed in the synthesis of **268** provided stereoselectively (+)-diplyne D in 56% yield (**271**) (Scheme 93),[143] which is the enantiomer of a second brominated polyacetylene isolated from *Diplastrella* sp.[144]



Scheme 93. Synthesis (+)-diplyne D (**271**).

Moreover, these authors prepared compound **273**, the (+)-enantiomer of diplyne E, in 42% yield by the $Pd(PPh_3)_4$/CuI-catalyzed reaction of tetradec-11-en-3,5,13-triyn-1,2-diol (**272**) with 4 equiv of **264** in Et_3N (Scheme 94).[145] Diplyne E is another brominated polyacetylene isolated from *Diplastrella* sp.[144]



Scheme 94. Synthesis of (+)-diplyne E (**273**).

However, compound **273** proved to be contaminated by ca. 10% of its stereoisomer **274**[144] (Figure 11), a brominated polyacetylene originating from the Takai olefination reaction[146] which was employed to prepare a precursor to **272**.[145]

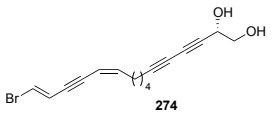


Figure 11. Structure of compound **274**.

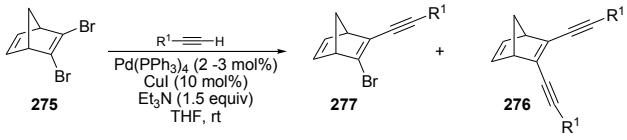
It is also worth noting that the stereochemical results of the Sonogashira-type reactions that provided stereoselectively compounds **268**, **271** and **273** were consistent with previous reports that (*E*)-1,2-dibromoethene is more reactive than the corresponding (*Z*)-stereoisomer in Pd-catalyzed cross-coupling reactions.[66f]

In 2002, in order to synthesize unsymmetrically substituted norbornadiene-2,3-diynes **276**, Tranmer and Tam investigated the Sonogashira monoalkynylation of 2,3-dibromonorbornadiene (**275**) (Figure 12).[147]

Figure 12. Structures of compounds **275** and **276**.

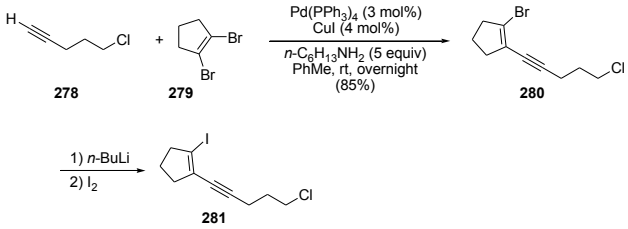
The best results in the synthesis of 2-(1-alkynyl)-3-bromonorbornadienes **277** were obtained when 1-alkynes were reacted with 2–5 equiv of **275**, 2–3 mol% $Pd(PPh_3)_4$, 10 mol% CuI, and 1.5 equiv of Et_3N in THF at room temperature (Table 1).[147] Unfortunately, unsatisfactory selectivity was observed for the reactions reported in Table 1, except for the one (entry 7) that provided compound **277e** in 70% yield. Nevertheless, in all cases examined, the required monocoupling products **277** were readily separated from the corresponding dialkynylation derivatives **276** by column chromatography. Compounds **277** could then be employed in the synthesis of unsymmetrically substituted norbornadien-2,3-diynes **276** by a second Sonogashira coupling with 1.2 equiv of terminal alkynes, 3 mol% $Pd(PPh_3)_4$, 10 mol% CuI, and 1.5 equiv of Et_3N in toluene at room temperature. Noteworthy is that the reactions gave compounds **276** in good-to-excellent yields when carried out within a dry box under argon.[147]

Table 1. Synthesis of monocoupling enynes **277** from 2,3-dibromonorbornadiene (**275**).



Entry	Equiv of **275**	R^1	**277**		**276**	
				Yield (%)		Yield (%)
1	2	Ph	**a**	45	**a**	39
2	5	Ph	**a**	48	**a**	47
3	5	Me_3Si	**b**	47	**b**	50
4	2	*n*-Bu	**c**	51	**c**	33
5	5	*n*-Bu	**c**	63	**c**	35
6	5	CH_2OH	**d**	49	polymeric material	
7	5	$(CH_2)_2OH$	**e**	70	polimeryc material	

In 2006, Buchwald and coworkers found that the reaction of 5-chloro-1-pentyne (**278**) with 2.5 equiv of 1,2-dibromocyclopentene (**279**) in toluene at room temperature in the presence of 3 mol% $PdCl_2(PPh_3)_2$, 4 mol% CuI and 5 equiv of *n*-hexylamine gave 1-bromo-2-(5-chloropent-1-ynyl)cyclopent-1-ene (**280**) in 85% yield (Scheme 95).[148]



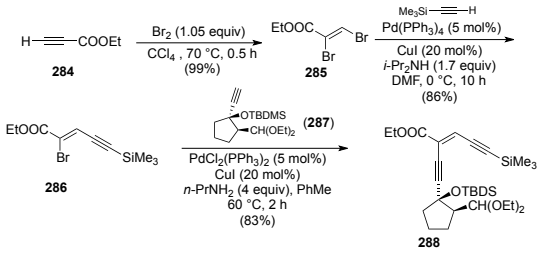
Scheme 95. Synthesis of 1-bromo-1-en-3-yne **280**.

Compound **280** was then chemoselectively converted into iodoenyne **281** by treatment with *n*-BuLi followed by the addition of iodine.[148]

1-Bromo-2-(phenylethynyl)cyclopent-1-ene (**282**) and the corresponding 1-iodo derivative **283** (Figure 13) were similarly prepared from phenylacetylene and 1,2-dibromocyclopentene (**279**).[148]

Figure 13. Structures of compounds **282** and **283**.

Some interesting examples of the syntheses of stereodefined highly functionalized 3-en-1,5-diynes via regio- and stereospecific Sonogashira monoalkylation reactions of alkyl (*Z*)-2,3-dibromopropenoates with 1-alkynes have also been reported in the literature. Myers and coworkers described the treatment of ethyl (*Z*)-2,3-dibromopropenoate (**285**) with 1.7 equiv of trimethylsilylacetylene, 5 mol% $Pd(PPh_3)_4$, 20 mol% CuI, and 1.7 equiv of *i*-Pr_2NH in DMF at 0 °C for 10 h to give 87–94% pure (*Z*)-bromoenyne **286** in 48–86% yields (Scheme 96).[149a,150]

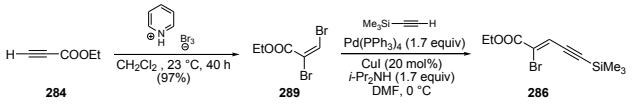


Scheme 96. Synthesis of (Z)-bromoenyne **286** and enediyne **288**.

Moreover, the $PdCl_2(PPh_3)_2$/CuI-catalyzed reaction of alkyne **287** with 1.2 equiv of **286** in toluene at 60 °C in the presence of 4 equiv of *n*-$PrNH_2$ produced enediyne **288** in 83% yield (Scheme 96).[149a] Compound **285** was readily available in quantitative yield by the reaction of ethyl propiolate (**284**) with 1.05 equiv of bromine in CCl_4 at 70 °C for 0.5 h (Scheme 96).[149a]

As regards the regioselectivity observed in the Pd/Cu-catalyzed monoalkynylation reaction of **285**, it should be noted that the result illustrated in Scheme 96 could be expected taking into account that the C–Br bond in the β-position of **285**, due to the conjugative effect in this α,β-unsaturated ester, is more electrophilic than the C–Br bond in the α-position and, therefore, undergoes preferentially the oxidative addition reaction with the catalytically active Pd(0) species.

An unexpected stereochemical result was, however, observed when stereoisomerically pure ethyl (*E*)-2,3-dibromopropenoate (**289**), readily available in 81% yield by treatment of ethyl propiolate (**284**) with a suspension of 1.3 equiv of pyridinium bromide perbromide in CH_2Cl_2 at 20 °C for 40 h,[149a,b] was reacted with trimethylsilylacetylene under the same conditions employed in the synthesis of **286** from **285**.

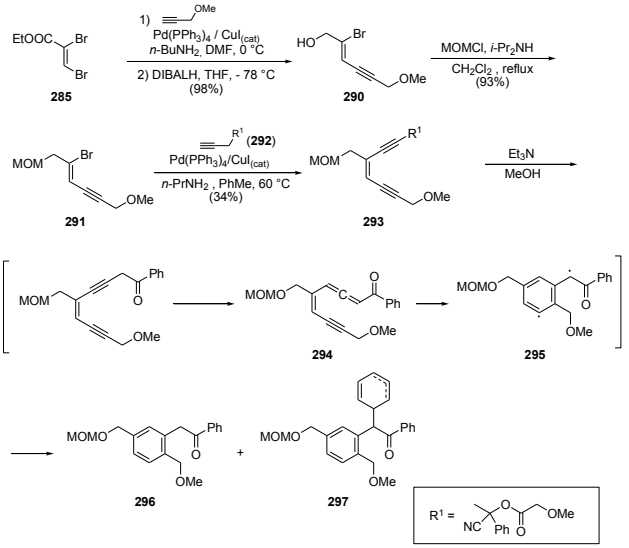


Scheme 97. Synthesis of (*Z*)-bromoenyne **286** from ethyl (*E*)-2,3-dibromopropenoate (**289**).

In fact, the reaction produced the (*Z*)-coupling product **286** (Scheme 97).[149a] Unfortunately, the yield of the reaction and the stereoisomeric purity of the cross-coupling product were not reported.

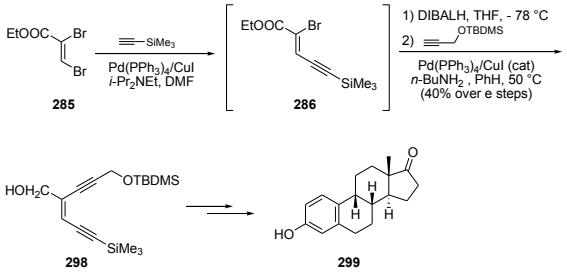
In 2002, bromoenyne **290** was regioselectively synthesized in 63.7% yield by monoalkynylation of **285** with methyl propargyl ether according to the protocol described by Myers, followed by reduction of the resulting monocoupling compounds with DIBALH in THF at -78 °C (Scheme 98). Compound **290** further participated in a Sonogashira reaction with alkyne **292** possessing a cyanohydrin moiety to give compound **293**, which upon treatment with Et_3N in MeOH produced efficiently the enyne-allenyl ketone **294**. The reaction of **294** with 1.2 equiv of Et_3N in the presence of 50 equiv of 1,4-cyclohexadiene gave the cycloaromatized derivative **296** and the adduct **297** via the biradical **295** (Scheme 98).[151] Interestingly, in basic buffer solution, biradical **295** showed potent DNA-cleaving ability.[151]

In 2007, crude compound **286**, which was obtained from ethyl (*Z*)-2,3-dibromopropenoate (**285**) according to the procedure reported by Myers and coworkers.[149a,150] was reduced with DIBALH in toluene at -78°C and the resulting alcohol was dissolved in benzene and treated with 3-(*t*-butylsimethylsilyloxy)-1-butyne and *n*-$BuNH_2$ in the presence of catalytic amounts of $Pd(PPh_3)_4$ and CuI at 60 °C for 6 h (Scheme 99).[152]



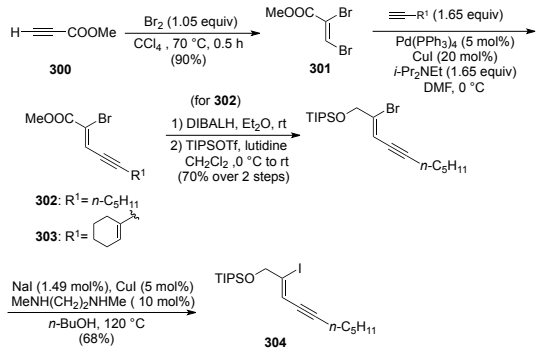
Scheme 98. Synthesis of compounds **296** and **297** from **285**.

The resulting (*E*)-configured enediyne **298**, which was obtained in 40% yield over 3 steps, was then employed as precursor to the racemic form **299**[152] of (+)-estrone, an estrogenic hormone secreted by ovary as well as adipose tissue.



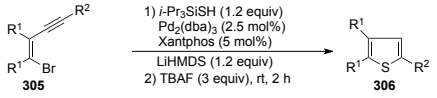
Scheme 99. Synthesis of racemic estrone (**299**) from ethyl (*Z*)-2,3-dibromopropenoate (**285**).

Myers' protocol[149a,150] was also employed for the synthesis of methyl (*Z*)-2-bromo-2-en-4-ynoates **302** and **303** in 56% and 63% yield, respectively, from methyl (*Z*)-2,3-dibromopropenoate (**301**) and the required terminal alkynes (Scheme 100).[148] Scheme 100 illustrates the synthesis of compound **301** in 90% yield, which was carried out by the dropwise addition of bromine to a CCl_4 solution of methyl propiolate (**300**) heated at 70 °C, its conversion into enynes **302** and **303**, and the three-step synthesis of iodoenyne **304** from **302**.[148]



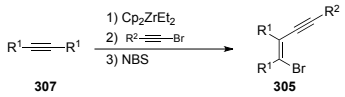
Scheme 100. Synthesis of iodoenyne **304** from methyl propiolate (**300**).

Recently, 2,3,5-trisubstituted thiophenes **306** were synthesized from (*Z*)-1-bromo-1-en-3-ynes **305** according to the procedure illustrated in Scheme 101.[153]



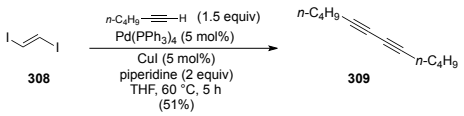
Scheme 101. Synthesis of 2,3,5-trisubstituted thiophenes **306**.

However, compounds **305** were not obtained by Sonogashira monoalkynylation of the corresponding (Z)-1,2-dibromoalkenes, but their synthesis was performed by stereocontrolled alkynylzirconation of alkynes **307** with Cp_2ZrEt_2 and 1-bromo-1-alkynes and subsequent addition of *N*-bromosuccinimide (Scheme 102).[154,155]



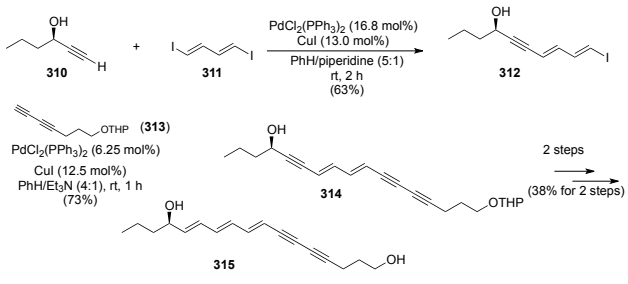
Scheme 102. Synthesis of (*Z*)-1-bromo-1-en-3-ynes **305**.

We would also like to point out that, as far as we know, no protocol has been reported to date for the successful synthesis of stereodefined 1-iodo-1-en-3-ynes by Sonogashira reaction of stereodefined 1,2-diiodoalkenes with terminal alkynes.[156] In the only study carried out so far on this type of reaction, Organ and coworkers found that treatment of (*E*)-1,2-diiodoethene (**308**) with 1-hexyne in THF at 60 °C in the presence of 2 equiv of piperidine, 5 mol% $Pd(PPh_3)_4$, and 5 mol% CuI gave 1,3-diyne **309** in 51% yield and did not produce the required (*E*)-1-iodo-1-en-3-yne (Scheme 103).[142]



Scheme 103. Formation of diyne **309** from 1-hexyne and (*E*)-1,2-diiodoethene (**308**).

Nevertheless, in 2009, Gong and Omollo succeeded in performing the Sonogashira monoalkynylation of (*E*,*E*)-1,4-diiodo-1,3-butadiene (**311**).[157] In fact, the reaction of 2 equiv of **311** with 1 equiv of enantiomerically pure (*R*)-1-hexyn-3-ol (**310**) in a 5:1 mixture of benzene and pyridine at room temperature for 1 h, in the presence of 16.8 mol% $PdCl_2(PPh_3)_2$ and 13 mol% CuI, gave iodoenyne **312** in 63% yield (Scheme 104). The subsequent Sonogashira reaction between **312** and 1.34 equiv of 1,3-diyne **313** produced (*R*) (7*E*,9*E*)-10-dodeca-7,9-dien-5-yn-1-ol (**314**) in 73% yield, which was then employed as a precursor to (*R*)-cicutoxin (**315**) (Scheme 104),[157] a major toxic component of the water hemlocks, *Cicuta virosa* and *C. maculata*.[158–160]



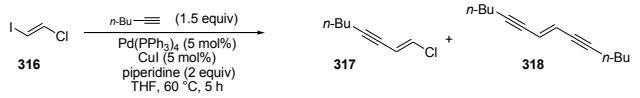
Scheme 104. Synthesis of (*R*)-cicutoxin (**315**).

2.3 Monoalkynylation reactions of stereodefined 1-bromo-2-chloro-, 1-bromo-2-iodo-, 1-bromo-2-

trifluoromethanesulfonyloxy-, 1-chloro-2-iodo-, and 1-fluoro-2-iodo-1-alkenes, and (1*Z*,3*E*)-1-chloro-3-iodo-1,3-butadiene

Before presenting and commenting on the results of the title reactions, we feel it is worth mentioning that, although the exact mechanism of the Pd/Cu-catalyzed Sonogashira reactions is still at present unknown, it is generally believed that (i) the catalytic cycle of the reactions involving alkenyl (pseudo)halides is initiated by the oxidative addition of these electrophiles to a catalytically active Pd(0) species,[4d,5d] and that (ii) this addition, which is considered to be the rate-determining step, is the main source of the selectivity observed in Pd/Cu-catalyzed monoalkynylation reactions of alkenes bearing two different C(sp^2) electrophilic sites. The observed order of reactivity of these sites is as follows: C(sp^2)–I > C(sp^2)–OTf > C(sp^2)–Br > C(sp^2)–Cl >> C(sp^2)–F. This order is related to the relative bond-dissociation energies of the C(sp^2)–(pseudo)halogen bonds.

In accordance with the foregoing, in 2004, Organ and coworkers found that the reaction of (*E*)-1-chloro-2-iodoethene (**316**) with 1.5 equiv of 1-hexyne in THF at 60 °C in the presence of 5 mol% $Pd(PPh_3)_4$, 5 mol% CuI, and 2 equiv of piperidine gave (*E*)-1-chloro-1-octen-3-yne (**317**) in 42% yield along with a trace amount of (*E*)-enediyne **318** (Scheme 105).[142]



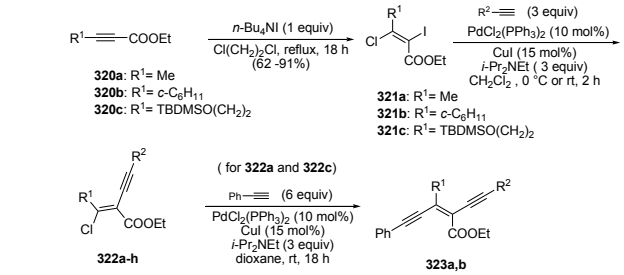
Scheme 105. Synthesis of (*E*)-1-chloro-1-en-3-yne **317**.

On the contrary, the reaction of (*E*)-1-bromo-2-iodoethene (**319**) (Figure 14) with 1-hexyne under similar experimental conditions provided 5,5-dodecadiyne in 62% yield[142] and the required 1-bromo-1-en-3-yne could not be detected.

Figure 14. Structure of compound **319**.

Compound **316** was synthesized in 59% yield by bubbling acetylene gas through a solution of ICl in HCl at -10 °C[161] and (*E*)-1-bromo-2-iodoethene (**319**) was obtained in 56% yield by bubbling acetylene gas through a solution of IBr in 48% HBr at 0 °C.[142]

In 2006, Ogilvie and coworkers synthesized ethyl (*E*)-3-chloro-2-iodo-2-alkenoates **321a-c** by exposure of the corresponding ethyl 2-alkynoates **320a-c** to *n*-Bu_4NI in refluxing dichloroethane and found that the reaction of compounds **321a-c** with 3 equiv of 1-alkynes in CH_2Cl_2 at room temperature in the presence of 10 mol% $PdCl_2(PPh_3)_2$, 15 mol% CuI, and 3 equiv of *i*-Pr_2NEt produced chemoselectively and stereospecifically ethyl (*Z*)-2-(1-alkynyl)-3-chloro-2-alkenoates **322a-h** in good yields (Scheme 106).[162]



Compounds **322**			Yield(%)
	R^1	R^2	
a	Me	Ph	78
b	Me	4-FC_6H_4	77
c	Me	Me_3Si	68
d	Me	*n*-C_6H_{13}	74
e	Me	$(CH_2)_2OTBDMS$	72
f	Me	$CH_2OTBDMS$	76
g	*c*-C_6H_{11}	Ph	68
h	$TBDMSO(CH_2)_2$	$SiMe_3$	79

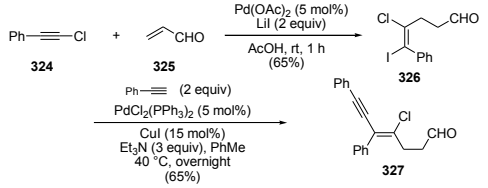
Compounds **323**			Yield(%)
	R^1	R^2	
a	Me	Ph	79
b	Me	$SiMe_3$	42

Scheme 106. Synthesis of chloroenynes **322** and enediynes **323**.

Notably, the alkynylation reaction occurred exclusively at the 2-position of compounds **321**, which in principle is less activated than the 3-position towards oxidative addition to a catalytically active Pd(0) species. Thus, the coupling was halogen selective and this result can be explained taking into account the higher reactivity of the C(sp^2)–I bond over the C(sp^2)–Cl bond.

As shown in Scheme 106, compounds **322a** and **322c** proved to be able to undergo a Sonogashira reaction with a large molar excess of phenylacetylene to give the sterically crowded enediynes **323a** and **323b** in satisfactory yields.[162]

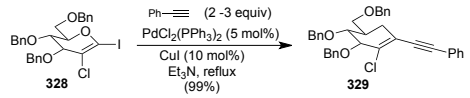
In 2011, Zhu and coworkers reported that the $PdCl_2(PPh_3)_2$/CuI-catalyzed reaction of (*Z*)-4-chloro-5-iodo-5-phenyl-4-pentenal (**326**) with 2 equiv of phenylacetylene in toluene at 40 °C in the presence of 3 equiv of Et_3N occurred with halogen selectivity similar to that observed for the Sonogashira reaction of compounds **321**[162] to give chloroenyne **327** in 65% yield (Scheme 107).[163]



Scheme 107. Synthesis of chloroenyne **327**.

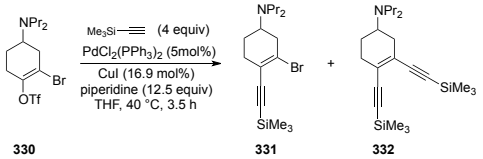
Compound **326** was prepared in 65% yield by treatment of 1-chloro-2-phenylacetylene (**324**) with a solution of 5 equiv of acrolein (**325**), 2 equiv of LiI, and 5 mol% $Pd(OAc)_2$ in AcOH at room temperature (Scheme 107).[163]

More recently, efforts by Koester and Werz to react perbenzylated 2-chloro-1-iodoglucal **328** with phenylacetylene resulted in a halogen-selective monoalkynylation of the pseudoanomeric position that provided 1-phenylethynyl-3,4,6-tri-*O*-benzyl-2-chloroglucal (**329**) in quantitative yield (Scheme 108). The reaction was carried out in refluxing Et_3N for 12 h in the presence of 5 mol% $PdCl_2(PPh_3)_2$ 10 mol% CuI. Even the use of an elevated temperature did not lead to the formation of the required enediyne.[164]



Scheme 108. Halogen-selective synthesis of compound **329**.

The first and only example of chemoselective Sonogashira monocoupling of a 2-bromo-1-enyl triflate was reported by Gmeiner and coworkers in 2005.[165] They found that the reaction of 2-bromocyclohex-1-en-1-yl triflate (**330**) with 4.4 equiv of trimethylsilylacetylene in THF at 40 °C for 3.5 h in the presence of 15.2 mol% $Pd(PPh_3)_4$, 16.9 mol% CuI and 12.9 equiv of piperidine gave dipropyl-[3-bromo-4-(trimethylsilylethynyl)-cyclohex-3-en-1-yl]amine (**331**) in 67% yield along with the 1,2-dialkynylation derivative **332** in 7% yield (Scheme 109).[165]



Scheme 109. Synthesis of compounds **331** and **332**.

As expected, a lower selectivity was observed when **330** was reacted with 5.9 equiv of trimethylsilylacetylene at 95 °C in the presence of 10 mol% $Pd(PPh_3)_4$, 11.1 mol% CuI and 9.5 equiv of piperidine. The reaction gave **324** in 42% yield along with **332** in 24% yield.[165] Interestingly, cleavage of the C(sp)–$SiMe_3$ groups of **332** with TBAF led to the neuroceptor-active enediyne **333** (FAUC 88) (Figure 15), which displayed a highly selective dopamine D_3 receptor affinity.[165]

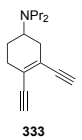
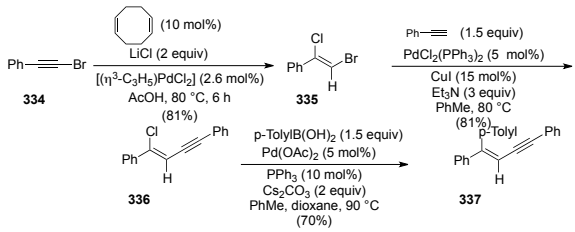


Figure 15. Structure of enediyne **333** (FAUC 88).

Very recently, Zhu and coworkers reported the first example of chemo-, regio- and stereoselective Sonogashira monoalkynylation of a stereodefined 1-bromo-2-chloro-1-alkene.[166] They prepared (*Z*)-1-bromo-2-chloro-2-phenylethene (**335**) in 87% yield by treatment of 1-bromo-2-phenylacetylene (**334**) with 2 equiv of LiCl, 2.6 mol% $[(\eta^3\text{-}C_3H_5)PdCl]_2$ and 10 mol% *cis,cis*-1,5-cyclooctadiene in AcOH at 80 °C for 6 h. Compound **335** was then reacted with 1.5 equiv of phenylacetylene, 3 equiv of Et_3N, 5 mol% $PdCl_2(PPh_3)_2$ and 15 mol% CuI in toluene at 80 °C to give (*Z*)-chloroenyne **336** in 81% yield with complete halogen selectivity (Scheme 110).[166]

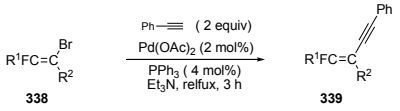


Scheme 110. Synthesis of enynes **336** and **337**.

Moreover, the $Pd(OAc)_2/PPh_3$-catalyzed Suzuki-Miyaura reaction[167] of **336** with *p*-tolylboronic acid gave the trisubstituted enyne **337** in 70% yield (Scheme 110).[166]

In 1991, Eddarir and coworkers reported some examples of chemo-and regioselective copper-free Sonogashira monocoupling reactions of 1-bromo-2-fluoro-1-alkenes.[168,169] As expected on the basis of the significant difference in reactivity between C(sp^2)–F and C(sp^2)–Br bonds in Pd-catalyzed reactions, the Sonogashira reactions produced 1-fluoro-1-en-3-ynes. On the other hand, it should also be taken into account that successful Sonogashira reactions of alkenyl fluorides have not been described to date.

Eddarir and coworkers found that the reaction of stereoisomeric mixtures of 1-bromo-2-fluoro-1-alkenes **338a-d** with 2 equiv of phenylacetylene, 2 mol% $Pd(OAc)_2$ and 4 mol% PPh_3 in refluxing Et_3N for 3 h gave fluoroenynes **339a-d** in satisfactory-to-good yields. (Scheme 111).[168] However, unexpectedly, not all couplings proved to be stereoselective. For example, the Pd/Cu-catalyzed reaction between phenylacetylene and an *E/Z* mixture of compound **338d** in a 2:98 ratio, respectively, provided in 63% yield an *E/Z* mixture of **339d** in a 45:55 ratio, respectively (Scheme 111).



338 339

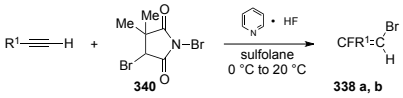
Compounds **338**			*E*/*Z*
	R^1	R^2	
a(i)	Ph	H	92/8
b	n-C_5H_{11}	H	90/10
c	COOEt	Ph	5/95
d	COOEt	2-AcO -3-$MeOC_6H_3$	2/98

(i) Reaction run in n-$BuNH_2$ instead of Et_3N.

Compounds **339**	Yield (%)	*E*/*Z*
a(i)	83	92/8
b	74	90/10
c	68	40/60
d	63	45/ 5

Scheme 111. Synthesis of fluoroenynes **339**.

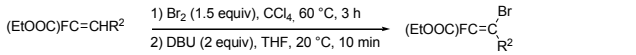
Compounds **338** were not commercially available and those with R^2 = H, *i.e.* **338a** and **338b**, were prepared from the corresponding 1-alkynes by treatment with 1,3-dibromo-5,5-dimethylhydantoin (**340**) and pyridine·HF complex in sulfolane at 0–20 °C (Scheme 112).[168]



340 338 a, b

Scheme 112. Synthesis of 1-bromo-2-fluoro-1-alkenes **338a** and **338b**.

On the other hand, compounds **338c** and **338d** were synthesized in 100 and 74% yield, respectively, by the addition of 1.5 equiv of bromine to (*Z*)-unsaturated esters **341**[170] followed by dehydrobromination with 2 equiv of DBU in THF at 20 °C (Scheme 113).[168]



341

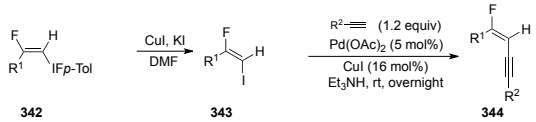
338c: R^2 = Ph(100%)
338d: R^2 = 2-AcO-3-$MeOC_6H_4$(74%)

Scheme 113. Synthesis of compounds **338c** and **338d**.

It is worth noting that the use of a copper-free protocol for the Sonogashira reaction between phenylacetylene and compounds **338** allowed the phenylacetylene dimerization via copper-mediated Glaser coupling to be avoided,[171] thus making it easier to isolate compounds **339**.

In 2001, Yoshida and coworkers[172] synthesized chemo- and stereoselectively (*E*)-1-fluoro-1-en-3-ynes **344a-o**, in high yields by $Pd(OAc)_2$/CuI-catalyzed reaction of 1-alkynes with β-fluoroalkenyl iodides **343a-o**, which were obtained by treatment of (*E*)-(β-fluoroalkenyl)iodonium salts **342a-o**[173] with CuI and KI in DMF (Scheme 114).

The usefulness of the method for preparing compounds **344** was then illustrated by the synthesis of 9-fluorodehydrocoriolic acid methyl ester (**345**) in 91% yield from methyl (*E*)-10-iodo-9-fluoro-9-decenoate (**343p**) and racemic 1-octyn-3-ol (Scheme 115).[172]

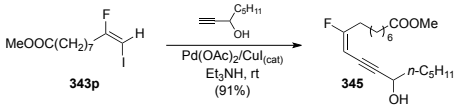


342 343 344

Compounds **344**			Yield%
	R^1	R^2	
a	$MeOOC(CH_2)_8$	n-Bu	85
b	$MeOOC(CH_2)_8$	$SiMe_3$	80
c	$MeOOC(CH_2)_8$	Ph	84
d	$MeOOC(CH_2)_8$	$THPOCH_2$	88
e	$MeOOC(CH_2)_8$	EtOOC-CMe_2CH_2	77
f	$Cl(CH_2)_9$	$SiMe_3$	92
g	$Cl(CH_2)_9$	$AcO(CH_2)_9$	78
h	$Cl(CH_2)_9$	Ph	84
i	$AcO(CH_2)_9$	cyclohexenyl	78
j	$AcO(CH_2)_9$	Ph	84
k	Ph	$THPOCH_2$	85
l	Ph	EtOOC-CMe_2CH_2	67
m	Ph	$MeOOC(CH_2)_8$	90
n	n-$C_{10}H_{21}$	$THPOCH_2$	90
o	n-$C_{10}H_{21}$	n-Bu	78

Scheme 114. Stereoselective synthesis of (*E*)-fluoroenynes **344**.

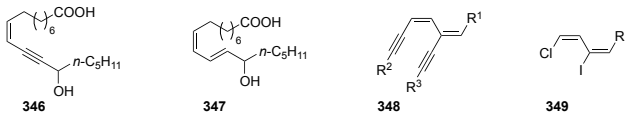
Compounds **344** included polyfunctional derivatives such as **344d**, **344e** and **344g**.



343p 345

Scheme 115. Stereoselective synthesis of compound **345**.

It should be noted that the carboxylic acid corresponding to methyl ester **345** is a fluorinated analogue of 11,12-dehydrocoriolic acid (**346**) (Figure 16), a polyunsaturated carboxylic acid, which was found to exhibit a stronger inhibitory activity than the naturally occurring coriolic acid (**347**) (Figure 16) against rice blast fungus.[174,175]

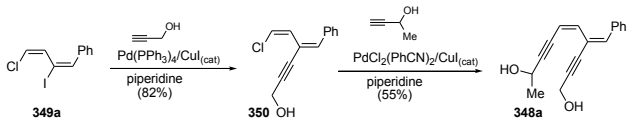


346 347 348 349

Figure 16. Structures of compounds **346–349**.

In concluding this subsection, we wish to mention the results obtained by Alami and coworkers in the context of a study on the synthesis of dienediynes of general formula **348** by sequential chemoselective Sonogashira reactions of 1-chloro-3-iodo-1,3-butadienes **349** (Figure 16).[176] They found that the $Pd(PPh_3)_4$/CuI-catalyzed reaction of **349a** with propargyl alcohol in piperidine provided chemo- and regioselectively 3-(1-alkynyl)-1,3-butadiene **350** in 82% yield (Scheme 116). Treatment of this compound with 3-hydroxy-1-butyne in piperidine in the presence of a

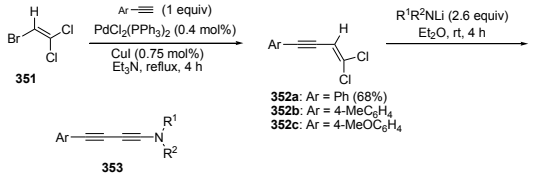
$PdCl_2(PhCN)_2$/CuI catalyst system gave compound **348a** in 55% yield (Scheme 116).[176] However, during the purification step, compound **348a** underwent a partial stereomutation of its trisubstituted double bond.[176]



Scheme 116. Synthesis of compounds **350** and **348a** from 1-chloro-3-iodo-1,3-butadiene **349a**.

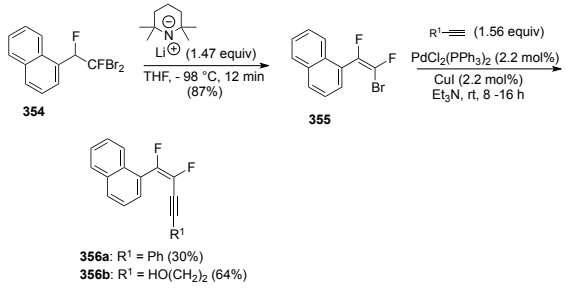
2.4 Monoalkynylation reactions of trihalogenated ethene derivatives bearing two different halogen atoms

A few examples of Sonogashira monoalkynylation reactions of trihalogenated ethene derivatives bearing two different halogen atoms have ben reported in the literature to date. In 1990, Löffler and Himbert[177] described that the reaction of arylacetylenes with 1.57 equiv of 2-bromo-1,1-dichloroethene (**351**)[178] and catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI in refluxing Et_3N occurred chemo- and stereoselectively to give 1,1-dichloro-1-buten-3-ynes **352a-c** in modest-to-satisfactory yields, which could be converted to (1,3-butadiynyl)amines **353** by treatment with 2.6 equiv of lithium amides in Et_2O at room temperature (Scheme 117).[177]



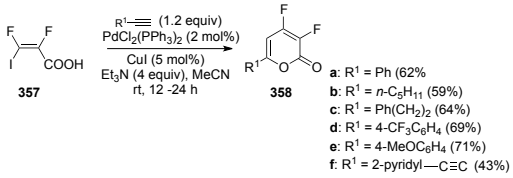
Scheme 117. Synthesis of 1,1-dichloro-1-en-3-ynes **352** and diynes **353**.

Eight years later, it was found that 1-bromo-1,2-difluoro-2-(1-naphthyl)ethene (**355**), which was obtained by treatment of 1,1-dibromo-1,2-difluoro-2-(1-naphthyl)ethane (**354**) with 1.47 equiv of lithium 2,2,6,6-tetramethylpiperidide in THF at -98 °C, was able to react with 1.56 equiv of terminal alkynes, such as phenylacetylene or 1-butyn-3-ol, 2.2 mol% $PdCl_2(PPh_3)_2$ and 2.2 mol% CuI in Et_3N at room temperature to give (*Z*)-1,2-difluoro-1-en-3-ynes **356a**,**b** in modest yields and with retention of configuration (Scheme 118).[179]



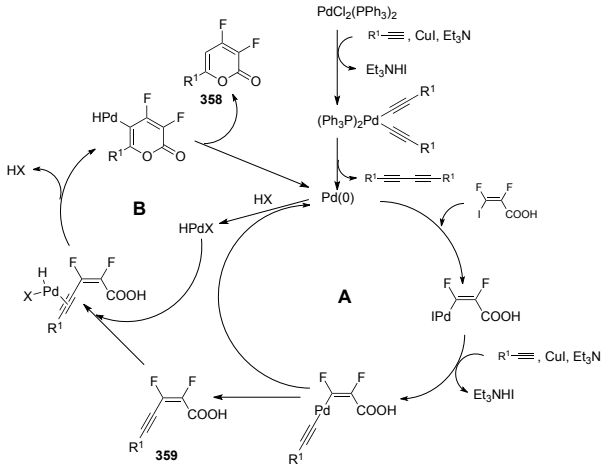
Scheme 118. Synthesis of (*Z*)-1,2-difluoro-1-en-3-ynes **356a**,**b**.

More recently, a tandem process involving a chemoselective Pd/Cu-catalyzed Sonogashira monoalkynylation reaction followed by a 6-*endo-dig* cyclization reaction was employed to prepare in satisfactory yields 3,4-difluoro-6-substituted-2-pyrones **358a–f** as the sole products from (*E*)-2,3-difluoro-3-iodoacrylic acid (**357**), 1.1 equiv of the required terminal alkyne, 2 mol% $PdCl_2(PPh_3)_2$, 5 mol% CuI, and 4 equiv of acetonitrile at room temperature (Scheme 119).[180]



Scheme 119. Synthesis of 3,4-difluoro-6-substituted-2-pyrones **358a–f**.

The mechanism which was proposed to explain the formation of compounds **358** (Scheme 120) involved two catalytic cycles.[180] In the first of these (cycle A), (*Z*)-2,3-difluoro-2-en-4-ynoic acids **359** were formed by a typical Pd/Cu-catalyzed Sonogashira reaction. In the second catalytic cycle (cycle B), compounds **359** were transformed into the final products **358** by a Pd(II)-catalyzed 6-*endo-dig* cyclization reaction. It should be noted, however, that this mechanism does not take into account that the Pd(II)-catalyzed cyclization reactions of (*Z*)-2-en-3-ynoic acids generally occur with poor regioselectivity, affording mixtures of 2-pyrones and γ-alkylidenebutenolides.[181]

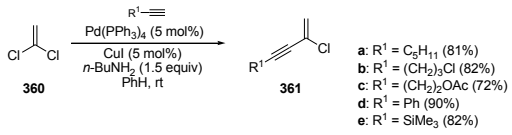


Scheme 120. Proposed mechanism for synthesis of compounds **358**.

3. Monoalkynylation reactions of 1,1-dihalogenated 1-alkenes

3.1 Monoalkynylation reactions of 1,1-dichloro-1-alkenes[182]

The first examples of Sonogashira monoalkynylation reactions of 1,1-dichloroethene (**360**) were described in 1987 by Linstrumelle and coworkers.[183] They reported that the reaction of 5 equiv of **360** with 1 equiv of 1-alkynes, 5 mol% $Pd(PPh_3)_4$, 5 mol% CuI, and 1.5 equiv of *n*-$BuNH_2$ in benzene at room temperature gave 2-chloro-1-en-3-ynes **361** in excellent yields and with high selectivity. The synthesis of compounds **361a–e** is depicted in Scheme 121.



Scheme 121. Synthesis of compounds **361a–e**.

In the case of the synthesis of compound **361a**, less than 4% of the symmetrically 1,1-disubstituted dialkynyl derivative **362a** (Figure 17) was in fact detected in the crude reaction mixture.

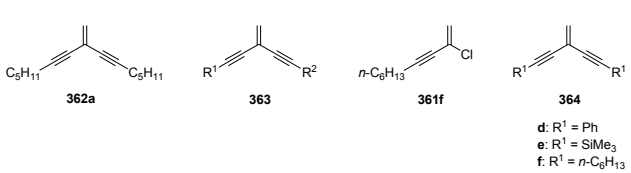
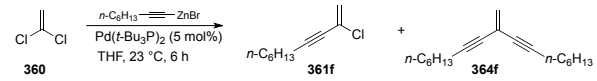


Figure 17. Structures of compounds **362a**, **363** **361f**, and **364d-f**.

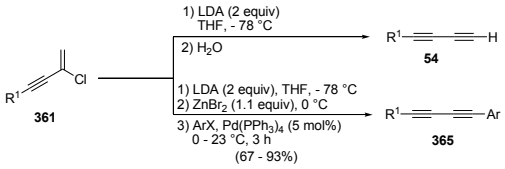
It was also found that compounds **361**, under conditions similar to those reported in Scheme 121, were able to react with 2.2 equiv of 1-alkynes different from those employed for their synthesis to give unsymmetrical enediynes **363** (Figure 17) in 70–75% yield.[183]

In 2003, Qian and Negishi[184] employed the valuable protocol developed by Linstrumelle[183] to prepare compounds **361d**, **361e** and 2-chloro-1-decen-3-yne (**361f**) (Figure 17) in 82, 69 and 66% yield, respectively. These substances were formed along with 5, < 1 and 4%, respectively, of the symmetrical enediynes **364d**, **364e** and **364f** (Figure 17).[183] Interestingly, the selectivity of the reaction that produced **361f** proved to be significantly higher than that of the $Pd(t\text{-}Bu_3P)_2$-catalyzed cross-coupling reaction between 1-octynylzinc bromide and 5 equiv of **360** which provided **361f** in 33% yield along with **364f** in 22% yield (Scheme 122).[184]



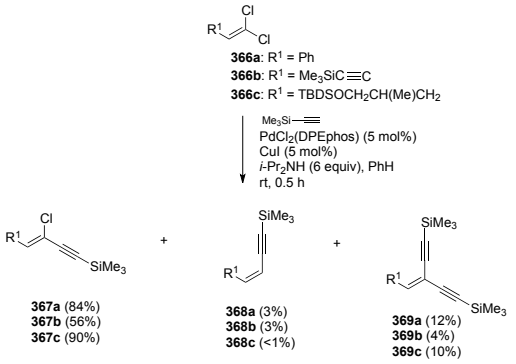
Scheme 122. Synthesis of compounds **361f** and **364f** via Negishi cross-coupling reaction.

Compounds **361** were then found to be useful precursors to terminal 1,3-diynes **54**[184–186] and unsymmetrically 1,4-disubstituted 1,3-diynes **365**[184,187] (Scheme 123).



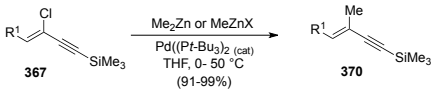
Scheme 123. Synthesis of 1,3-diynes **54** and **365**.

Again in 2003,[188] Negishi and coworkers carried out the Sonogashira-type monoalkynylation reaction of 1,1-dichloro-1-alkenes **366** under experimental conditions significantly different from those used in the synthesis of compounds **361**.[187] Specifically, compounds **366a–c** were reacted with 1.5 equiv of trimethylsilylacetylene, 5 mol% $PdCl_2$(DPEphos), 5 mol% CuI, and 6 equiv of *i*-Pr_2NH in benzene at room temperature. The resulting (*Z*)-configured monocoupling products **367a–c**, which were obtained in 56–90% yields, were, however, accompanied by significant amounts of the corresponding bis-alkynylation derivatives **369a–c** and, in the case of the reactions involving **366a** and **366b**, by the (*E*)-configured derivatives **368a** and **368b**, respectively, in 3% yield, and by compound **368c** in less than 1% yield (Scheme 124).[188]



Scheme 124. Sonogashira-type reactions of 1,1-dichloro-1-alkenes **366a–c**.

Interestingly, compounds **367**, which could also be obtained stereoselectively and in good yields by $PdCl_2$(DPEphos)-catalyzed reaction of dichloroalkenes **366** with trimethylsilylethynylzinc chloride or bromide, proved to be able to undergo stereospecific Pd(*t*-$Bu_3P)_2$-catalyzed methylation with dimethylzinc or methylzinc halides to give the (*E*)-configured derivatives **370** (Scheme 125).[188]



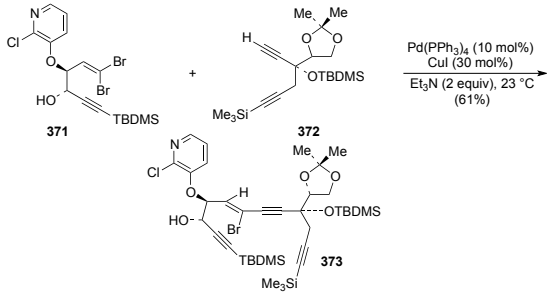
Scheme 125. Synthesis of compounds **370**.

In concluding this subsection, it also seems appropriate to mention that, as far as we know, selective Sonogashira monoalkynylation reactions of 2,2-disubstituted 1,1-dichloroethenes have not been reported to date.

3.2 Monoalkynylation reactions of 1,1-dibromo-1-alkenes[189]

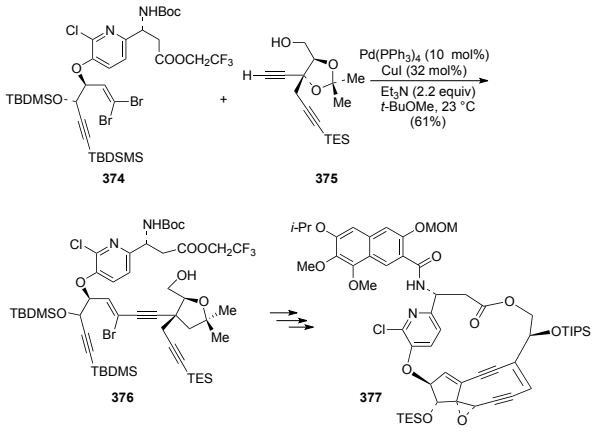
The Sonogashira-type monoalkynylation reactions of 1,1-dibromo-1-alkenes,[190] in contrast to those of 1,1-dichloro-1-alkenes, have received considerable attention. The first example of these coupling reactions was reported in 2000 by Myers and Goldberg.[191] In the context of a study on the synthesis of the core structure of the chromoprotein enediyne antibiotic, kedarcidin,[192] they found that the $Pd(PPh_3)_4$/CuI-catalyzed reaction of dibromoalkene **371** with monoprotected diyne **372** in Et_2O in the presence of Et_3N proceeded optimally to give stereoselectively (*Z*)-alkenyl bromide **373** in 61% yield (Scheme 126).[191]

Such a stereoselectivity can be explained by taking into account that it is presumably of steric origin[191] and involves the oxidative addition of a Pd(0) species to the less hindered C–Br bond in the *E*-position of **371**. Moreover, the stereochemical result of the alkynylation reaction shown in Scheme 126 could be anticipated by taking into account that the rates of the Pd-catalyzed cross-coupling reactions of (*E*)- and (*Z*)-1-bromo-1-alkenes are substantially different and that (*E*)-bromides undergo preferentially intermolecular Pd-catalyzed cross-coupling reactions.[66]



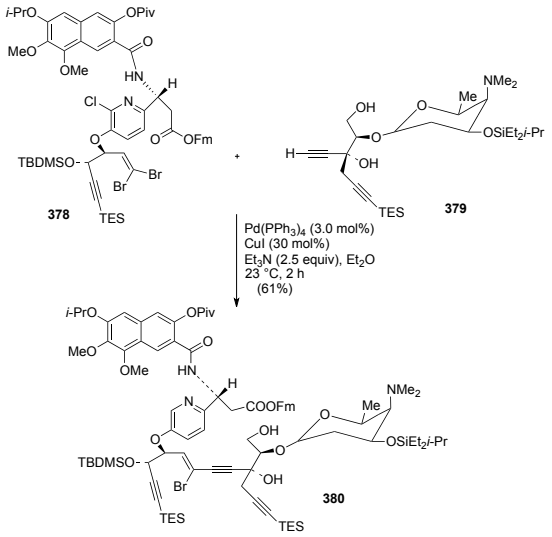
Scheme 126. Synthesis of bromoenyne **373**.

In 2002, Myers and coworkers described the first enantioselective synthesis of the kedarcidin chromophore aglycon in a differentially protected form **377**.[193] 2-Bromo-1-en-3-yne **376**, which was prepared in 61% yield by $Pd(PPh_3)_4$/CuI-catalyzed reaction of 1,1-dibromo-1-alkene **374** with alkyne **375** in *t*-BuOMe at 23 °C in the presence of 2.2 equiv of Et_3N (Scheme 127), was a key intermediate of this appealing route, which was 25 steps in the longest linear sequence.[193]



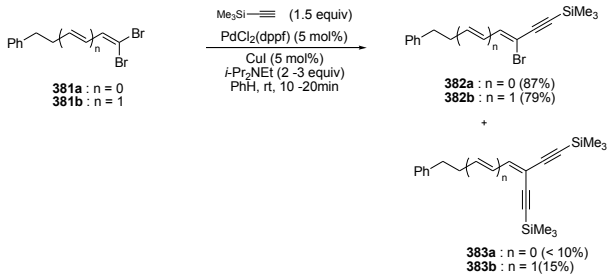
Scheme 127. Stereoselective synthesis of compound **377**.

Five years later, Myers and coworkers performed the synthesis of the proposed structure of the kedarcidin chromophore.[194] A step of this route was the Sonogashira-type stereoselective monoalkynylation of 1,1-dibromo-1-alkene **378** with 1-alkyne **379** in Et_2O at 23 °C in the presence of 2.5 equiv of Et_3N and a high loading of $Pd(PPh_3)_4$ (30 mol%) and CuI (30 mol%) (Scheme 128). The reaction provided bromotrienyne **380** in 61% yield.[195] It is noteworthy that the results of this investigation allowed the proposal of a stereochemical revised structure for the chromophore component of kedarcidin.[194]



Scheme 128. Stereoselective synthesis of compound **380**.

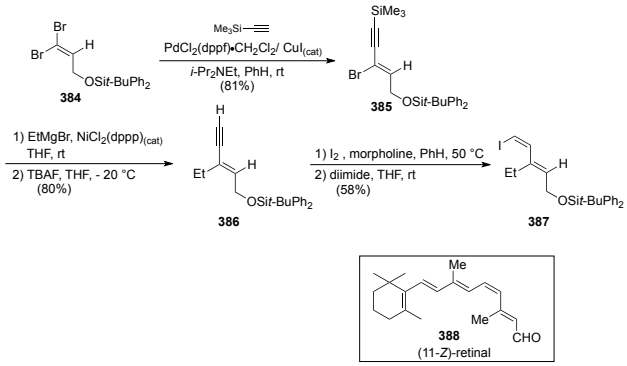
In the early 2000s, a catalyst system consisting of a mixture of 5 mol% $PdCl_2$(dppf) and 4 mol% CuI was used by Uenishi and Matsui for the reactions of trimethylsilylacetylene with 1,1-dibromo-1-alkenes **381a,b** in benzene at room temperature in the presence of 2–3 equiv of *i*-Pr_2NEt (Scheme 129).[195,196]



Scheme 129. Synthesis of compounds **382a,b** and **383a,b**.

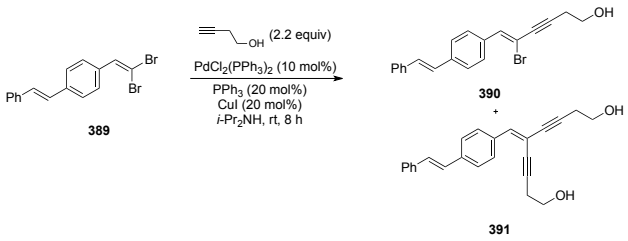
The coupling reactions occurred stereoselectively and that involving **381a** gave the monocoupling compound **382a** in 87% yield along with the bis-alkynylation derivative **383a** in less than 10% yield. On the other hand, the reaction involving **381b** provided compound **382b** in 79% yield along with compound **383b** in 15% yield (Scheme 129).[195,196] It should be noted that the use of $PdCl_2$(dppf) as component of the catalyst system largely improved the selectivity of the couplings. In fact, other Pd complexes such as $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$ and $Pd(dppe)_2$ provided mixtures of bromoenynes, enediynes and the starting 1,1-dibromoalkenes with poor selectivity.[195,196]

The protocol illustrated in Scheme 129 was then used in a key step of the synthesis of (2*E*,4*Z*)-3-ethyl-5-iodopentadienyl silyl ether (**387**), a C11–C15 part of a 13-ethyl-substituted analogue of (11*Z*)-retinal (**388**)[197] which is an important chromophore for the visual system. Indeed, the $PdCl_2$(dppf)·CH_2Cl_2/CuI-catalyzed reaction between 1,1-dibromoalkene **384** and trimethylsilylacetylene gave compound **385** in 81% yield (Scheme 130). Subsequent $NiCl_2$(dppp)-catalyzed reaction of **385** with ethylmagnesium bromide, followed by treatment of the resulting cross-coupling product with TBAF in THF at -20 °C, gave the branched enyne **386** in 58% yield. Finally, iodination of **386** in the presence of morpholine and *cis*-reduction of the resulting 1-iodo-1-alkyne with diimide[198] led to compound **387** in 58% yield (Scheme 130).[19]



Scheme 130. Synthesis of (2*E*,4*Z*)-3-ethyl-5-iodopentadienyl silyl ether (**387**).

In 2001, Kim and coworkers investigated the influence of the amine solvents and the molar ratio between 1-alkyne and 1,1-dibromo-1-alkene on the ratio of the products of the $PdCl_2(PPh_3)_2$/CuI/PPh_3-catalyzed reaction of 2-[(*E*)-4-stilbenyl]-1,1-dibromoethene (**389**) and 3-butyn-1-ol.[199] They found that bromoenyne **390** was the main product only when **389** was reacted with 2.2 equiv of 3-butyn-1-ol in *i*-Pr_2NH for 8 h and that, under these conditions, the reaction (Scheme 131) provided **390** in 68% yield along with enediyne **391** in 20% yield.



Scheme 131. Synthesis of compounds **390** and **391**.

However, when the same Sonogashira reaction was carried out in piperidine, 1,3-diyne **392** (Figure 18) was obtained in 56% yield.[199,200]

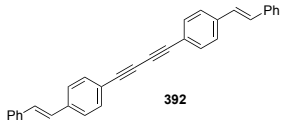
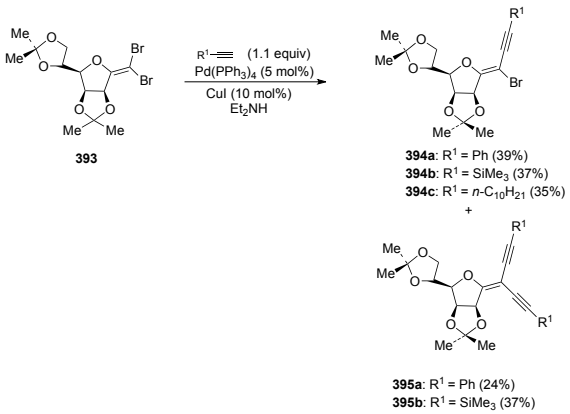


Figure 18. Structure of compound **392**.

More recently, Gómez, López and coworkers investigated the Sonogashira reactions of 1',1'-dibromo-*exo*-glucal **393** with 1,1 equiv of phenylacetylene, trimethylsilylacetylene and 1-dodecyne in Et_2NH, in the presence of catalytic quantitites of $Pd(PPh_3)_4$ and CuI.[201] Unexpectedly, the reaction involving phenylacetylene gave a stereoisomeric mixture of 2-bromo-1-en-3-yne **394a** in 39% yield along with the bis-alkynylation derivative **395a** in 24% yield (Scheme 132).



Scheme 132. Sonogashira reaction of compound **393**.

Bromoenyne **394b** was also obtained as a stereoisomeric mixture in 37% yield along with compound **395b** in 37% yield from the reaction of **393** with trimethylsilylacetylene (Scheme 132). However, the Sonogashira reaction of **393** with 1-dodecyne could be stopped at the monoalkynylation derivative **394c**, but this compound was still obtained as a stereoisomeric mixture in 35% yield (Scheme 132).[202]

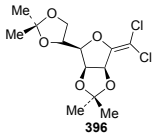
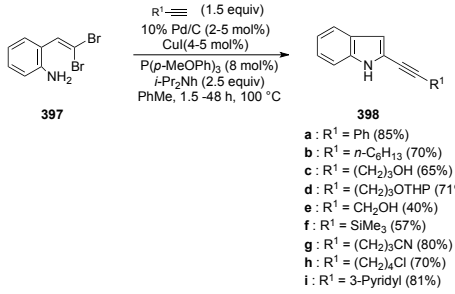


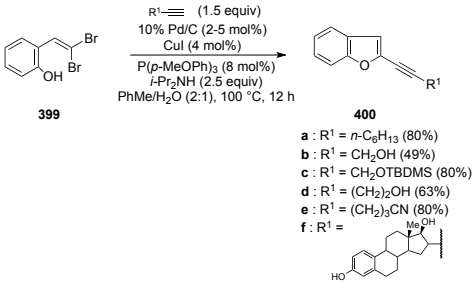
Figure 19. **S**tructure of dichloro-*exo*-glucal **396**.

Interestingly, dichloro-*exo*-glucal **396** (Figure 19) did not undergo a Sonogashira reaction under the various conditions attempted.

In concluding this subsection, we wish to mention the rapid access to a variety of 2-(1-alkynyl)-substituted indoles and benzofurans by Pd/C-CuI-P(*p*-MeOPh)$_3$-catalyzed tandem stereoselective Sonogashira-Ullman coupling of geminal dibromovinyl substrates with terminal alkynes.[202] In 2007, Lautens and coworkers found that treatment of *o*-gem-dibromovinylaniline (**397**) with 1.5 equiv of 1-alkynes, 2–5 mol% of 10% Pd/C, 4–5 mol% CuI, 8 mol% P(*p*-MeOPh)$_3$, and 2.5 equiv of *i*-Pr_2NH in toluene at 100 °C for 1.5–48 h gave 2-(1-alkynyl)indoles **398a-i** in high yields (Scheme 133). Moreover, 2-(1-alkynyl)benzofurans **400a-f** were obtained from *o*-gem-dibromovinylphenol (**399**) and 1-alkynes using a protocol similar to that employed to prepare compounds **394**. However, the use of a 2:1 mixture of toluene and water instead of toluene as the solvent provided better yields of compounds **400** (Scheme 134).[202]



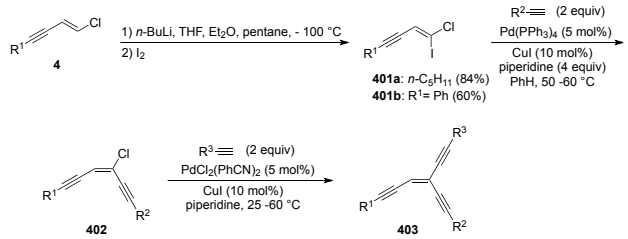
Scheme 133. Synthesis of compounds **398**.



Scheme 134. Synthesis of compounds **400**.

3.3 Monoalkynylation reactions of 1,1-dihalogenated 1-alkenes bearing different halogen atoms

In 1995, Linstrumelle and coworkers reported that metalation of (*E*)-1-chloro-1-en-3-ynes **4** with *n*-BuLi (1 equiv) at -100°C followed by treatment with iodine gave (*Z*)-1-chloro-1-iodo-1-en-3-ynes **401** in good yields (Scheme 135).[203] Coupling of **401a** and **401b** with 2 equiv of 1-alkynes in the presence of 2 equiv of piperidine, 5 mol% $Pd(PPh_3)_4$ and 10 mol% CuI gave chemoselectively and stereospecifically chloroenediynes **402a-i** in excellent yields (Scheme 135).[203]



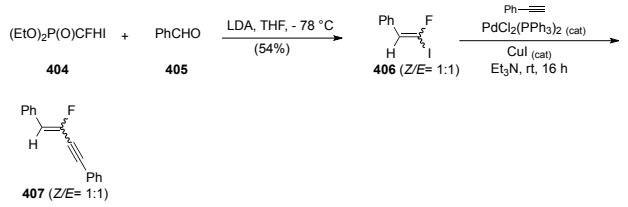
Compound 402			Yield (%)
	R^1	R^2	
a	*n*-C_5H_{11}	CH_2OH	79
b	*n*-C_5H_{11}	$(CH_2)_2OH$	87
c	*n*-C_5H_{11}	Ph	90
d	*n*-C_5H_{11}	$SiMe_3$	72
e	*n*-C_5H_{11}	*n*-C_5H_{11}	85
f	Ph	$SiMe_3$	75
g	Ph	CH_2OH	71
h	Ph	$(CH_2)_2OH$	90
i	Ph	Ph	81

Compound 403				Reaction Temp (°C)	Yield (%)
	R^1	R^2	R^3		
a	*n*-C_5H_{11}	$(CH_2)_2OH$	Ph	25	72
b	*n*-C_5H_{11}	Ph	$(CH_2)_2OH$	60	44
c	*n*-C_5H_{11}	$SiMe_3$	CH_2OH	25	45
d	*n*-C_5H_{11}	*n*-C_5H_{11}	Ph	60	64
e	Ph	$(CH_2)_2OH$	Ph	25	78
f	Ph	Ph	Ph	25	59

Scheme 135. Synthesis of chloroenediynes **402** and enetriynes **403**.

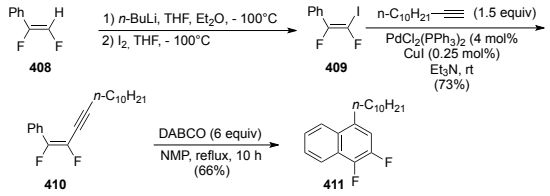
Compounds **402** were then converted to stereoisomerically pure enetriynes **403a-f** in moderate-to-good yields by $PdCl_2(PhCN)_2$/CuI-catalyzed coupling with 1-alkynes in piperidine at 25–60 °C (Scheme 135).[203]

In 2001, Zhang and Burton synthesized a stereoisomeric mixture of 1-fluoro-1-iodostyrene (**406**) (*E*/*Z* = 1:1) by a Wittig-Horner reaction of diethyl fluoroiodomethylphosphate (**404**) with benzaldehyde (**405**) and showed that the coupling of **406** with phenylacetylene in Et_3N at room temperature for 16 h, in the presence of catalytic quantities of $PdCl_2(PPh_3)_2$ and CuI, gave a 1:1 mixture of (*Z*)- and (*E*)-1,4-diphenyl-2-fluoro-1-buten-3-yne (**407**) in 38% yield after chromatographic purification of the resulting crude reaction mixture (Scheme 136).[204] Interestingly, the 1:1 *Z*/*E* ratio for **407** improved to 7:3 after a modest reaction time.[204]



Scheme 136. Synthesis of compound **407**.

An example of a chemoselective and stereospecific Sonogashira monoalkynylation reaction of a stereodefined 1-fluoro-1-iodo-1-alkene was described in 2006 by Burton and coworkers.[205] They prepared (*E*)-1,2-difluoro-1-iodo-2-phenylethene (**409**) in 83% yield by the reaction of (*Z*)-1,2-difluorostyrene (**408**) with *n*-BuLi in THF/Et_2O at -100 °C for 0.5 h followed by the addition of a THF solution of iodine. Compound **409** was subsequently reacted with 1.5 equiv of 1-dodecyne, 4 mol% $PdCl_2(PPh_3)_2$ and 0.25 mol% CuI in Et_3N at room temperature to give (*Z*)-1,2-difluoro-1-phenyl-1-tetradecen-3-yne (**410**) in 73% yield.

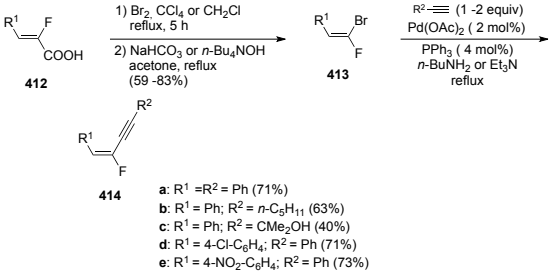


Scheme 137. Synthesis of compounds **409–411** from (*Z*)-1,2-difluorostyrene (**408**).

Moreover, it was discovered that **410** underwent cyclization to produce 4-decyl-1,2-difluoronaphthalene (**411**) in 66% yield when treated with 6 equiv of DABCO in refluxing NMP for 10 h (Scheme 137).[205]

As far as we know, examples of Sonogashira monoalkynylation reactions of 1-iodo-1-bromo-, 1-bromo-1-chloro-, and 1-chloro-1-fluoro-1-alkenes have not been reported in the literature to date. On the contrary, significant attention has been directed to Pd/Cu-catalyzed or Cu-free Pd-catalyzed reactions of stereodefined and (*E*/*Z*)-mixtures of 1-bromo-1-fluoro-1-alkenes[206,207] with 1-alkynes.

In 1990, Eddarir and coworkers synthesized (*E*)-2-fluoro-1-en-3-ynes **414a–e** by $Pd(OAc)_2$/PPh_3-catalyzed chemoselective and stereospecific crosscoupling of 1-alkynes with the required (*Z*)-1-bromo-1-fluoroalkenes **413** in refluxing *n*-$BuNH_2$ or Et_3N (Scheme 138).[206a] Compounds **413** were prepared by bromination of the corresponding (*E*)-2-fluoro-2-alkenoic acids **412** followed by debromocarboxylation (Scheme 138).[206a]



Scheme 138. Synthesis of fluoroenynes **414a-e**.

Notably, compound **414e** could not be synthesized in *n*-$BuNH_2$. In fact, the Sonogashira reaction in *n*-$BuNH_2$ gave carboxyamide **415** (Figure 20) of instead the expected enyne.[206a] Nevertheless, **414e** was prepared in 72% yield by a copper-free Pd-catalyzed reaction of (*Z*)-1-bromo-1-fluoro-2-(4-nitrophenyl)ethene (**413c**) with phenylacetylene in Et_3N.

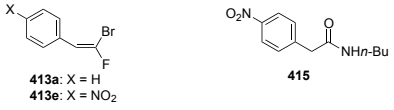
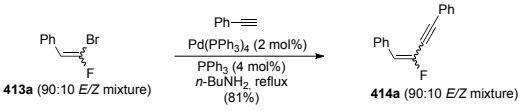


Figure 20. Structures of compounds **413a**, **413e** and **415**.

It was also observed that (Z)-1-bromo-1-fluorostyrene (**413a**) (Figure 20) underwent stereomutation by heating at 60 °C in the presence of 0.1 equiv of $Pd(OAc)_2$ and that the Sonogashira reaction of the resulting 90:10 *E/Z* stereoisomeric mixture with phenylacetylene, according to the protocol used to prepare stereoisomerically pure **414a**, provided a 90:10 *Z/E* mixture of this fluoroenyne (Scheme 139).[206a]

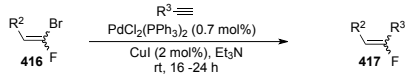


Scheme 139. Synthesis of 90:10 mixture of (Z)- and (*E*)-**414a**.

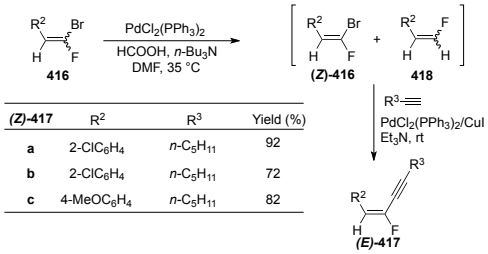
In 2001, Zhang and Burton reported that the reaction of *E/Z* mixtures of 1-bromo-1-fluoro-1-alkenes **416** with equimolar amounts of 1-alkynes in Et_3N at room temperature in the presence of 0.7 mol% $PdCl_2(PPh_3)_2$ and 2 mol% CuI occurred stereoselectively to give predominantly (*Z*)-2-fluoro-1-en-3-ynes **417** in satisfactory yields (Table 2, entries 1–10).[204] On the other hand, the coupling reactions involving *Z*-configured compounds **416** were found to produce fluoroenynes (*E*)-**417** in high yields (entries 11–16, Table 2).[204]

In 2002, Burton and coworker described a new protocol for the synthesis of (*E*)-2-fluoro-1-en-3-ynes **410** from stereoisomeric mixtures of 1-bromo-1-fluoro-1-alkenes.[208] They reported that 1:1 mixtures of (*E*)- and (*Z*)-configured compounds **416** could be stereoselectively reduced using the HCOOH/*n*-Bu_3N/$PdCl_2(PPh_3)_2$/DMF system to give mixtures of (*Z*)-1-bromo-1-fluoro-1-alkenes, (*Z*)-**416**,[206] and (*E*)/(*Z*)-1-fluoro-1-alkenes **418** (Scheme 140). It was subsequently reported that, when these mixtures were treated with terminal alkynes, 4 mol% $PdCl_2(PPh_3)_2$, and 1 mol% CuI in Et_3N at room temperature, stereoisomerically pure compounds (*E*)-**417** were obtained in high yields (Scheme 140).[209]

Table 2. Stereoselective $PdCl_2(PPh_3)_2$/CuI-catalyzed coupling of (*E/Z*)-1-bromo-1-fluoro-1-alkenes **416** with 1-alkynes.



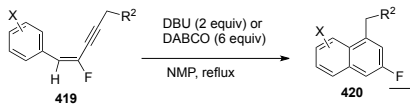
Entry	Compounds **416**		Compounds **417**			Yield (%)
	R^1	*E/Z*	R^2	R^3	*E/Z*	
1	Ph	6/5	Ph	Ph	100:0	38
2	Ph	1/1	Ph	n-C_5H_{11}	98:2	46
3	Ph	3/2	Ph	$CH_2OCH(OEt)Me$	95:5	54
4	Ph	6/5	Ph	$SiMe_3$	99:1	23
5	Ph	1/1	Ph	CH(OH)Me	95:5	49
6	Ph	1/1	Ph		99:1	45
7	4-ClC_6H_4	1/1	4-ClC_6H_4	CH(OH)Me	99:1	48
8	n-C_7H_{15}	7/3	n-C_7H_{15}	Ph	90:10	64
9	PhHMe	7/3	PhCHMe	CH(OH)Me	92:8	53
10	n-C_7H_{15}	1/1	n-C_7H_{15}	$CH_2OCH(OEt)Me$	93:7	46
11	Ph	3/97	Ph	Ph	3:97	88
12	Ph	0/100	Ph	n-C_5H_{11}	0:100	87
13	Ph	>2/98	Ph	$CH_2OCH(OEt)Me$	>2:98	89
14	Ph	0/100	Ph	CH(OH)Me	>1:99	89
15	4-ClC_6H_4	0/100	4-ClC_6H_4	CH(OH)Me	0:100	77
16	PhCHMe	0/100	PhCHMe	CH(OH)Me	0:100	78



(*Z*)-**417**	R^2	R^3	Yield (%)
a	2-ClC_6H_4	n-C_5H_{11}	92
b	2-ClC_6H_4	n-C_5H_{11}	72
c	4-$MeOC_6H_4$	n-C_5H_{11}	82

Scheme 140. Stereoselective synthesis of (*E*)-2-fluoro-1-en-3-ynes (*E*)-**417**.

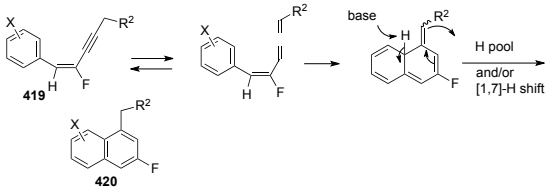
It was also found that some compounds obtained as described above, *i.e.* (*E*)-1-aryl-2-fluoro-1-en-3-ynes **419**, underwent cyclization by treatment with DABCO or DBU in refluxing NMP to give 3-fluoro-1-substituted naphthalenes **420** in good-to-excellent yields (Scheme 141).[209]



	Compounds **420**		
	X	R^2CH_2	Yield%
a	4-F	n-Pr	77
b	4-F	n-Bu	77
c	4-CF_3	n-Pr	89
d	4-CF_3	n-Bu	82
e	4-CF_3	n-C_9H_{19}	74
f	4-CF_3	Bn	69
g	3,5-F_2	n-Pr	55
h	3,5-F_2	n-Bu	66

Scheme 141. Synthesis of 3-fluoro-1-substituted naphthalenes **420**.

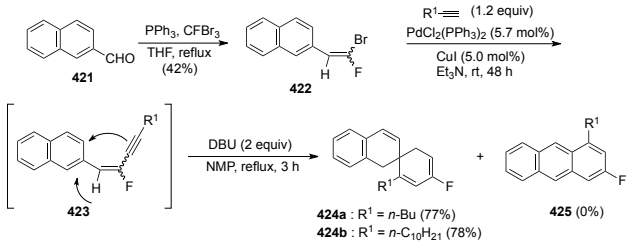
The mechanism of the cyclization (Scheme 142) was thought to involve a base-catalyzed isomerization of the 1,3-enyne system of compounds **419** to the corresponding allene and a subsequent 6π-cyclization to form a two-ring system.[205,209]



Scheme 142. Proposed mechanism for synthesis of naphthalenes **420**.

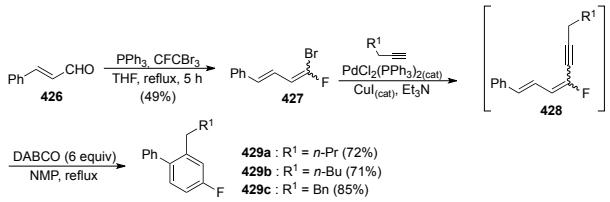
Compounds **420** might then be formed from a [1,7]-H shift without assistance of the base or from the abstraction of H from C-9 by the base, followed by acquisition of H from the proton pool (a trace of moisture in the system or the protonated base) (Scheme 142).[205,209]

In 2006, Burton and coworkers also described a facile procedure for the site-specific preparation of fluorinated phenanthrene derivatives from 1-bromo-1-fluoro-1-alkenes.[209] Specifically, a stereoisomeric mixture of 1-bromo-1-fluoro-2-(2-naphthyl)ethene (**422**), which was prepared in 42% yield from 2-naphthaldehyde (**421**), was reacted with 1.2 equiv of 1-alkynes, 5.7 mol% $PdCl_2(PPh_3)_2$ and 5 mol% CuI in Et_3N at room temperature to afford 2-fluoro-1-en-3-ynes **423** as stereoisomeric mixtures. Finally, treatment of the crude compounds **423** with 0.2 equiv of DBU in NMP under reflux for 2 h was found to provide site selectively the fluorinated phenanthrene derivatives **424a**, **b** in good yields (Scheme 143).[209] Noteworthy is that no anthracene derivatives **425** were obtained.



Scheme 143. Synthesis of phenanthrenes **424a,b**.

Again in 2006, Wang and Burton synthesized fluorodienynes **428** by $PdCl_2(PPh_3)_2$/CuI-catalyzed chemoselective Sonogashira reaction of 1-alkynes with a mixture of (1*E*,3*E*)- and (1*Z*,3*E*)-1-bromo-1-fluoro-4-phenyl-1,3-butadiene (**427**), which was prepared in 49% yield from *trans*-cinnamaldehyde (**426**) (Scheme 144).[210] They also described that the reaction of crude compounds **428** with 6 equiv of DABCO in refluxing NMP yielded 2-substituted-4-fluorobiphenyls **429a-c** in high yields (Scheme 144).[210]



Scheme 144. Synthesis of fluorobiphenyls **429a-c**.

The cyclization mechanism (Scheme 145), which is similar to that illustrated for the synthesis of compounds **420**, was proposed to involve the DABCO-catalyzed isomerization of the dienyne system of compounds **428** to a diene-allene system, followed by the formation of intermediates **430** by a 6π-cyclization reaction, and, finally, isomerization of these cyclized intermediates to the aromatic derivatives **429** (Scheme 145).[210]

Scheme 145. Proposed mechanism for synthesis of compounds **429**.

4. Monoalkynylation reactions of stereodefined bis(enol triflates)

In the last three decades, enol triflates, due to their facile preparation from carbonyl compounds,[211] have been widely used as electrophiles in transition metal-catalyzed cross-coupling reactions.[212] The first examples of Pd-catalyzed coupling reactions of enol triflates with terminal alkynes were described in 1986 by Cacchi and coworkers.[213] The reactions, which were carried out at 60 °C in the presence of a base and $Pd(OAc)_2$ as catalyst, were found to give conjugated enynes in good yields. It was also observed that the addition of CuI as co-catalyst allowed the reactions to proceed at room temperature.[213]

A few years later, site-selective Pd/Cu-catalyzed Sonogashira couplings of 1-alkynes with bis(enol triflates) (*Z*)-**431**,[214,215a,b] (*E*)-**431**,[214,216a,b] (*Z*)-**432**,[217a–d] and (*E*)-**432**[217c] (Figure 21) were extensively used by the research teams of Terashima and Brückner to construct monocyclic dienediyne models of the neocarzinostatin chromophore.[218]

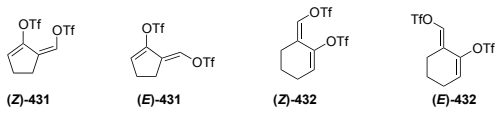
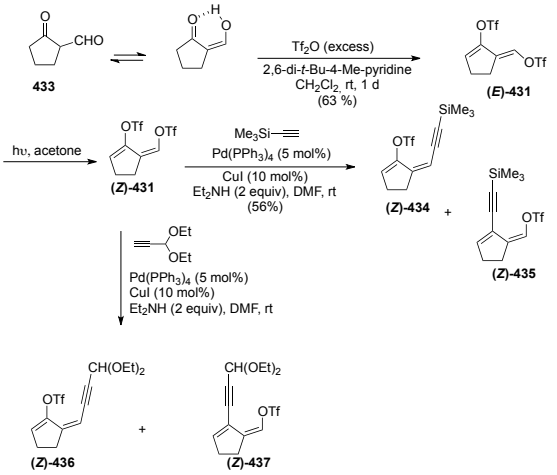


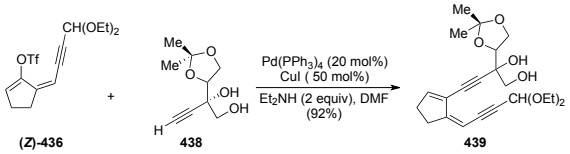
Figure 21. Structures of compounds (*Z*)- and (*E*)-**431** and (*Z*)- and (*E*)-**432**.

In 1992, Terashima and coworkers prepared (*E*)-5-[(trifluoromethanesulfonyloxy)methylene]-1-cyclopenten-1-yl trifluoromethanesulfonate [(*E*)-**431**] and its (*Z*)-stereoisomer, (*Z*)-**431**, as follows.[214]



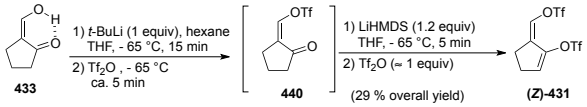
Scheme 146. Synthesis of compounds (*Z*)-**434**, (*Z*)-**435**, (*Z*)-**436**, and (*Z*)-**437**.

The reaction of 2-formylcyclopentanone (**433**) with a molar excess of triflic anhydride in the presence of 2,6-di-*t*-butyl-4-methylpyridine afforded (*E*)-**431** in 63% yield, which, by irradiation in acetone with a high-pressure mercury lamp, produced stereomutation of the *exo*-cyclic double bond to give (*Z*)-**431** in 37% yield along with (*E*)-**431** in 48% recovery (Scheme 146). The site-selective monoalkynylation of (*Z*)-**431** was then investigated and it was found that the reaction of equimolar amounts of trimethylsilylacetylene and (*Z*)-**431** in DMF at room temperature in the presence of 5 mol% $Pd(PPh_3)_4$, 10 mol% CuI and 2 equiv of Et_2NH produced an inseparable mixture of regioisomeric compounds (*Z*)-**434** and (*Z*)-**435** in a ca. 4:1 molar ratio, respectively (Scheme 146).[183] However, treatment of (*Z*)-**431** with 3,3-diethoxy-1-propyne under the same conditions as mentioned above resulted in the formation of the regioisomeric compounds (*Z*)-**436** and (*Z*)-**437**, which could be separated in 50 and 10% yield, respectively (Scheme 146). Interestingly, compound (*Z*)-**436** proved to be suitable to undergo a coupling reaction with 1-alkyne **438** in the presence of 2 equiv of Et_2NH and high loadings of $Pd(PPh_3)_4$ and CuI to give the (*Z*)-dienediyne diol acetal **439** in 92% yield (Scheme 147).[214]



Scheme 147. Synthesis of dienediyne **439**.

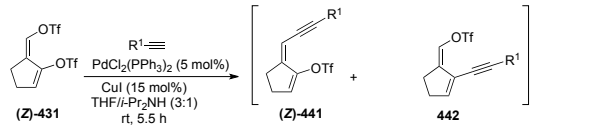
Again in 1992, bis(enol triflate) (*Z*)-**431** was synthesized by Brückner, Suffert and coworkers[215a] from 2-formylcyclopentanone (**433**) using a procedure different from that illustrated in Scheme 146. Specifically, **433** was reacted with 1 equiv of *t*-BuLi in hexane and THF at -65 °C for 15 min and the resulting lithium enolate was treated with 1 equiv of triflic anhydride for a few minutes to give the unstable monotriflate **440** (Scheme 148). This compound was then converted without purification into (*Z*)-**431** in 29% overall yield by deprotonation with lithium hexamethylsilazide at -65 °C followed by reaction with triflic anhydride. Remarkably, *N,N*-bis(trifluoromethanesulfonyl)aniline,[216b] which had previously been employed instead of triflic anhydride, secured a 36% overall yield of (*Z*)-**431** but at higher costs.



Scheme 148. Synthesis of (*Z*)-**431** according to Brückner, Suffert and coworkers.[215a]

In complete agreement with the results reported by Terashima,[214] Brückner, Suffert and coworkers observed that the exocyclic triflate moiety of (*Z*)-**431** underwent faster Pd/Cu-catalyzed Sonogashira coupling than its endocyclic counterpart.[215] In fact, when (*Z*)-**431** was reacted with 1.1 equiv of trimethylsilylacetylene, 10 mol% $PdCl_2(PPh_3)_2$ and 30 mol% CuI in a 3:1 mixture of THF and *i*-Pr_2NH, an inseparable 4:1 mixture of compounds (*Z*)-**434** and (*Z*)-**435** was isolated in 76% yield.[215b]

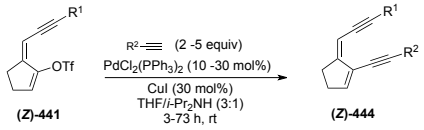
Brückner and coworkers also developed a procedure for the isolation of the major components (*Z*)-**441** of the mixtures of regioisomeric compounds (*Z*)-**441** and **442**, which were obtained by $PdCl_2(PPh_3)_2$/CuI-catalyzed Sonogashira monoalkynylation reactions of bis(enol triflate) (*Z*)-**431** with terminal alkynes.[215a] These mixtures, still containing the catalytically active Pd(0) species, could be resolved kinetically by the addition of another terminal alkyne in substoichiometric amounts (0.3–0.4 equiv), which reacted preferentially with the minor components **442** of the mixtures by converting them into the biscoupling derivatives (*Z*)-**443** and (*Z*)-**444** (Scheme 149).[215a] Compounds (*Z*)-**441** now proved to be separable and were obtained in 37–52% yields based on (*Z*)-**431**.[215a]



Compounds (*Z*)-**441**		
	R^1	Yield (%)
a	CH_2OTHP	47
b	$CH_2OSiMePh_2$	35
c	$(CH_2)_2OH$	36
d	$(CH_2)_3OH$	37
e	CH_2SiMe_3	37
f	$SiMe_3$	52

Scheme 149. Procedure for synthesis and separation of compounds (*Z*)-**441**.

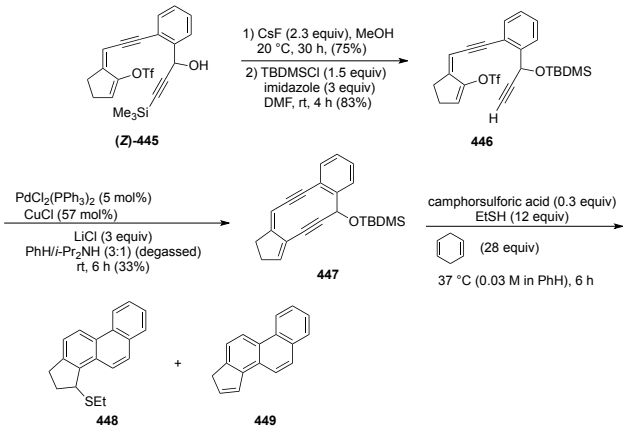
It was also found that dienediynes (*Z*)-**444** containing differentiated alkynyl groups could be accessed in modest to good yields by $PdCl_2(PPh_3)_2$/CuI-catalyzed coupling of enol triflates (*Z*)-**441** with a molar excess of 1-alkynes in a 3:1 mixture of THF and *i*-Pr_2NH at room temperature (Scheme 150).[215a]



Compounds (*Z*)-**444**			Yield%
	R^1	R^2	
a	CH_2OTHP	$SiMe_3$	77
b	CH_2OTHP	CH_2SiMe_3	52
c	$CH_2OSiMePh_2$	CH_2SiMe_3	55
d	CH_2OTHP	*n*-C_4H_9	29
e	$(CH_2)_2OH$	$SiMe_3$	73
f	$(CH_2)_2OH$	CH_2SiMe_3	65
g	$(CH_2)_3OH$	$SiMe_3$	72
h	CH_2SiMe_3	$(CH_2)_2OH$	60
e	$SiMe_3$	$(CH_2)_2OH$	60
j	$SiMe_3$	$(CH_2)_3OH$	57

Scheme 150. Synthesis of dienediynes (*Z*)-**444**.

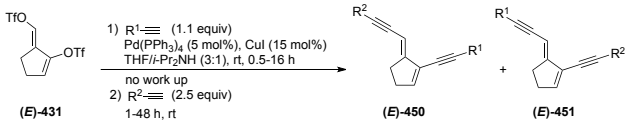
In 1994, Suffert and Brückner[219] synthesized enynyl triflate (*Z*)-**445** using their earlier-developed protocol[215a] and then converted this compound into the terminal acetylene derivative (*Z*)-**446**, which was found to decompose readily in the absence of solvent (Scheme 151).



Scheme 151. Synthesis of compounds **448** and **449**.

Intramolecular $PdCl_2(PPh_3)_2$/CuCl/LiCl-catalyzed alkynylation of (*Z*)-**446** led to dienediyne **447** in 33% yield, which could be stored at -30 °C for several days (Scheme 151).[217b,219] It was also established that treatment of **446** with 0.3 equiv of camphorsulfonic acid, 28 equiv of 1,4-cyclohexadiene and 12 equiv of ethylthiol in benzene at 37 °C furnished the cyclopenta[*b*]phenanthrene **448** in 31% yield through cycloaromatization along with compound **449** in 6% yield (Scheme 151).[217b,219] Remarkably, when the Sonogashira-type intramolecular reaction of (*Z*)-**445** was performed using a typical $PdCl_2(PPh_3)_2$/CuI catalyst system, compound **448** was obtained in only 10% yield.[219]

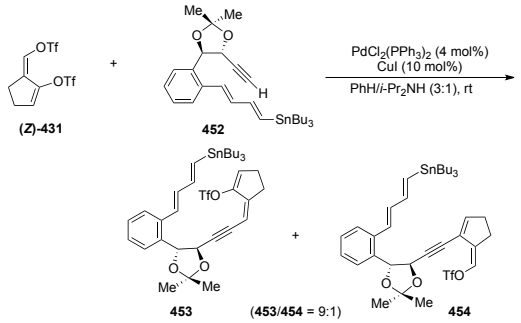
Surprisingly, bis(enol triflate) (*E*)-**431** proved to be able to undergo $Pd(PPh_3)_4$/CuI-catalyzed coupling with terminal alkynes in a 3:1 mixture of THF and *i*-Pr_2NH preferentially at the endocyclic more sterically hindered triflate site. In fact, consecutive additions of two different terminal alkynes furnished dienediynes (*E*)-**450** and (*E*)-**451** as 87:13÷68:32 mixtures in 48–91% yields after flash chromatography on silica (Scheme 152).[216b]



R^1	R^2	Total Yield(%)	(*E*)-**450**	(*E*)-**451**	(*E*)-**450**/(*E*)**451**
4-$ClC_6H_4OTBDMS$	CH_2SiMe_3	48	a	a	75:25
CH_2SiMe_3	4-$ClC_6H_4OTBDMS$	55	b	b	68:32
$SiMe_3$	$CH_2OTBDMS$	83	c	c	80:20
$CH_2OTBDMS$	$SiMe_3$	91	d	d	80:20
CH_2OTHP	$CH_2OTBDMS$	63	e	e	77:23
$CH_2OTBDMS$	CH_2OTHP	74	f	f	81:19
CH_2OTHP	CH_2OSi*t*-$BuPh_2$	72	g	g	82:18
CH_2OSi*t*-$BuPh_2$	CH_2OTHP	62	h	h	87:13
CH_2OSi*t*-$BuPh_2$	$SiMe_3$	53	i	i	80:20
CH_2SiMe_3	4-$ClC_6H_4COTBDMS$	68	j	j	75:25
4-$ClC_6H_4OTBDMS$	CH_2SiMe_3	54	k	k	80:20
$SiMe_3$	$CH_2OTBDMS$	68	l	l	80:20

Scheme 152. Selective synthesis of dienediynes (*E*)-**450** and (*E*)-**451**.

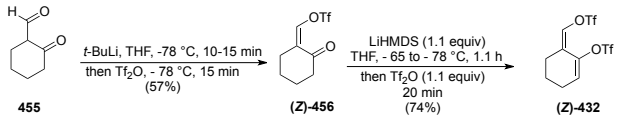
More recently, in the context of a study on the synthesis of polycyclic substructures present in several natural products, Suffert and coworkers found that the reaction of bis(enol triflate) (*Z*)-**431** with 1.1 equiv of alkyne **452** in a 3:1 mixture of benzene and *i*-Pr_2NH at room temperature, in the presence of 4 mol% $PdCl_2(PPh_3)_2$ and 10 mol% CuI, produced chemoselectively a 9:1 mixture of compounds **453** and **454** (Scheme 153) from which the required monotriflate **453** was isolated in 79% yield.[220]



Scheme 153. Selective synthesis of monotriflate **453**.

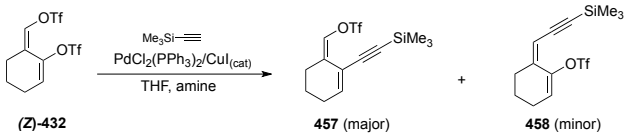
Compound **453** was separated from **454** by applying a previously described procedure,[215a] *i.e.* the addition of a substoichiometric amount of a terminal alkyne different from **452**, which reacted preferentially with **454** by converting this compound into a bis-coupling derivative that was readily separated from **453**.[220]

The research group of Brückner also paid significant attention to site-selective Sonogashira monoalkynylation reactions of the six-membered bis(enol triflate) (*Z*)-**432**,[217a,217b,217d,221–223] which, as shown in Scheme 154, was stereoselectively prepared in two steps from 2-formylcyclohexanone (**455**) via the *Z*-configured monotriflate **456** in 42.2% yield.[217a]



Scheme 154. Synthesis of bis(enol triflate) (*Z*)-**432**.

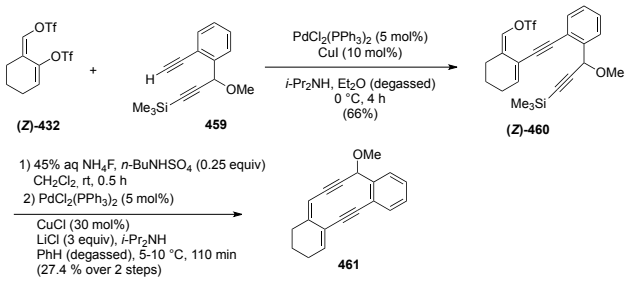
Surprisingly, the $PdCl_2(PPh_3)_2$/CuI-catalyzed monocoupling reaction of (*Z*)-**432** with trimethylsilylacetylene was shown to occur with site selectivity opposite to that observed for the analogous reaction of the five-membered bis(enol triflate) (*Z*)-**431** to give compound **457** as the major product and **458** as the minor component.[217a] Interestingly, this monotriflate was best obtained when the Sonogashira reaction was performed in THF in the presence of a primary amine and, in particular, when *n*-$PrNH_2$ was used as base (Scheme 155).[217a]



Amine	**457**/**458** molar ratio	Total Yield (%)
n-$PrNH_2$	>99:1	49
$PhCH_2NH_2$	98:2	66
Et_3N	94:4	62
i-Pr_2NH	91:9	73
piperidine	98:2	54
piperidine	96:4	75
morpholine	95:5	64

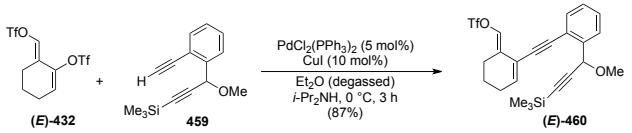
Scheme 155. Selective synthesis of compound **457**.

However, in a subsequent study, the monoalkynylation derivative (*Z*)-**460** was synthesized in 66% yield by treatment of (*Z*)-**432** with 1.1 equiv of diyne **459** in a degassed mixture of *i*-Pr_2NH and Et_2O at 0 °C using a mixture of 5 mol% $PdCl_2(PPh_3)_2$ and 10 mol% CuI as catalyst (Scheme 156).[217c] Desilylation of (*Z*)-**460** followed by intramolecular coupling by the catalytic action of 5 mol% $PdCl_2(PPh_3)_2$, 30 mol% CuCl, 3 equiv of LiCl in *i*-Pr_2NH and degassed benzene at 5–10 °C provided the 10-membered dienediyne **461** in 27.4% yield (Scheme 156).[217c]



Scheme 156. Synthesis of dienediyne **461**.

Site selectivity analogous to that observed for the Sonogashira reaction between (*Z*)-**432** and **459** was observed for the $PdCl_2(PPh_3)_2$/CuI-catalyzed reaction between bis(enol triflate) (*E*)-**432** and alkyne **459** (Scheme 157).[217c]



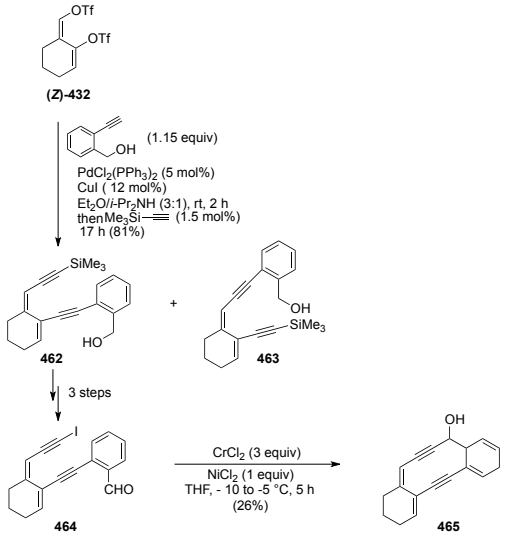
Scheme 157. Synthesis of compound (*E*)-**460**.

Compound (*Z*)-**432** proved also to be capable of undergoing a one-pot/two-component $PdCl_2(PPh_3)_2$/CuI-catalyzed bis-

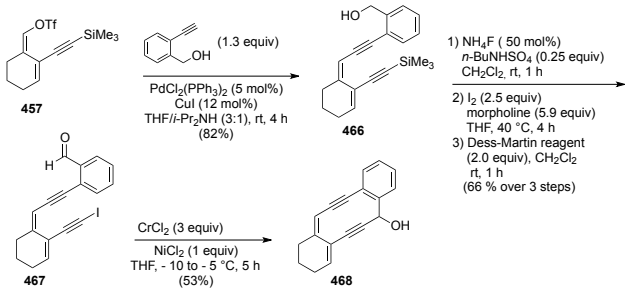
coupling reaction with two different terminal alkynes.[221] The first coupling partner was *o*-ethynylbenzyl alcohol and the second was trimethylsilylacetylene. The reaction (Scheme 158) provided a 96:4 mixture of the C-silylated dienediyne **462** and its regioisomer **463** in 81% yield.[221] Compound **462** was then converted into the unstable 6-/10-membered ring dienediyne **465** by a four-step route involving cyclization of the iodinated dienediyne aldehyde **464** by a Nozaki-Hiyama reaction[224] (Scheme 158).[221]

On the other hand, the synthesis of compound **468**, an isomer of **465**, was accomplished via a reaction sequence in which dienediyne **466** was obtained in 82% yield by treatment of monotriflate **457** with *o*-ethynylbenzyl alcohol, 5 mol% $PdCl_2(PPh_3)_2$ and 12 mol% CuI in a 3:1 mixture of THF and *i*-Pr_2NH at room temperature (Scheme 159).[221] Desilylation of **466** and iodination of the resulting 1-alkyne with iodine and morpholine, followed by oxidation with the Dess-Martin reagent,[225] delivered the desired iodinated aldehyde **467**. Finally, a Nozaki-Hiyama-type cyclization of **467** provided compound **468** in 53% yield, which proved to be less prone to decomposition during flash chromatography than its isomer **465** (Scheme 159).[221]

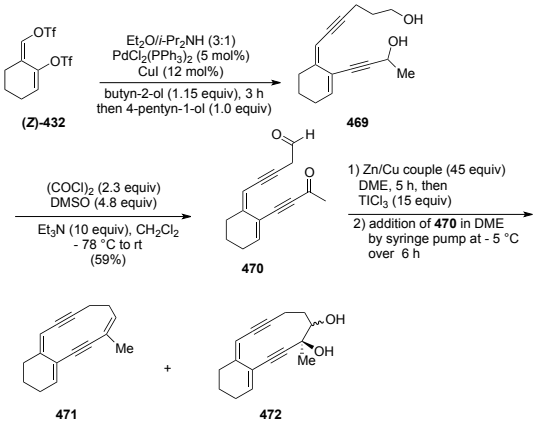
Compound (*Z*)-**432** was also used to prepare dienediyne **469** in 73% yield by a one-pot, two-step $PdCl_2(PPh_3)_2$/CuI-catalyzed coupling reaction with 3-butyn-2-ol and 4-pentyn-1-ol (Scheme 160).[222] A double Swern oxidation of **469** provided the keto-aldehyde **470** in 59% yield, which underwent an intramolecular McMurry coupling[226] using the reagent prepared from $TiCl_3$·1.5 DME and a Zn/Cu couple, to give trienediyne **471** in 47% yield (Scheme 160).[222] Compound **471** was formed along with the diastereomeric dienediyne pinacols **472**, which were isolated in 23% yield.[222]



Scheme 158. Selective synthesis of compound **462** and conversion into dienediyne **465**.



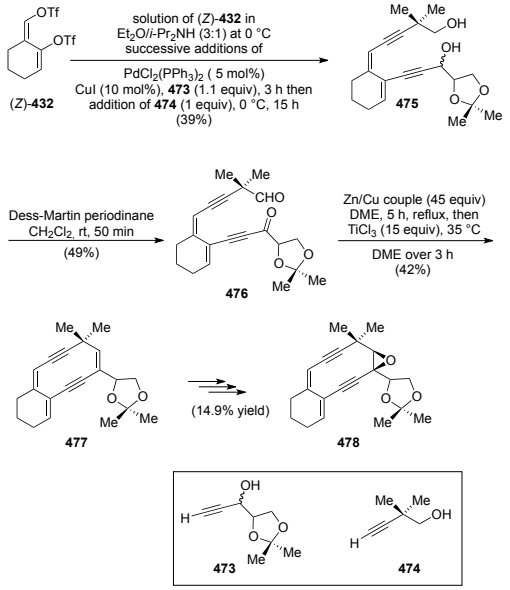
Scheme 159. Synthesis of compound **468**.



Scheme 160. Synthesis of dienediyne **469** and conversion into compounds **471** and **472**.

Finally, the strategy used for the synthesis of trienediyne **471** from (*Z*)-**432** was extended to generate the dienediyne epoxycarbonate **476**[223] possessing a structure more closely related to the neocarzinostatin chromophore than that of earlier analogues prepared by the Brückner team. In particular, bis(enol triflate) (*Z*)-**432** was coupled at its endocyclic carbon–carbon double bond with alkyne **473** and subsequently at its semicyclic carbon-carbon double bond with alkyne **474** to give dienediyne **475** in 39% yield (Scheme 161).[223]

Dess-Martin oxidation of **465** led to the keto-aldehyde **476** in 39% yield, which was subjected to a McMurry ring-closure reaction that yielded trienediyne **477** in 43% yield. Finally, a five-step reaction sequence allowed the convertsion of **477** into the required 6-/10-membered dienediyne epoxycarbonate **478** (Scheme 161).[223]



Scheme 161. Synthesis of dienediyne **475** and conversion into dienediyne epoxycarbonate **478**.

5. Conclusions

This review has illustrated how highly selective Sonogashira-type single couplings of terminal alkynes with (cyclo)alkenes and 1,3-dienes bearing two or three identical or different electrophilic sites and bis(enol triflates) are nowdays a valuable methodology of significant importance for the synthesis of building blocks that find application in a wide range of organic processes such as the synthesis of biologically active compounds, pharmacologically active substances, and natural products. As shown in the preceding subsections, most of these selective monoalkynylation reactions have been carried out in the presence of catalyst systems consisting of a mixture of a Pd complex and CuI and only a few have been accomplished using catalytic amounts of a Pd complex. Alone, although the latter are certainly more advantageous. In fact the presence of copper may catalyze the oxidative coupling of terminal alkynes (Glaser reaction)[171] giving rise to lower yields of the desired cross-coupling products and complicating their isolation. It should also be taken into account that the high loadings of copper can produce large amounts of copper(I) acetylides that, depending on the terminal alkyne used, can be highly explosive. Therefore, it is desirable that, in the near future, more attention is paid to the application of highly selective Sonogashira-type copper-free Pd-catalyzed monoalkynylation reactions of olefinic substrates containing two or more electrophilic sites.

Another challenge to be overcome in the near future concerns the development of highly selective Sonogashira- or Cassar-Heck-type reactions of olefinic substrates bearing two or more electrophilic sites using low or ultra-low loadings of Pd, a very expensive and toxic metal.[227] In fact, numerous investigations have been performed on couplings of terminal alkynes with aryl halides that involve the use of very high substrate/Pd catalyst molar ratios,[228] but, to our knowledge, no similar studies have been carried out to date on alkynylation reactions of alkenyl halides or pseudohalides and, in particular, of olefinic substrates bearing two or three different electrophilic sites.

However, in our view, one of the major goals to be achieved is the development and application of highly selective transition-metal-free Sonogashira monocoupling reactions involving (cyclo)alkenes bearing two or more identical or different electrophilic sites. These couplings should be inexpensive and simple to perform by eliminating the need to remove trace transition metals. Unfortunately, little attention has so far been devoted to the study of transition-metal-free Sonogashira couplings.[229]

Finally, we can expect that a significant expansion of the synthetic potential of the alkynylation reactions summarized and discussed in this review will result from their use in one-pot multicomponent processes able to produce highly sophisticated complex structures.[230]

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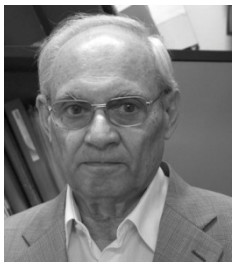
Biographical sketch



Renzo Rossi was born in Pisa (Italy) and graduated in Organic Chemistry with first-class honours at the

University of Pisa defending a thesis performed under the guidance of Professor Piero Pino. In 1969, he became Assistant Professor and in 1971 he earned the *libera docenza* in Organic Chemistry. After holding other intermediate positions at the University of Pisa and the Scuola Normale Superiore of Pisa, in 1980 he became Full Professor of Organic Chemistry at the University of Calabria. In 1982, he again joined the University of Pisa where he has held the Chair of Chemistry of Naturally Occurring Compounds. In 1999, the University of Pisa awarded him the *Ordine del Cherubino*. His current research interests include: i) new catalytic methods for the synthesis of oxygen-containing heterocycles; *ii)* the preparation of substances which exhibit significant cytotoxicity against human tumor cell lines and antivascular properties; i*ii)* the study of new methodologies for carbon–carbon bond formation that involve the use of organometallic reagents; *iv)* transition metal-catalyzed direct arylation reactions of substrates with activated sp^3-hybridized C–H bonds with aryl halides and pseudohalides; *v)* the design, development and applications of new, highly chemo- and regioselective methods for the transition metal-catalyzed direct *C*- and *N*-arylation reactions of electron-rich heteroaromatic systems, including free (NH)-azoles, with aryl halides and pseudohalides. In recent years, several successful studies have also been performed by his research group in the field of the synthesis and evaluation of the biological properties of insect sex pheromone components, insecticidal carboxyamides, natural phototoxins, and naturally-occurring compounds of marine origin and their structural analogues which are characterized by the 2(5*H)*-furanone ring. Professor Rossi, who has coauthored over 230 research publications and a number of highly cited review articles and patents, is a fellow of the Royal Society of Chemistry, the American Chemical Society, and the Società Chimica Italiana. He is a reviewer for several international journals dealing with synthetic organic chemistry and organometallics.

Fabio Bellina was born in Catania (Italy) in 1964. He studied Chemistry at the University of Pisa and received his Laurea Degree with first-class honours in 1990. In 1992, he joined the University of Pisa as an Organic Chemistry Researcher in the Department of Chemistry and Industrial Chemistry. In October 2003, he was appointed by the Faculty of Science of the University of Pisa as an Associate Professor of Organic Chemistry. His research interests were initially mainly devoted to the total synthesis of naturally occurring compounds of biological and/or pharmacological interest and to the synthesis of structural analogues of naturally occurring fungicidal derivatives of agrochemical interest. More recently, Prof. Bellina focused his attention on new and efficient protocols for regioselective transition-metal-mediated carbon-carbon and carbon-heteroatom bond-forming reactions, with a particular interest in the selective functionalization of oxygen-containing unsaturated heterocycles such as 2(5*H*)-furanones and 2(2*H*)-pyranones. Currently, he is working on the development of novel and efficient protocols for the transition metal-catalyzed direct C–H and N–H bond arylation of heteroarenes, the direct functionalization of active $C(sp^3)$-H bonds, the alkynylation of (hetero)aromatic scaffolds, and on the application of these new procedures to the selective preparation of bioactive natural and synthetic compounds and to new organic chromophores.

Marco Lessi was born in Livorno (Italy) in 1979. He studied Chemistry at the University of Pisa and received his Laurea Degree with first-class honours in June 2004 defending a thesis performed under the guidance of Professor Dario Pini. In January 2005, he began his PhD fellowship in the laboratory of Professor Pini and received his PhD degree in 2008, submitting a thesis on the preparation and applications of new insoluble polymer-bound (IPB) enantioselective catalytic systems. These studies were focused on the synthesis of transition-metal complexes obtained from bisoxazoline and BINOL ligands. In the period January 2008–March 2009, Dr. Lessi worked for Solvay Solexis S.p.A. on the development of new routes for the preparation of high-fluorinated low-molecular-weight molecules and oligomers. In March 2009, he re-joined the University of Pisa where he currently cooperates with Professor Bellina. The current research interests of Dr. Lessi involve the development of novel and efficient protocols for highly selective transition metal-catalyzed direct $C(sp^3)$-H and $C(sp^2)$-H arylation reactions, and the discovery of new synthetic routes and applications of functionalized ionic liquids obtained from naturally occurring building blocks.

Chiara Manzini was born in Lucca (Italy) in 1986 and graduated in Chemistry with first-class honours at the University of Pisa in 2011 defending a thesis performed under the guidance of Professor Anna Iuliano. Currently, she holds a position as PhD student at the Department of Chemistry and Industrial Chemistry of the University of Pisa under the guidance of Professor Fabio Bellina. She is currently working on the development and application of new protocols for the selective arylation of N-containing heteroaromatics.