



Sonogashira Coupling in Natural Product Synthesis

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Sonogashira Coupling in Natural Product Synthesis

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Abstract: This review will focus on selected applications of Sonogashira coupling and subsequent transformations as key steps in the total synthesis of natural products. A brief introduction of the history and development of Sonogashira coupling will be presented. The organization of the synthetic applications is based on the structure of target molecules and the transformations followed by the Sonogashira coupling, which includes (1) preparation of natural products containing conjugated enynes or enediynes; (2) Sonogashira coupling followed by **stereoselective** reduction and (3) Sonogashira coupling followed by regioselective annulations.

1 Introduction

Significant advances have been made over the past four decades in palladium (Pd)-catalyzed cross-coupling reactions to form carbon-carbon (C-C) bonds.¹ As a result, Pd-catalyzed inter- and intramolecular reactions and cyclizations are widely used to synthesize natural products, therapeutic agents and organic materials.² These reactions dramatically improve the efficiency of organic syntheses, such as those involving the formation of $sp-sp^2$ bonds. These bonds occur in arylalkynes, conjugated enynes and enediynes, synthons that occur in such natural products as phorboside A (**1**),³ pyrroxanthin (**2**),⁴ dynemicin A (**3**),⁵ kedarcidin chromophore (**4**)⁶ and calicheamicin γ_1 (**5**)⁷ (Figure 1). **The value of such natural products as medicinal chemistry targets and as inspiration for methodological advances makes $sp-sp^2$ bond formation particularly important in organic synthesis.**

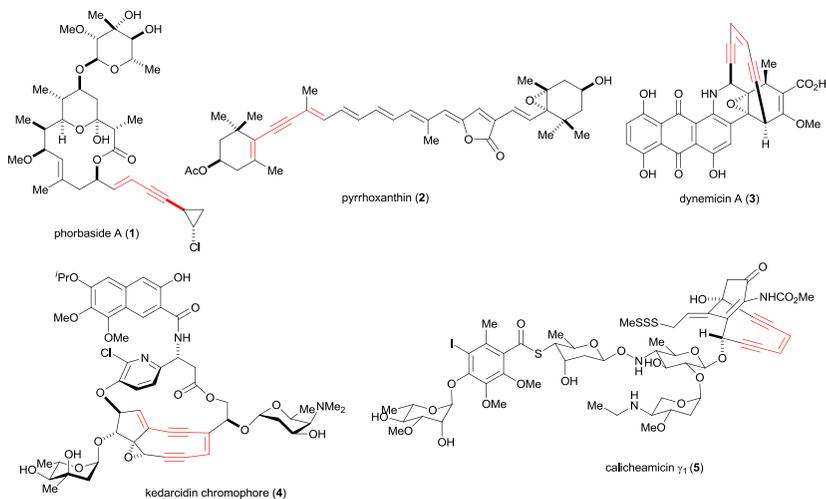
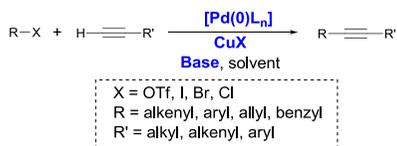


Figure 1. Selective natural products containing conjugated enynes.

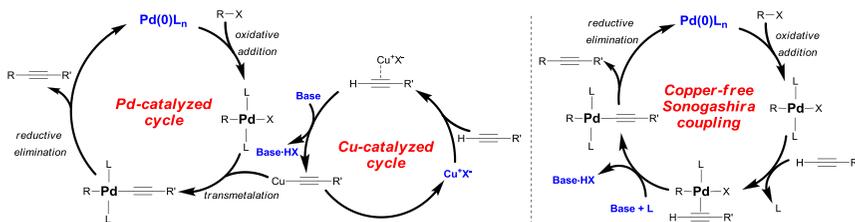
In 1975, Heck⁸ and Cassar⁹ independently reported the Pd-catalyzed arylation and alkenylation of **alkynes** in the presence of organic or inorganic bases at temperatures around 100 °C. Subsequently, Sonogashira and Hagihara demonstrated that adding a catalytic amount of copper(I) iodide dramatically improved the rate of this alkylation, even allowing the cross-coupling to be performed at room temperature.¹⁰ The core of the Sonogashira-Hagihara protocol, known as Sonogashira coupling, has become a generally accepted method; in this reaction, Pd and Cu co-catalyze the construction of sp-sp² bonds involving terminal alkynes and aryl or alkenyl halides or triflates (Scheme 1). Since its discovery, Sonogashira coupling has been extensively studied in efforts to understand its mechanism as well as explore different catalysts, ligands, and additives.²



Scheme 1. Sonogashira coupling

Despite these efforts, the mechanism of Pd/Cu-cocatalyzed cross-coupling remains unclear. It is assumed to proceed through the combination of Pd-catalyzed and Cu-catalyzed cycles (Scheme 2). In the Pd-catalyzed cycle, in situ reduction of **Pd(II)** complexes may give rise to a catalytically active species Pd(0)L₂, which facilitates the fast oxidative addition of R-X. The **rate of oxidative addition** of R-X depends on the electronic properties of the R-X bond as well as on the reactivity of X (I ≥ OTf ≥ Br > Cl). Normally, electron-withdrawing groups activate the R-X bond by decreasing its electron density. Next, in the Cu-catalyzed cycle, the copper acetylide undergoes transmetalation. This step, which is the rate-determining reaction in the overall coupling, generates a RPd(-C≡CR')L₂ species, which then undergoes reductive elimination to yield the final coupled alkyne and regenerate the Pd(0)L₂ catalyst.

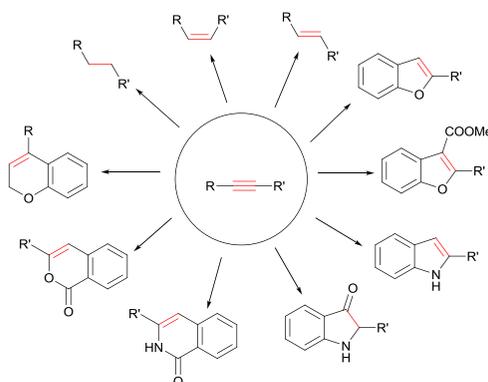
One problem with Pd/Cu-cocatalyzed Sonogashira coupling is that the alkyne can undergo homocoupling in the presence of oxygen via the Hay/Glaser reaction.¹¹ To avoid this side reaction, researchers have explored Cu-free Sonogashira coupling.² While the mechanism of this reaction is poorly understood, it is thought that reversible π-coordination and deprotonation, analogous to those in the Cu-catalyzed cycle of Pd/Cu-cocatalyzed coupling, generate an alkyne-Pd (II) complex [RPd(-C≡CR')L₂].



Scheme 2. The proposed mechanism of Sonogashira coupling.

Sonogashira coupling efficiently produces arylalkynes and conjugated enynes that

can participate in a broad variety of transformations. For example, reduction or regioselective annulation of Sonogashira products can generate diverse building blocks and heterocycles, such as alkyl, alkene, benzofuran, indole, oxyindole, isoquinolinone, isochromenone systems and related structures (Scheme 3). Comprehensive reviews of Sonogashira reaction covered the catalysts system, mechanism studies and applications have been published in recent years,² which indicated a trend of its rapid expansion and applications. In this review, we focus on selected applications of Sonogashira coupling and subsequent transformations as key steps in the total synthesis of natural products.



Scheme 3. Transformations of arylalkynes and conjugated enynes generated by Sonogashira coupling.

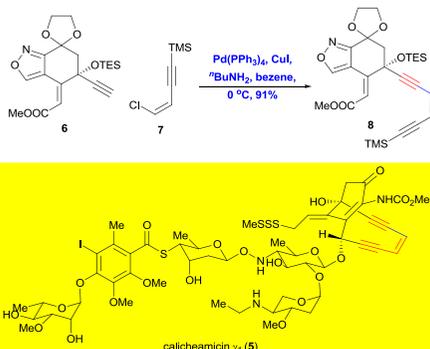
2 Synthetic Applications

Efficiency is essential in organic synthesis, particularly natural product synthesis. Designing efficient reactions means satisfying several constraints, including the need for chemoselectivity,¹² atom economy,¹³ step economy¹⁴ and redox economy.¹⁵ Achieving all these things is made more challenging by the fact that total synthesis of complex natural products nearly always requires several steps.^{16,17} In many cases, these steps can be carried out in a straightforward linear procedure, but this sometimes leads to low yields because of relatively poor material balance and supply, which suppress its practicability.¹⁷ In these and other cases, a convergent approach can prove much more efficient than a linear one because it couples the synthesis of individual fragments. Its advantages rely on: (1) convergent synthesis is usually simpler to execute than linear synthesis; (2) it involves better material balance and supply and (3) it gives higher overall yields.¹⁷ On the other hand, convergent synthesis requires designing effective coupling steps involving efficient reactions that are tolerant of diverse functional groups. **Sonogashira couplings enable convergent synthesis strategies, which are of value due to their advantages in efficiency over more linear synthesis strategies.** Here we describe examples where the Sonogashira reaction serves as a key coupling step in the convergent synthesis of natural products.

2.1. Natural Products Containing Conjugated Enynes.

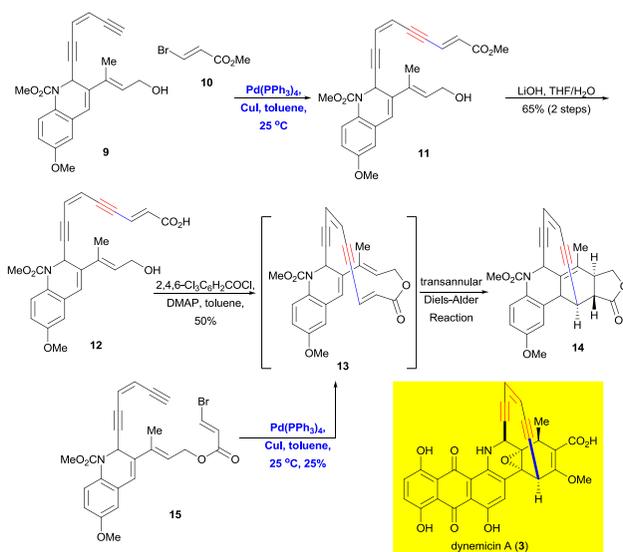
Natural products containing conjugated **enynes** or enediynes have attracted considerable attention from organic chemists and biologists because of their

sensitive structural features and their potential as bioactive compounds and as starting compounds in chemical biology studies.³⁻⁷ The total synthesis of these natural products is challenging mostly because of the difficulty in efficiently constructing the sensitive motif containing the conjugated enynes and enediynes. Inter- or intramolecular Sonogashira reactions to construct the sp-sp² bond have proven useful for achieving this step. In pioneering work in 1992, Nicolaou and co-workers demonstrated the power of Sonogashira coupling in the total synthesis of calicheamicin γ_1 (**5**).⁷ The Pd/Cu-cocatalyzed coupling of alkyne **6** with vinyl chloride **7** gave the enediyne product **8** in 91% yield (Scheme 4). This reaction proceeded smoothly under mild conditions at low temperatures, preserving the sensitive protecting groups as well as the *Z* conformation of the alkene.



Scheme 4. Construction of enediyne motif using a Sonogashira coupling in the total synthesis of calicheamicin γ_1 (**5**).

Schreiber and co-workers performed Sonogashira coupling followed by a transannular Diels-Alder reaction to construct the core skeleton of dynemicin A (**3**),⁵ a potent enediyne-containing antibiotic. Coupling enediyne **9** with vinyl bromide **10** in the presence of Pd(PPh₃)₄ and CuI gave the polyunsaturated ester **11**, which was transformed through alkaline hydrolysis into the corresponding carboxylic acid **12** (Scheme 5). Subsequent Yamaguchi macrocyclization gave the pentacyclic product **14** in 50% yield. The proposed mechanism involves formation of the macrocyclic ring **13**, followed by a spontaneous transannular Diels-Alder reaction. Dramatically, Schreiber and co-workers showed that intramolecular Sonogashira coupling of **15** in the presence of Pd(PPh₃)₄ and CuI yielded **14** directly in 25% yield. This impressive one-pot cascade reaction efficiently constructed three rings with a highly strained enediyne motif and four contiguous stereocenters.

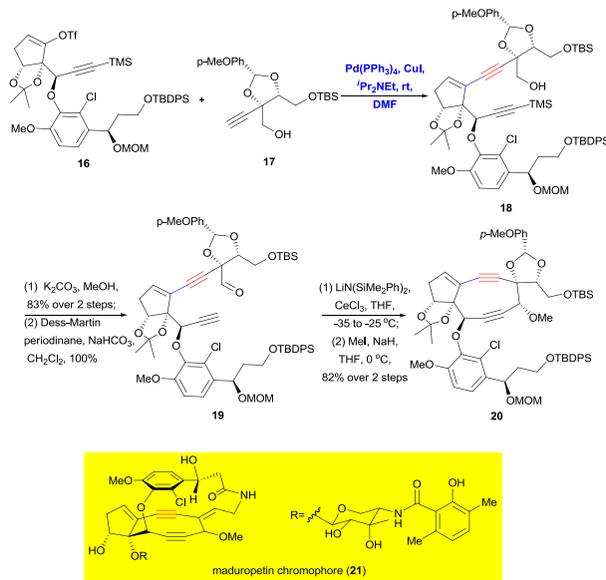


Scheme 5. Sonogashira coupling followed by the transannular Diels-Alder reaction to construct the core skeleton of **dynamycin A**.

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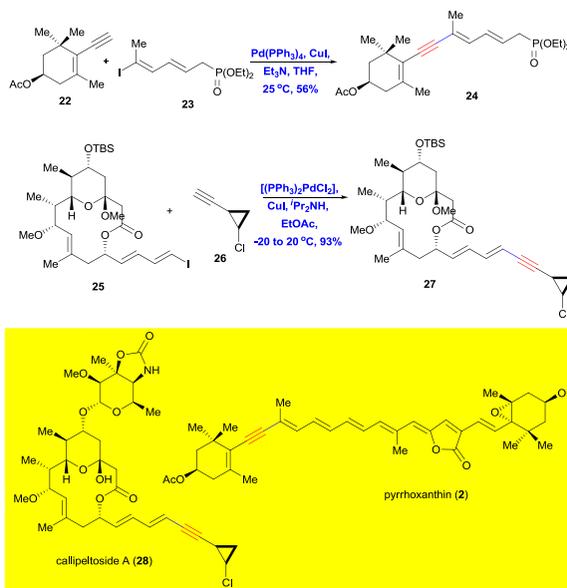
Sonogashira coupling **also proved** useful for synthesizing the highly complex **maduropeptin** chromophore (**21**), which contains a bicyclo[7.3.0]enediynes and a 15-membered ansa-macrolactam with atropisomerism. This compound exhibits potent antitumor and antibacterial activity through a mechanism that differs from that of other enediyne natural products. In 2007, Inoue and co-workers used a convergent approach including Sonogashira coupling to synthesize the aglycon of **21** (Scheme 6).¹⁸ Coupling vinyl triflate **16** with the densely functionalized terminal alkyne **17** under mild Pd/Cu-cocatalytic conditions yielded the corresponding product **18** in quantitative yield, and this was converted to aldehyde **19** through deprotection and oxidation. Remarkably, scaling up this Sonogashira coupling (7.35 mmol) gave excellent yield in only 20 min, helping ensure sufficient substrate for the next step of the synthesis. Ring closure of the strained nine-membered diyne ring was achieved by acetylide-aldehyde condensation promoted by $\text{LiN}(\text{SiMe}_2\text{Ph})_2$ and CeCl_3 .



Scheme 6. Sonogashira coupling of fragments to synthesize the aglycon of maduropeptin chromophore (**21**).

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The Sonogashira reaction is also used as a key coupling step in the convergent syntheses of pyrroloxanthin (**2**)⁴ and callipeltoside A (**28**),³ both of which contain conjugated enynes (Scheme 7). Coupling a trisubstituted diene **22** with terminal alkyne **23** in the presence of $\text{Pd}(\text{PPh}_3)_4$ and CuI in $^i\text{BuNH}_2$ in benzene gave the desired product **24** in 56% yield. In contrast, reacting diene **25** with terminal alkyne **26** under the same conditions failed to provide the desired product. Andrus et al. reported the same problem during the synthesis of stipiamide and related polyenes.¹⁹ Those authors screened reaction conditions of the Sonogashira coupling and found $\text{Pd}(\text{II})$ chloride [$(\text{PPh}_3)_2\text{PdCl}_2$] to be a much better catalyst than $\text{Pd}(\text{PPh}_3)_4$, especially for couplings involving the electron-deficient alkynyl amides. Using this improved catalyst together with CuI and $^i\text{Pr}_2\text{NH}$ in ethyl acetate, they obtained the protected aglycon **27** in 93% yield with retention of double-bond geometry.



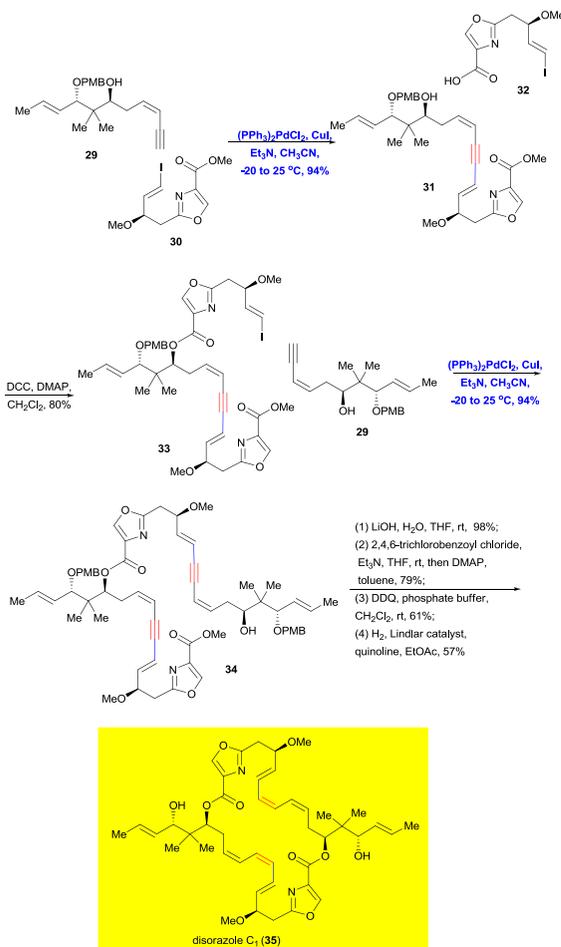
Scheme 7. Sonogashira coupling in the total syntheses of pyrrooxanthin (**2**) and callipeltoside A (**28**).

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2.2. Sonogashira Coupling followed by reduction

Since Sonogashira coupling provides a reliable and effective method of constructing inter- and intramolecular $sp-sp^2$ C-C bonds, it can be combined with reduction reactions to convert the triple bonds of alkyne–alkene systems into sp^2-sp^2 , sp^2-sp^3 and sp^3-sp^3 bonds in a regio- and stereoselective fashion. In addition, reaction conditions can be adjusted to control the *E* or *Z* geometry of the alkene. This combination of Sonogashira coupling followed by stereoselective reduction has been used in many convergent syntheses of natural products, including polyketides, alkaloids and polycyclic xanthenes.

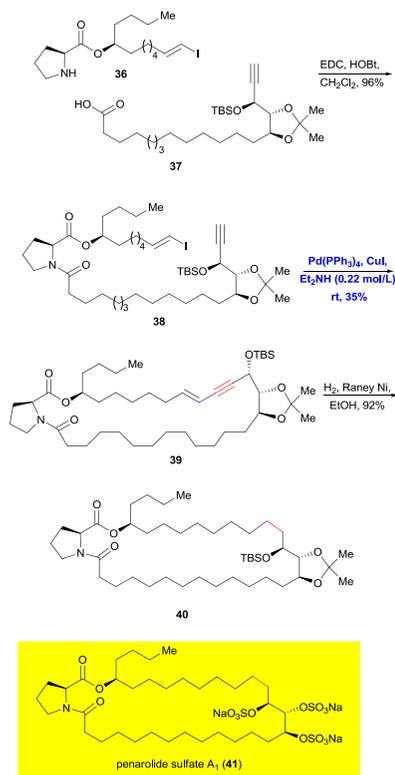
In 2004, Wipf and co-workers used a convergent, stereoselective approach to achieve the total synthesis of Disorazole C₁ (**35**),²⁰ which has significant cytotoxic and antitubulin activities at nanomolar concentrations. To generate **35**, which has a dimeric structure composed of a macrocyclic-heterocyclic ring with labile polyene systems (*E*, *Z*, *Z*), the authors assembled four fragments using double Sonogashira coupling, esterification and Yamaguchi macrocyclization (Scheme 8). Coupling terminal alkyne **29** with vinyl iodide **30** in the presence of $(PPh_3)_2PdCl_2$ and CuI gave the coupling product in 94% yield, which was then esterified with fragment **32** to achieve vinyl iodide **33**. A second Sonogashira coupling under the same conditions was performed to introduce segment **29**. A subsequent series of simple transformations, including saponification, Yamaguchi lactonization, deprotection and stereoselective reduction, completed the total synthesis of **35**. Notably, this approach allowed the labile triene to remain protected until late in the synthesis, when the Lindlar catalyst was used to construct *Z* olefins stereoselectively.



Scheme 8. Convergent total synthesis of disorazole C₁ (35).

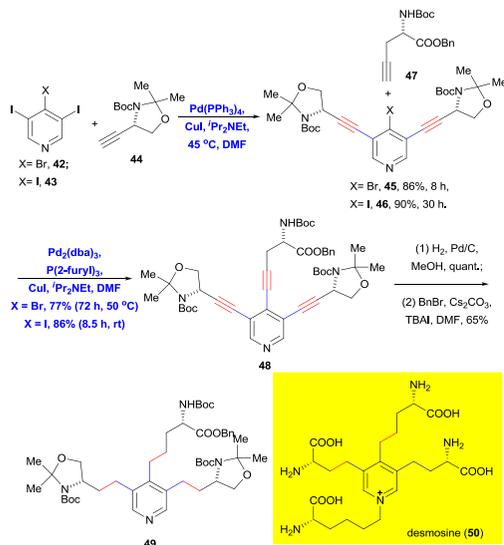
5 Intramolecular Sonogashira coupling has been reported less often in total
 6 syntheses, partly because it is effective only for constructing macrocycles with more
 7 than approximately 15 members as the conjugated enyne produces ring strain. One
 8 of the few examples of intramolecular Sonogashira coupling in total synthesis is the
 9 strategy reported by Mohapatra and co-workers in 2008 for making penarolide
 10 sulfate A1 (**41**) (Scheme 9).²¹ Fragments **36** and **37** were connected in high yield
 11 using EDC/HOBt-mediated coupling, and then an intramolecular Sonogashira
 12 reaction catalyzed by Pd(PPh₃)₄ and CuI in Et₂NH solvent furnished the 30-
 13 membered macrocyclic ring. Finally the conjugated enyne was hydrogenated using
 14 Raney Ni in ethanol to generate the saturated ring system.

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Scheme 9. Total synthesis of penarolide sulfate **A₁** (**41**) using intramolecular Sonogashira coupling.

Selectivity of the Sonogashira coupling of terminal alkynes to different electrophilic groups is normally controlled by adjusting the reactivity of the C-X bond ($\text{I} \geq \text{OTf} \geq \text{Br} > \text{Cl}$). If the steric effects of specific substrates are adjusted as well, the coupling can be carried out in a stepwise, regioselective fashion. One example is the total synthesis of desmosine (**50**) reported by Usuki and co-workers in 2012.²² This compound contains four amino acid side chains of different lengths. In their approach, those authors performed the regioselective Sonogashira coupling of **42** or **43** with terminal alkyne **44** at the 3- and 5-positions in the presence of $\text{Pd}(\text{PPh}_3)_4$ and CuI in DMF and $^i\text{Pr}_2\text{NEt}$ (Scheme 10). Oxidative addition of I or Br at the C-4 position was avoided because of steric hindrance from the neighboring 3,5-diiodo groups. For the same reason, achieving the **third** Sonogashira coupling at the sterically hindered C-4 required a more reactive catalyst system. The authors created this catalyst by reacting $\text{Pd}_2(\text{dba})_3$ with the electron-rich phosphine ligand $\text{P}(\text{2-furyl})_3$ in the presence of CuI in DMF and $^i\text{Pr}_2\text{NEt}$. This catalyst facilitated the conversion of either **45** or **46** into the desired 3,4,5-trialkynyl pyridine **48** in good yield. Finally, Pd/C-catalyzed hydrogenation saturated the trialkynyl motif, generating the corresponding alkyl side chain.

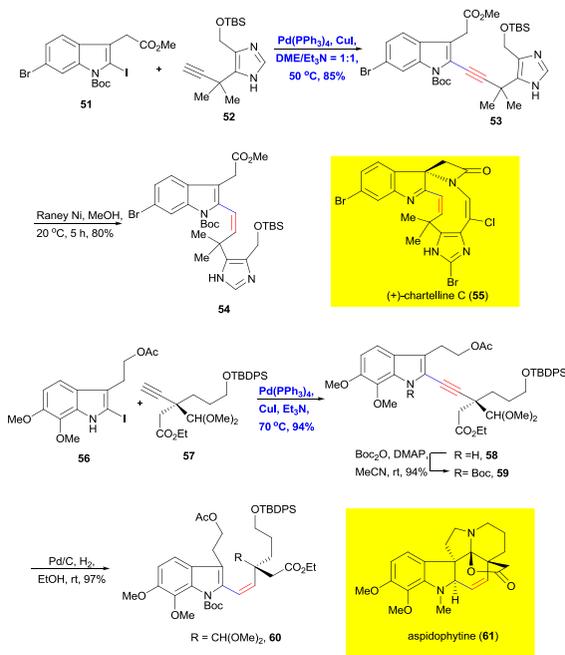


Scheme 10. Total synthesis of desmosine (50).

22 Regioselective Sonogashira coupling was also used by Baran and Shenvi in 2006
23 to combine the doubly halogenated indole **51** and imidazole-containing alkyne **52** in
24 the total synthesis of chartelline C (**55**).²³ The active C-I bond facilitated the Pd/Cu-
25 cocatalyzed cross-coupling and gave the desired indole-imidazole product **53** in 85%
26 yield, leaving the C-Br bond intact (Scheme 11). These results indicate that
27 Sonogashira coupling **can tolerate imidazoles**, which should be useful for
28 synthesizing alkaloids. The alkyne motif was then selectively reduced with Raney
29 nickel to olefin **54** with *Z* geometry and subsequently transformed by
30 macrocyclization.

31 Another example of Sonogashira coupling followed by stereoselective reduction
32 was reported by Tokuyama and Fukuyama and co-workers in 2003 with the
33 convergent total synthesis of indole-type alkaloid aspidophylline (**61**).²⁴ Pd(PPh₃)₄
34 and CuI in Et₃N solvent reliably cross-coupled **56** and terminal alkyne **57**, which
35 contains an all-carbon quaternary center, furnished the corresponding product in
36 94% yield (Scheme 11). The conjugated enyne allowed subsequent construction of
37 the *Z* olefin in aspidophylline (**61**).
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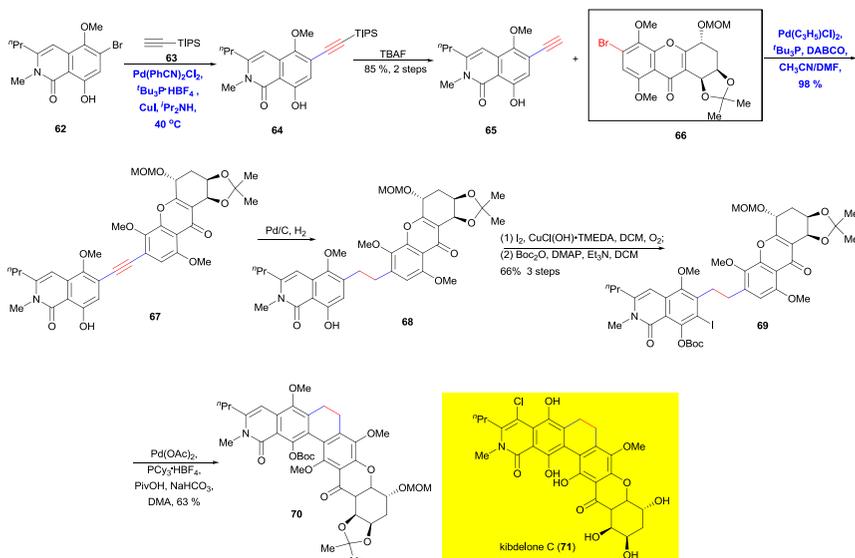
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Scheme 11. Total synthesis of chartelline C (**55**) and aspidophylline (**61**).

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5 Silyl acetylene carrying either the TMS or TIPS group is a two-carbon alkyne building block that can act as a mono- or double cross-coupling component to elongate a carbon chain or couple fragments. This building block has been used by Ready and co-workers in the total synthesis of kibelone C (**71**) (Scheme 12).²⁵ Cross-coupling of **62** and (triisopropyl)acetylene **63** followed by desilylation generated another terminal alkyne **65** in 85% yield. A second Sonogashira coupling of **65** with **66** gave the desired coupling product in nearly quantitative yield; this reaction was carried out in the absence of Cu and with slow addition of the alkyne in order to avoid oxidative dimerization. Subsequent hydrogenation, iodination and protection generated **69**, which underwent ring closure via intramolecular C-H bond arylation.



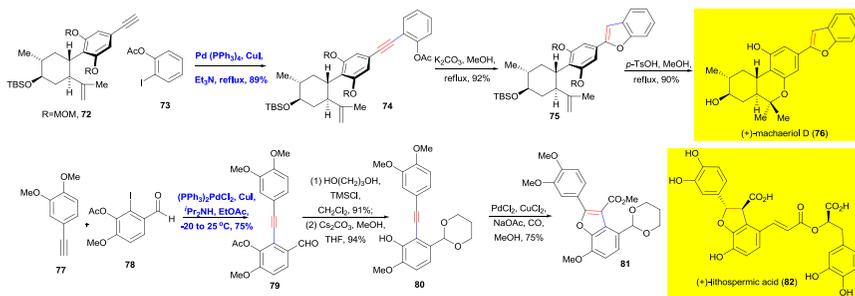
Scheme 12. Total synthesis of kibelone C (71).

2.3. Sonogashira Coupling Followed by Regioselective Annulation.

Heterocycles are ubiquitous in natural products, pharmaceuticals, dyes and organic materials. “Of the more than 20 million chemical compounds currently registered, about one half contain heterocyclic systems.”²⁶ As a result, the efficient construction of heterocycles is of great significance in organic synthesis. Sonogashira coupling to generate substituted alkynes followed by their regioselective hetero-annulation can be used to construct furan, benzofuran, indole, oxyindole, isoquinoline, isochromenone rings and related structures. An even greater diversity of hetero-annulation products can be achieved by adding base to increase the nucleophilicity of hetero-nucleophiles or by using transition metal catalysts to activate the alkynes. Here we describe some examples of Sonogashira coupling in the total synthesis of natural products in which the alkyne is transformed into a heterocyclic ring.

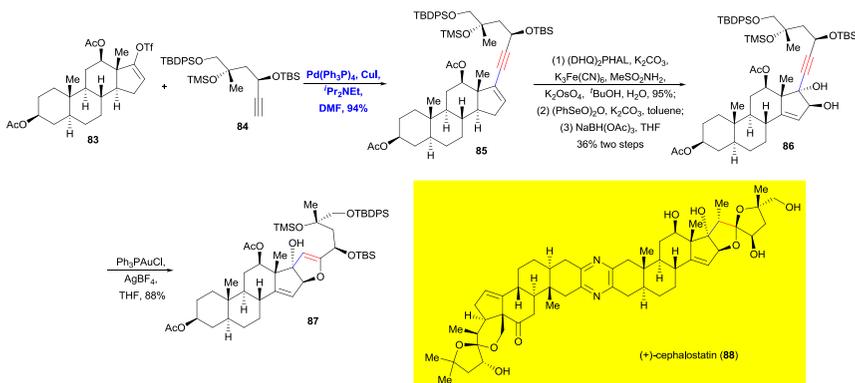
In 2006, Pan, She and co-workers reported using Sonogashira coupling followed by regioselective hetero-annulation to construct a benzofuran ring as part of the asymmetric synthesis of (+)-machaeriol D (76).²⁷ Cross-coupling 72 with ortho-iodophenyl acetate 73 in the presence of Pd-Cu cocatalyst gave intermediate 74 in 89% yield (Scheme 13). Subsequent saponification and cyclization of phenolic acetate 74 afforded the desired benzofuran 75 in high yield. A similar example is the total synthesis of frondosin B reported by Danishefsky and co-workers,²⁸ who used a one-pot, Pd/Cu-catalyzed Sonogashira coupling and hetero-annulation sequence to combine a terminal alkyne and ortho-iodophenol. Coster and co-workers used this approach in the formal total synthesis of lithospermic acid (82) (Scheme 13).²⁹ In this synthesis, Sonogashira coupling of fragments 77 and 78 generated 79 in good yield, during which the aldehyde group was protected as acetal. Deacetylation was carefully performed at low temperature to avoid direct annulation. Carbonylative annulation of ortho-hydroxydiarylalkyne 80 was catalyzed with PdCl₂ and CuCl₂ in the presence of CO, which not only installed the benzofuran but also introduced a

carbomethoxy functionality.



Scheme 13. Total synthesis of (+)-machaeriol D (**76**) and (+)-lithospermic acid (**82**).

A particularly impressive example of Sonogashira coupling followed by heteroannulation was reported by Shair and co-workers in the total synthesis of cephalostatin (**88**).³⁰ In this approach, Pd-catalyzed Sonogashira coupling and Au-catalyzed heteroannulation were used to construct the dihydrofuran ring (Scheme 14). Cross-coupling of vinyl triflate **83** and terminal alkyne **84** in the presence of Pd(PPh₃)₄, CuI and Pr₃NET in DMF produced the enyne **85** in 94% yield. After a two-step sequence in which Sharpless dihydroxylation and oxidation generated an α -hydroxy cyclopentenone, which was then reduced in a stereocontrolled manner, the *trans*-diol **86** was obtained in 36% yield. Activation of the alkyne motif with Au(I) and subsequent nucleophilic attack by a hydroxyl group led to the formation of dihydrofuran **87** in 88% yield through 5-*endo*-dig cyclization. This dihydrofuran was then used to install the spiroketal moiety in the right fragment of the natural cephalostatin (**88**).

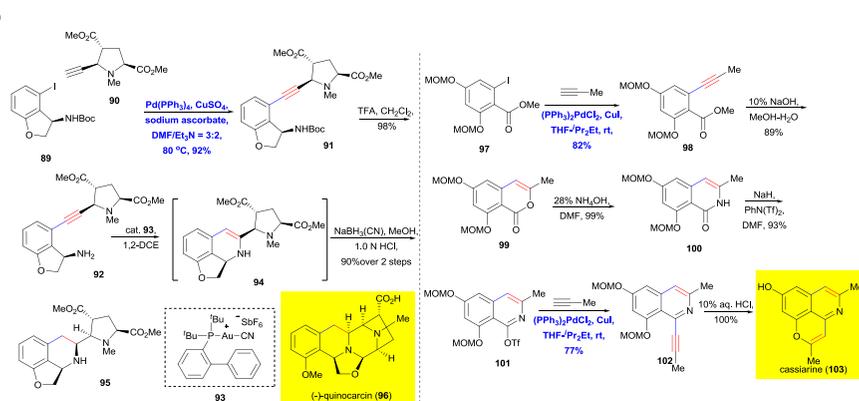


Scheme 14. Total synthesis of cephalostatin (**88**).

Tetrahydroisoquinoline-type alkaloids are a large family of isoquinoline natural products that have attracted considerable attention from chemists and biologists for their fascinating structures and remarkable biological activities.³¹ The isoquinoline core of these compounds has traditionally been constructed using Pictet–Spengler condensation³² and asymmetric imine hydrogenation.³³ Fujii, Ohno and co-workers reported a convergent synthesis of quinocarcin (**96**) using Sonogashira coupling and Au(I)-catalyzed hydroamination (Scheme 15).³⁴ Cross coupling of **89** and **90** at 80 °C in the presence of Pd(PPh₃)₄, CuSO₄, and sodium ascorbate in DMF and Et₃N

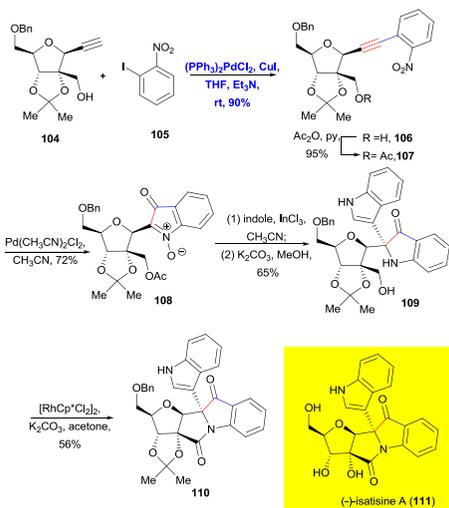
gave the coupling product **91** in 92% yield. Using equimolar amounts of CuSO_4 and sodium ascorbate effectively prevented the homocoupling side reaction. After extensively surveying reaction conditions and catalysts, the authors found **93** to be the most effective Au catalyst for hydroaminating the free amine-containing **92**. The desired 6-*endo*-dig annulation proceeded smoothly, giving **94** in high yield; this compound was then reduced with NaBH_3CN in a stereocontrolled fashion to form the tetrahydroisoquinoline core **95**.

An alternative way to generate the isoquinoline core via Sonogashira coupling was reported by Honda and co-workers, who prepared isoquinoline from isocoumarin to achieve the total synthesis of alkaloid cassiarin A (**103**) (Scheme 15).³⁵ The first Sonogashira coupling of iodide **97** and in situ-generated propyne was performed in the presence of Pd/Cu cocatalyst, yielding **98** in 82% yield. Hydrolysis followed by acidification generated the isocoumarin **99**, which was transformed into isoquinolone **100** after treatment with ammonium hydroxide in DMF and cyclization of a ketoamide intermediate. Impressively, this isoquinolone was converted into its active triflate form **101**, which underwent a second Sonogashira coupling with propyne to furnish isoquinoline **102**. Finally deprotection using HCl promoted the 6-*endo*-dig annulation and provided cassiarin A (**103**) in quantitative yield.



Scheme 15. Total synthesis of quinocarcin (**96**) and cassiarin A (**103**).

In 2012, Ramana and co-workers reported the total synthesis of (-)-isatisine A (**111**)³⁶ using four consecutive metal-mediated transformations: Sonogashira coupling, Pd-catalyzed nitroalkyne cycloisomerization, InCl_3 -promoted indole addition and Rh-catalyzed oxidative N-heterocyclization (Scheme 16). The standard Sonogashira coupling furnished the nitroalkyne **106** in 90% yield, which underwent nitroalkyne cycloisomerization catalyzed by 5 mol% of $\text{Pd}(\text{CH}_3\text{CN})_2\text{Cl}_2$, yielding isatogen **108** in 72% yield. Then the basic skeleton of **110** was efficiently constructed using another two metal-mediated transformations.



Scheme 16. Total synthesis of (-)-isatisine A (**111**).

- 5 A selection of recent reports of total syntheses of natural products with intriguing
 6 structural features and involving Sonogashira coupling is shown in Figure 2. They
 7 include moracin P (**112**, Kyeong Lee and co-workers, 2009);³⁷ indole-3-acetonitrile-
 8 4-methoxy-2-C-b-D-glucopyranoside (**113**, Thomas G. Minehan and co-workers,
 9 2012);³⁸ smyrindiol (**114**, Dieter Enders and co-workers, 2012);³⁹ 7',8'-
 10 dihydroaigialospirol (**115**, Margaret A. Brimble and co-workers, 2012);⁴⁰ linorexepin
 11 (**116**, Lutz F. Tietze and co-workers, 2013),⁴¹ borrelidin (**117**, James P. Morken and
 12 co-workers, 2003),⁴² murisolin (**118**, Tetsuaki Tanaka and co-workers, 2004);⁴³
 13 cylindramide (**119**, Sabine Laschat and co-workers, 2005),⁴⁴ leucascandrolide A
 14 (**120**, James S. Panek and co-workers, 2007);⁴⁵ thuggacin B (**121**, Andreas
 15 Kirschning and co-workers, 2008);⁴⁶ neopeltolide (**122**, Martin E. Maier, 2008);⁴⁷
 16 Cortistatin J (**123**, K. C. Nicolaou, David Y.K. Chen, and co-workers, 2009);⁴⁸
 17 Bryostatin 7 (**124**, Michael J. Krische and co-workers, 2011);⁴⁹ 8-
 18 Deshydroxyajudazol B (**125**, Mark A. Rizzacasa and co-workers, 2011)⁵⁰ and
 19 Psymberin = Irciniastatin A (**126**, Jef K. De Brabander and co-workers, 2012).⁵¹

20

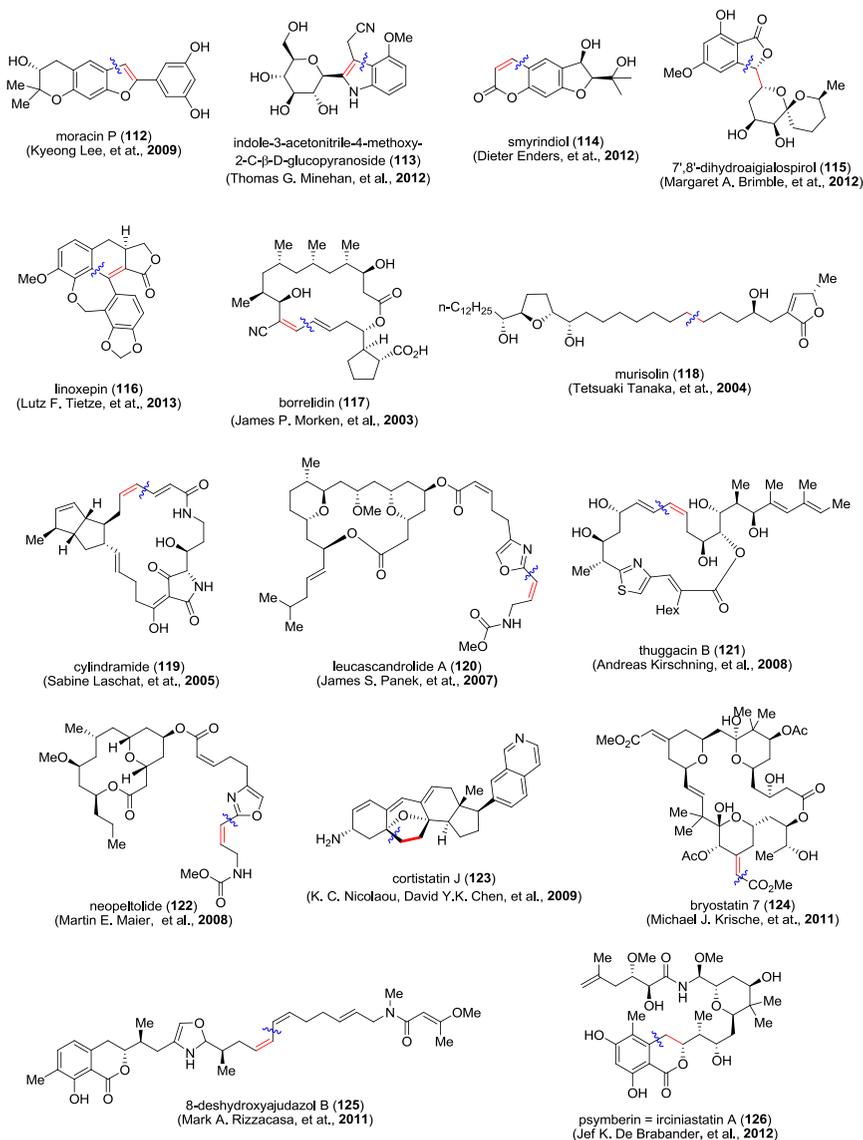
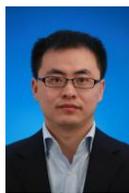


Figure 2. Total synthesis of natural products involving Sonogashira coupling.

3 Conclusion

Palladium-catalyzed inter/intramolecular cross-coupling reactions have dramatically improved the efficiency of organic synthesis. As we demonstrate herein, Sonogashira coupling provides an effective methodology for the construction of C-C bonds ($sp-sp^2$) which has been widely used in the synthesis of natural products. Rational design using Sonogashira coupling and transformations based on the Sonogashira products facilitates the fragment coupling and construction of heterocycles in convergent approaches. To date, the traditional reaction procedure using a Pd-Cu co-catalyzed system in the presence of an amine predominates in most

cases. **There** is no doubt that more synthetic applications will be reported with the improvement and development of catalysts, ligands and reaction conditions.

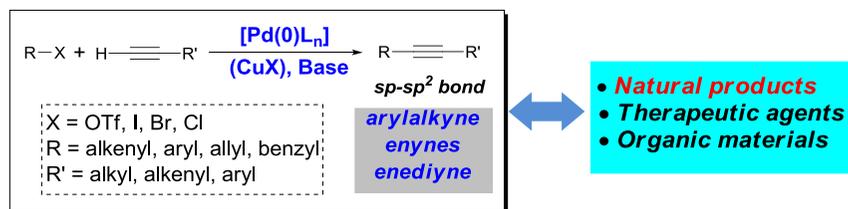


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Graphic Abstract:



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