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Transition Metal-catalyzed Couplings of Alkynes to 1,3-Enynes: Modern Methods and Synthetic Applications

Barry M. Trost*[a] and James T. Masters[a]

Abstract

The metal-catalyzed coupling of alkynes is a powerful method for the preparation of 1,3-enynes, compounds that are of broad interest in organic synthesis. Numerous strategies have been developed for the homo- and cross coupling of alkynes to enynes *via* transition metal catalysis. In such reactions, a major issue is the control of regio-, stereo-, and, where applicable, chemoselectivity. Herein, we highlight prominent methods for the selective synthesis of these valuable compounds. Further, we illustrate the utility of these processes through specific examples of their application in carbocycle, heterocycle, and natural product syntheses.

Introduction

Conjugated enynes are valuable structures in organic chemistry. The 1,3-enyne motif and its derivatives are found in numerous biologically active natural products,[1] and enynes are important intermediates in the synthesis of highly substituted aromatic rings,[2] compounds of interest in materials research,[3] and other complex molecules. Several methods for the preparation of enynes are known,[4] but the direct, catalytic coupling of alkynes to enynes is a particularly attractive approach given the ready availability of these precursor compounds. In the past few decades, significant advances have been made in this area. As a result, some efficient and highly atom economic[5] preparations of these products are evolving. These methods have been applied in syntheses of natural products, a fact that underscores their importance in modern organic chemistry. This Review will discuss salient methods for the transition metal-catalyzed coupling of alkynes to enynes. Particular attention will be paid to coupling reactions employing palladium catalysis and the synthetic applications thereof, due to the versatility and utility associated with these processes.

Regio- and Stereoselectivity

A transition metal-catalyzed homo- or cross coupling of two alkynes may potentially generate several regio- or stereoisomeric enyne products (Scheme 1).[6] A homocoupling process may yield a 1,1-disubstituted olefin by virtue of head-to-tail coupling, the (*E*)-isomer of an internal olefin upon head-to-head coupling, its (*Z*)-congener, or mixtures thereof (Eqn. A). In a cross coupling event involving two different terminal alkynes, an even greater distribution of products is possible depending on which substrate acts as the donor and which acts as the acceptor (Eqn. B).

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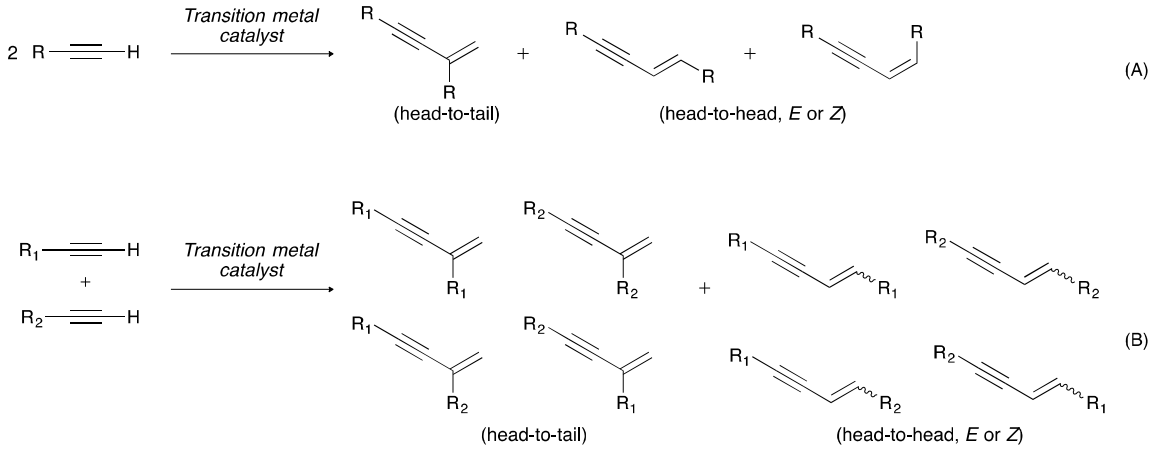
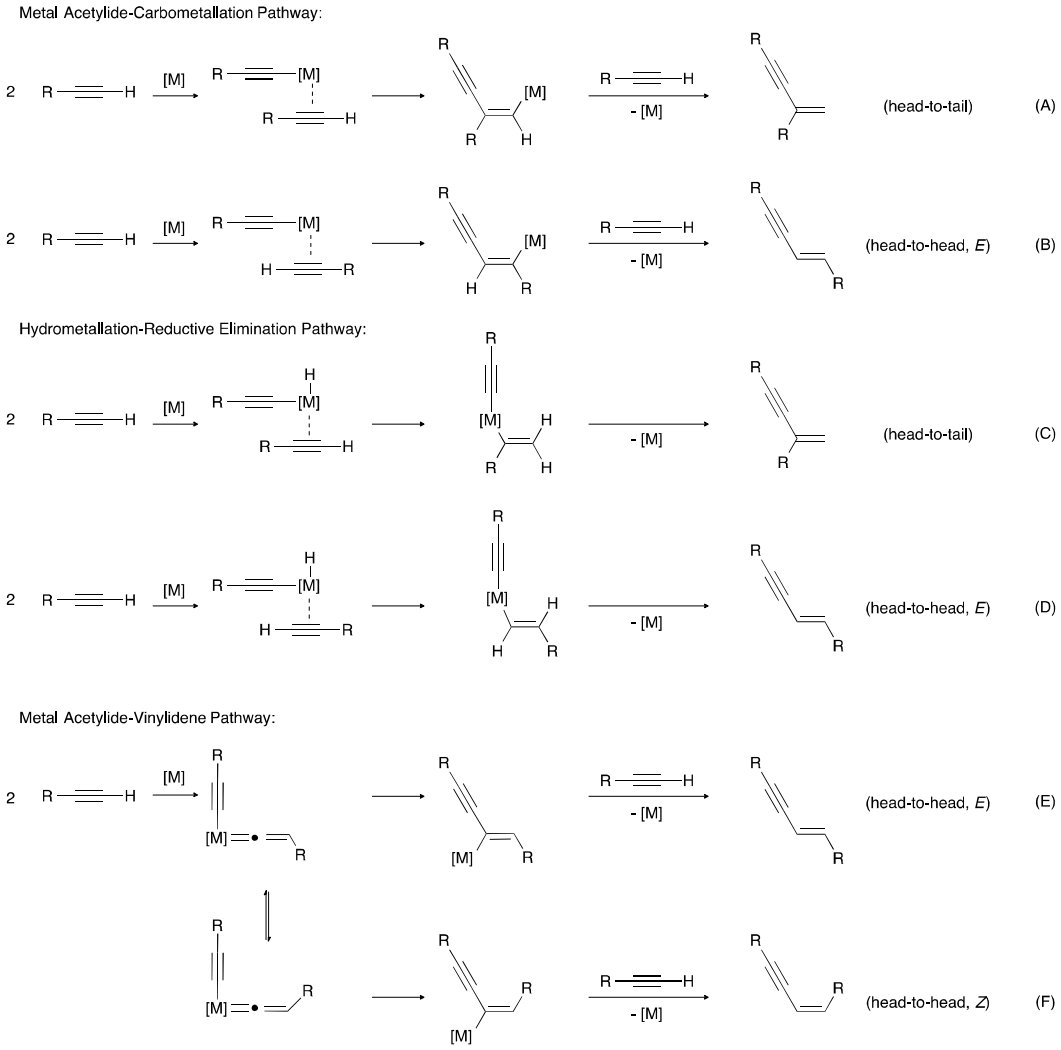
Several detailed studies have been performed in order to elucidate the various mechanisms through which these different products can be formed under transition metal catalysis.[7] From these studies, some general mechanistic understandings have emerged (Scheme 2). In one possible mode of reactivity, a metal acetylide may form upon the interaction of a terminal alkyne with a transition metal complex (Scheme 2, Eqns A and B). This species can coordinate a second, acceptor alkyne and undergo a *syn*-carbometallation event. Release of the enyne product can occur *via* protonolysis or metathesis with another terminal alkyne, events that regenerate either the metal catalyst or a metal acetylide. As will be shown, the regiochemical outcome of the process—that is, whether the coupling occurs in the head-to-tail fashion illustrated in Eqn. A or in the head-to-head fashion illustrated in Eqn. B—can depend upon the identity of the metal catalyst, its specific ligand sphere, and the substituents on the alkyne coupling partners. Of particular note, the steric interactions that develop between these entities in the transition state leading to the C–C bond-forming event can have a dramatic impact on the selectivity of the process.



Scheme 1: Regio- and Stereoisomeric 1,3-Enynes Resulting from Alkyne Coupling.



Scheme 2: Various Possible Mechanisms for the Coupling of Alkynes to 1,3-Enynes.

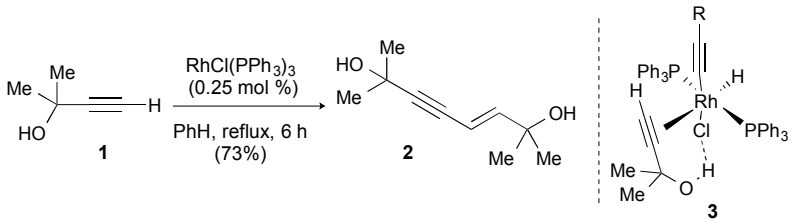
A hydrometallation-reductive elimination sequence can generate the same products (Scheme 2, Eqns. C and D). Hydrido(alkynyl)metal species have been identified spectroscopically, as have the alkynyl(vinyl)metal complexes that result upon regioselective insertion of an acceptor alkyne into the M□H bond.[7g] C–C bond formation can occur upon thermally promoted reductive elimination, generating either the head-to-tail (Eqn. C) or the (*E*)-head-to-head (Eqn. D) enyne product. As before, it has been suggested that the sense of regioselectivity associated with these couplings can be, at least in part, a function of the steric interactions that occur during the hydrometallation event.

Alternatively, either the (*E*)-head-to-head product or its (*Z*)-isomer may form through a metal acetylide-vinylidene intermediate (Scheme 2, Eqns. E and F). The interaction of two terminal alkynes with a transition metal may generate such a species, which can equilibrate between its rotameric forms. Migration of the acetylide ligand to the α-carbon of the vinylidene generates an enynylmetal species from which either the (*E*)- or (*Z*)-product isomer is derived. As will be demonstrated, the relative populations of the two rotamers—and, thus, the product distribution—can be influenced by several factors, including the ligand environment around the metal center.

The multitude of different reaction mechanisms through which terminal alkynes may be coupled, when combined with the fact that multiple mechanisms may operate simultaneously, can render efficient regio- and stereoselective alkyne coupling challenging. Further complicating matters is the issue of chemoselectivity[8] that arises in cross couplings involving dissimilar alkyne coupling partners. For example, the question arises of whether one of two terminal alkynes can be induced to act selectively as either the donor or acceptor. Similarly, in cross couplings between terminal alkyne donors and differentially disubstituted internal alkyne acceptors, an issue of regioselectivity occurs. Despite these challenges, several effective procedures have been developed for the selective formation of each of the various enyne products that result from alkyne coupling.

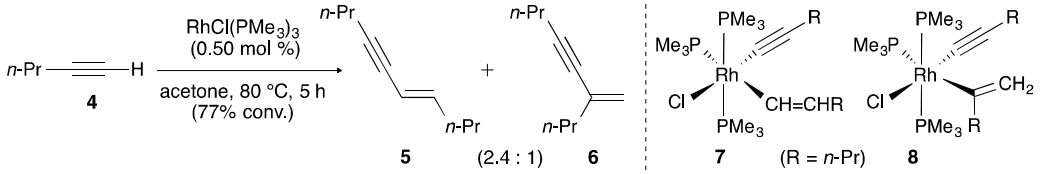
Rhodium Catalysis

Early work on transition metal-catalyzed alkyne coupling was performed by Wilkinson and Singer who, in 1968, reported the selective dimerization of propargylic alcohols under Rh catalysis.[9] Specifically, 2-methylbut-3-yn-2-ol (**1**) was smoothly converted to (*E*)-head-to-head product **2** in 73% yield by the action of $RhCl(PPh_3)_3$ in refluxing benzene (Scheme 3). 1-Ethynylcyclohexanol was similarly dimerized in high yield, but the reaction of an aryl alkyne afforded a complex product mixture. Alkyl alkynes and various acetylated α-hydroxyacetylenes failed to dimerize under these conditions. The high degree of reactivity associated with compound **1**, which bears a free hydroxyl group, suggested that hydrogen bonding between the substrate and a halide ligand on rhodium (as in complex **3**) might have facilitated reactivity. However, simpler α-hydroxyacetylenes such as propargyl alcohol itself failed to dimerize, suggesting that other factors (*e.g.*, a *gem*-dimethyl effect) might also have been involved. A carbometallation mechanism involving selective coordination of the acceptor alkyne with its bulk positioned away from the rhodium acetylide (as in Scheme 2, Eqn. B) was proposed, although detailed mechanistic studies were not performed.



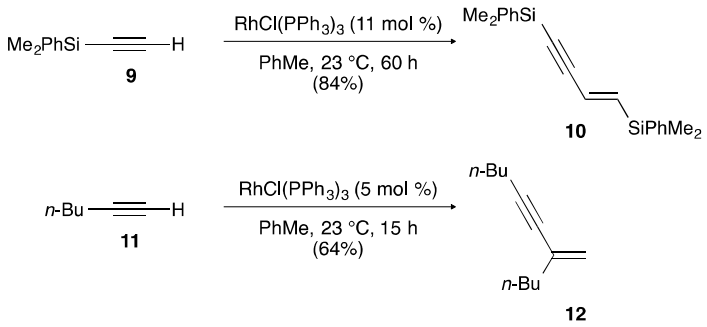
Scheme 3: Selective Homocoupling of an α-Hydroxyacetylene under Rhodium Catalysis.

Vinogradov and co-workers subsequently discovered that $RhCl(PMe_3)_3$ was an effective catalyst for the dimerization of aliphatic alkynes.[7g] 1-Pentyne (**4**) was converted to a 2.4:1 mixture of (*E*)-head-to-head product **5** and head-to-tail product **6** upon exposure to the catalyst in refluxing acetone (Scheme 4). Similar results were obtained with other aliphatic substrates, but aryl alkynes, ethyl propiolate, and ethoxyacetylene failed to dimerize. To distinguish between the carbometallation and hydrometallation mechanisms, detailed NMR studies were performed. Organorhodium species **7** and **8**, which putatively result from sequential coordination of an alkyne to a hydrido(alkynyl)rhodium complex and insertion of this coordinated alkyne into the Rh–H bond, were identified spectroscopically. These complexes were isolated in crystalline form from the reaction mixture. When a toluene solution containing both compounds was heated to 50 °C, enyne products **5** and **6** were formed. These results suggested that the catalytic process followed the hydrometallation-reductive elimination sequence (Scheme 2, Eqns. C and D).



Scheme 4: Dimerization of Aliphatic Alkynes under Rhodium Catalysis.

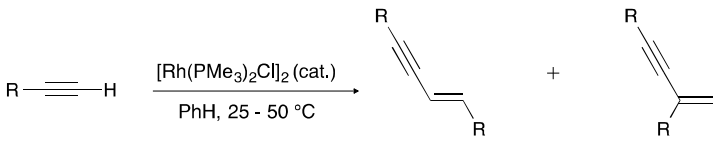
Contemporaneously, Ishikawa and co-workers reported that silyl acetylenes such as ethynyldimethylphenylsilane (**9**) were selectively dimerized to (*E*)-head-to-head products (*e.g.*, **10**) when exposed to $RhCl(PPh_3)_3$ in toluene at room temperature (Scheme 5).[10] In contrast to both the Wilkinson and Vinogradov reports, 1-hexyne (**11**) not only reacted smoothly under these conditions but also generated the head-to-tail product **12** selectively and in good yield. However, the catalyst loading for this process was significantly higher than that used previously (5 mol % *vs*. 0.25□0.50 mol %).



Scheme 5: Regioselective Alkyne Dimerizations Reported by Ishikawa.

Similarly, Goldman and Boese reported examples of $[Rh(PMe_3)_2Cl]_2$-catalyzed dimerizations wherein the regiochemical outcome was a function of the substrate (Table 1).[11] While the coupling of 1-pentyne (**4**) afforded a mixture of head-to-head and head-to-tail products **5** and **6**, the reaction of *tert*-butylacetylene (**13**) selectively formed the head-to-head dimer **14**, and phenylacetylene (**16**) yielded exclusively the head-to-tail enyne **18**. Taken together with the Ishikawa results, these examples illustrate how the regioselectivity of a coupling process can be strongly influenced by the steric and/or electronic nature of the acetylene substrate.

Table 1: Regioselectivity as a Function of Alkyne Substituent in Rh-catalyzed Alkyne Homocouplings.

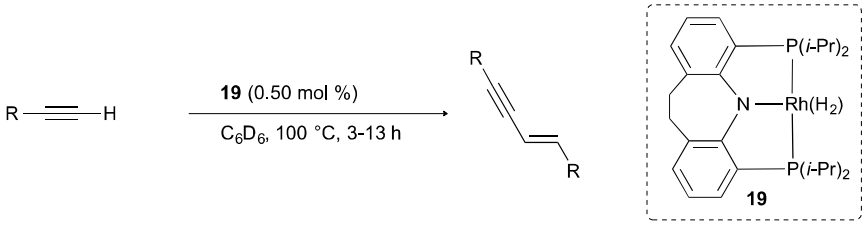


Alkyne	R	Product	Yield (%)	Product	Yield (%)
4	*n*-Pr	**5**	37	**6**	63
13	*t*-Bu	**14**	100	**15**	0
16	Ph	**17**	0	**18**	100

More recent efforts have led to the development of catalyst systems capable of effecting selective couplings over a broader range of substrates. In 2005, Ozerov and co-workers reported the synthesis and reactivity of dihydrido-Rh pincer complex **19** (Table 2).[12] This compound promoted the coupling of aryl, silyl, and alkyl acetylenes to the corresponding dimers with high reaction conversion and with excellent chemo- and regioselectivity, delivering the (*E*)-head-to-head dimer as the major product with only minor amounts of regioisomers and/or trimeric products. In addition to an impressive substrate scope, the process exhibited outstanding reactivity: very high conversion was typically achieved using 0.50 mol % of **19**. A hydrometallation-reductive elimination mechanism was proposed, and it was suggested that the regiochemical outcome might have been the result of steric interactions that favored placing the bulk of the Rh complex away from other substituents during the hydrometallation event (Scheme 2, Eqn. D). Ozerov and Pell have also described the preparation of several related phosphinito-

derived rhodium pincer complexes; these catalysts displayed greater reactivity but decreased selectivity in alkyne dimerization processes.[6a]

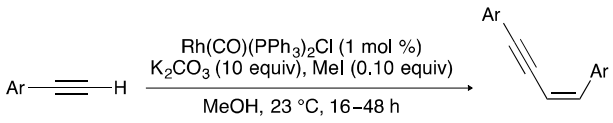
Table 2: Regioselective Alkyne Couplings Promoted by a Rhodium Pincer Complex



Alkyne	R	Conv. (%)	Product	Selectivity *E*-Head-to-Head: Σ(other products)
11	*n*-Bu	97	**21**	99:1
16	Ph	98	**17**	99:1
20	Me_3Si	92	**22**	90:10

Rhodium catalysis has also proven effective for (*Z*)-selective head-to-head alkyne coupling. Lin and co-workers identified that $Rh(CO)(PPh_3)_2Cl$, when combined with potassium carbonate and iodomethane in MeOH, promoted the coupling of electron-neutral and electron-deficient aryl acetylenes to the corresponding (*Z*)-enynes **26**-**28** (Table 3).[13] However, electron-rich substrates (such as *p*-tolylacetylene, **25**) failed to couple. It was proposed that a reactive intermediate might have been the Rh^{III} species resulting from oxidative addition of an alkynylrhodium(I) compound into iodomethane. Upon coordination of a second alkyne substrate, this complex could convert to a rhodium acetylide-vinylidene from which the (*Z*)-enyne is derived (Scheme 2, Eqn. F). The authors proposed that the decreased reactivity observed with electron-rich alkynes might have been due to a slower rate of vinylidene formation or less facile migration of the acetylide ligand to the vinylidene carbon atom.

Table 3: Rh-catalyzed (*Z*)-selective Dimerization of Aryl Alkynes.

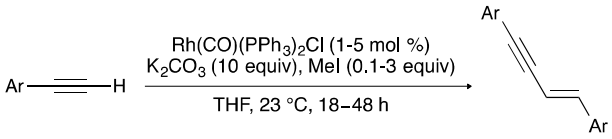


Alkyne	Ar	Product	Yield (%)
16	Ph	**26**	82
23	*p*-C_6H_4CN	**27**	82
24	*p*-$C_6H_4CF_3$	**28**	91
25	*p*-C_6H_4Me	**29**	0

When the same couplings were performed in THF, the selectivity was reversed, and the (*E*)-head-to-head products predominated (Table 4). Such products could be produced *via* the carbometallation, hydrometallation-reductive elimination, or (*E*)-head-to-head-selective alkylidene-vinylidene mechanisms. The fact that electron-rich alkynes

reacted smoothly in this case but not in the preceding transformation suggests that one of the first two mechanisms might have been operative under these conditions.

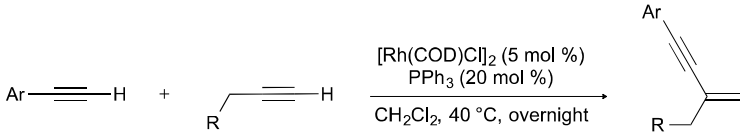
Table 4: Rh-catalyzed (*E*)-Head-to-Head-selective Dimerizations of Aryl Alkynes



Alkyne	Ar	Product	Yield (%)
16	Ph	**17**	75
23	*p*-C_6H_4CN	**30**	69
24	*p*-$C_6H_4CF_3$	**31**	90
25	*p*-C_6H_4Me	**32**	90

While the preceding examples reflect homocoupling processes, selective cross couplings between two different terminal alkynes are also possible under Rh catalysis. In a 2013 report, Xu and co-workers described the $[Rh(COD)Cl]_2/PPh_3$-catalyzed, head-to-tail-selective coupling of various terminal alkynes with propargyl alcohol (**33**) and with propargyl amine derivative **40** (Table 5).[6b] A variety of alkyl and aryl phosphine ligands were investigated, and the highest levels of conversion and regioselectivity were achieved using triphenylphosphine. Various aryl alkynes were examined, and each acted selectively as the donor alkyne to deliver the coupling products in good yields. However, couplings involving alkyl-substituted donor alkynes were less selective and led only to complex reaction mixtures.

Table 5: Chemoselective Alkyne Cross Coupling under Rh Catalysis.

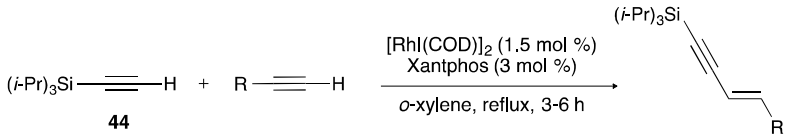


Donor	Ar	Acceptor	R	Product	Yield
34	*p*-C_6H_4OMe	**33**	OH	**37**	55
35	*p*-$C_6H_4NO_2$	**33**	OH	**38**	52
36	*o*-C_6H_4Br	**33**	OH	**39**	88
34	*p*-C_6H_4OMe	**40**	NHTs	**41**	92
35	*p*-$C_6H_4NO_2$	**40**	NHTs	**42**	77
36	*o*-C_6H_4Br	**40**	NHTs	**43**	95

Silyl-substituted alkynes have also been engaged selectively as donor alkynes in Rh-catalyzed cross couplings. Miura and co-workers discovered that

triisopropylsilylacetylene (**44**) smoothly coupled with various alkyl and aryl acetylene acceptors (**45**-**47**) in good yield (Table 6).[14] Excellent selectivity for the (*E*)-head-to-head product was achieved in all cases (> 89% selectivity). Several phosphine ligands promoted the coupling with high selectivity, but the best results were obtained using Xantphos, possibly due to the increased bite angle associated with the catalyst derived from this ligand.

Table 6: Chemoselective Rh-catalyzed Alkyne Cross Coupling using Triisopropylsilylacetylene as the Donor Alkyne.

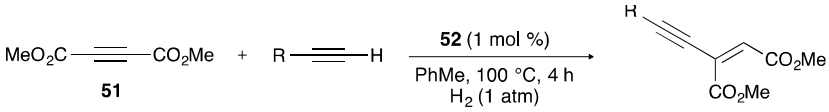


44

Acceptor	R	Product	Yield (%)
45	Bn	**48**	76
46	cyclohexyl	**49**	63
47	$MeO_2C(CH_2)_3$	**50**	85

Relative to those involving other metals, rhodium-catalyzed cross couplings of terminal alkyne donors with internal alkyne acceptors are fewer in number. Nevertheless, recent progress in this field is noteworthy. Nishiyama and co-workers reported the catalytic coupling of terminal alkynes with dimethyl acetylenedicarboxylate (**51**) by the action of Rh-Phebox complex **52** (Table 7).[15] High yields of the enyne products were obtained using aryl acetylene donors, but reactions with alkyl or silyl alkynes were less efficient (≤ 40% yield). Nevertheless, excellent (*Z*)-selectivity (> 96:4) was obtained in all cases. NMR studies of stoichiometric reactions revealed the formation of an Rh acetylide that subsequently generated an enynylrhodium species upon reaction with dimethyl acetylenedicarboxylate; this implicated a carbometallation pathway for the catalytic process.

Table 7: Rh-catalyzed Alkyne Cross Coupling using Dimethylacetylenedicarboxylate as the Acceptor.



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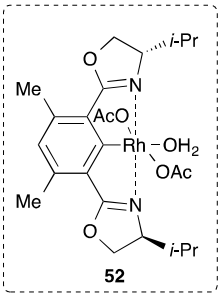
Donor	R	Product	Yield (%)
16	Ph	**56**	85
53	o-C_6H_4Me	**57**	85
54	p-C_6H_4Br	**58**	87
55	*n*-Hexyl	**59**	40
20	Me_3Si	**60**	26



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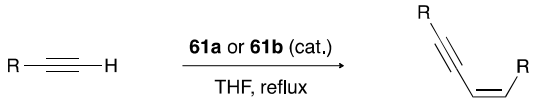
Ruthenium Catalysis

The ruthenium-catalyzed coupling of acetylenes has also enjoyed a rich history. As early as the 1970s, ruthenium-catalyzed dimerizations of alkyl alkynes to cumulenes were known.[7a,7b,16] While head-to-head and head-to-tail enyne products were also identified in those processes, they were present only as minor products. In the early 1990s, however, Bianchini and co-workers reported the selective, catalytic dimerization of both phenylacetylene (**16**) and trimethylsilylacetylene (**20**).[7f,17] In the presence of $[RuH(N_2)N(CH_2CH_2PPh_2)_3]BPh_4$ (**61a**) or $[Ru(C\alpha CSiMe_3)N(CH_2CH_2PPh_2)_3]BPh_4$ (**61b**), respectively, these substrates were converted to the corresponding (*Z*)-head-to-head enynes in high conversion and with > 90 % (*Z*)-selectivity (Table 8).

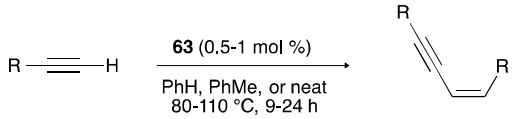
Table 8: Ru-catalyzed (*Z*)-selective Alkyne Dimerizations.



Alkyne	R	Conv. (%)	Product	Selectivity (*Z*)-Head-to-Head: (*E*)-Head-to-Head
16	Ph	90	**26**	92:8
20	Me_3Si	90	**62**	93:7

In 2005, Bianchini and co-workers reported that the use of $[RuH(MeCN)N(CH_2CH_2PPh_2)_3]OTf$ (**63**) delivered improved reactivity and could successfully dimerize aryl, alkyl, and silyl acetylenes in high yield and with excellent (*Z*)-selectivity (≤ 5% of other enyne isomers).[18] Substrates containing sensitive or potentially reactive functional groups, such as aldehydes, anilines, free alcohols, and aryl halides, were all smoothly coupled in high yield using low catalyst loadings (≤ 2 mol %) at 80□110 °C (Table 9).

Table 9: Further (*Z*)-selective Head-to-Head Alkyne Couplings Reported by Bianchini.

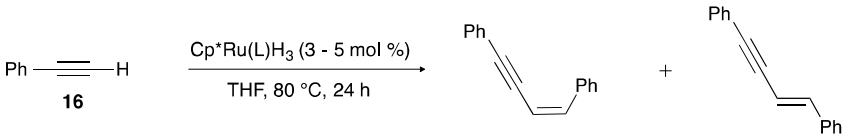


Alkyne	R	Product	Yield (%)
54	*p*-C_6H_4Br	**67**	90
64	*p*-C_6H_4CHO	**68**	86
65	*p*-$C_6H_4NH_2$	**69**	87
66	$HO(CH_2)_4$	**70**	77
20	Me_3Si	**62**	88

Over a series of publications in the late 1990s, Yi and co-workers described alkyne dimerizations promoted by phosphine-ligated

pentamethylcyclopentadienylruthenium hydride complexes. As described in initial reports, the product distribution resulting from the coupling of phenylacetylene (**16**) was strongly influenced by the choice of phosphine ligand (Table 10).[7e,19] When the tricyclohexylphosphine-derived catalyst was used, (*Z*)-head-to-head product **26** was formed selectively. However, the use of the analogous trimethylphosphino catalyst favored the (*E*)-isomer, **17**. In both cases, high conversion was obtained (82-86% combined yield of both isomers). Such a dramatic ligand effect was not observed with non-aromatic substrates, which generally yielded mixtures of enyne isomers regardless of the ligand used.

Table 10: Ligand-dependent Reversal of Regioselectivity in Ru-catalyzed Alkyne Dimerizations.



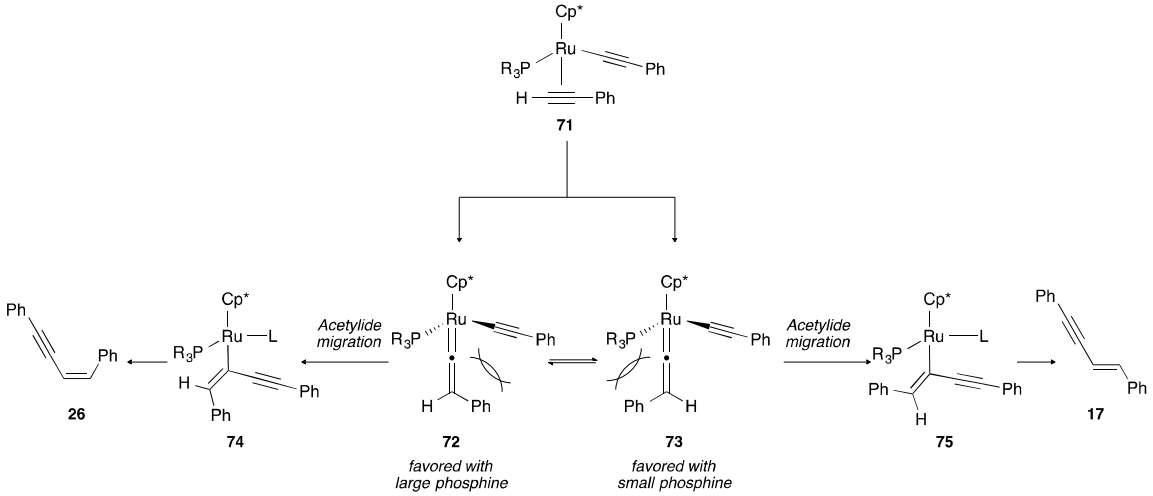
Ligand	Yield (%)	**26:17**
PCy_3	86	90:10
PMe_3	82	10:90

A possible explanation for these results is the existence of a metal acetylide-vinylidene mechanism involving the preferential formation of one vinylidene rotamer (Scheme 6). From alkynylruthenium species **71**, a mixture of ruthenium complexes **72** and **73** can form.[20] These intermediates may interconvert.[7b] The question of which rotamer is favored becomes a matter of the relative magnitude of the steric interactions occurring between (a) the phosphine ligand and the vinylidene substituent and (b) the phosphine ligand and the acetylide ligand. When a bulky ligand such as tricyclohexylphosphine is used, the significant steric repulsion that occurs between the cyclohexyl groups and the vinylidene substituent of rotamer **73** causes the alternative complex, **72**, to be favored. Upon migration of the acetylide to the vinylidene,[21] η^1-enynylruthenium complex **74** is formed,[22] and, from it, the (*Z*)-head-to-head coupling product **26** is obtained selectively.[23]

Alternatively, the use of a less bulky ligand such as trimethylphosphine favors the formation of rotamer **73**. In this case, the steric interactions between the phosphine substituents and the vinylidene substituent are reduced. This arrangement thus becomes preferable to that of rotamer **72**, which experiences steric clash between the vinylidene substituent and the acetylide ligand. From **73**, acetylide migration generates intermediate **75,** a precursor to (*E*)-product **17**.

This mechanism may explain why couplings involving alkyl and silyl acetylenes led to mixtures of (*E*)- and (*Z*)-head-to-head products and head-to-tail products under these conditions. The conversion of alkynylruthenium complex **71** to an acetylide-vinylidene species such as **72** or **73** is reported to be slower for non-aromatic alkyne derivatives.[24] As a result, alternative reactions involving **71**—such as the

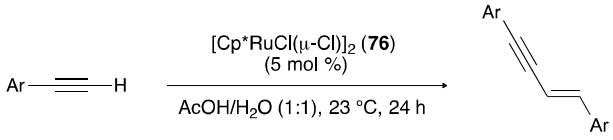
carbometallation pathway that leads to the head-to-tail or (*E*)-head-to-head product (Scheme 2, Eqns. (A) and (B), respectively)—may compete.



Scheme 6: Formation of Stereoisomeric Enynes *via* an Acetylide-Vinylidene Mechanism.

An analogous acetylide-vinylidene mechanism involving preferential rotamer formation was proposed by García-Garrido and co-workers who, in 2012, reported the (*E*)-head-to-head-selective dimerization of various aryl alkynes catalyzed by [Cp*RuCl(μ-Cl)]$_2$ (**76**, Table 11).[25] The process proved most effective in acetic acid-water solvent mixtures, and reactivity was increased further by the addition of sodium acetate. These results suggested that the formation of an active alkynylruthenium species might have resulted from carboxylate-assisted deprotonation of a metal-coordinated terminal alkyne.

Table 11: (*E*)-selective Head-to-Head Alkyne Couplings Catalyzed by [Cp*RuCl(μ-Cl)]$_2$ (76) Reported by García-Garrido.



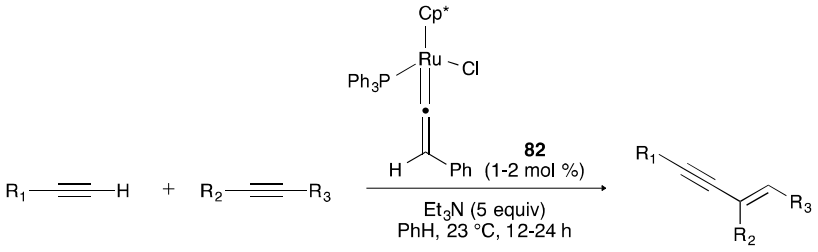
Alkyne	Ar	Product	Yield (%)
16	Ph	**17**	64
54	*p*-C$_6$H$_4$Br	**78**	74
64	*p*-C$_6$H$_4$CHO	**79**	85
77	*o*-C$_6$H$_4$OMe	**80**	37

Perhaps due to the plethora of different reaction mechanisms that may operate simultaneously, chemoselective alkyne cross couplings catalyzed by ruthenium are rare.

Taking advantage of the fact that terminal aryl alkynes generate vinylidene complexes of ruthenium more rapidly than do terminal alkyl or silyl alkynes (*e.g.*, **71**□**72** or **71**□**73**), Katayama and co-workers developed a protocol for the Ru-catalyzed (*Z*)-selective addition of silyl alkynes across terminal aryl alkynes.[26] However, it was necessary to employ a large excess (5–20 equiv) of the silyl alkyne in order to achieve high selectivity for cross coupling over aryl alkyne homocoupling.

Yi and Liu reported an efficient cross coupling of terminal alkyne donors with internal alkyne acceptors that was catalyzed by Cp*Ru(PPh_3)C≡CPh (**81**).[27] This complex, which was generated *in situ* from Cp*Ru=C=CHPh(PPh_3)(Cl) (**82**) and triethylamine, promoted the cross coupling of alkyl, silyl, and aryl alkyne donors with both unactivated internal alkynes and internal alkynes bearing electron-withdrawing, activating groups (Table 12). In the presence of only a slight excess of the internal alkyne (1.1 equiv), cross coupling generally predominated over homocoupling. Thus, *tert*-butylacetylene (**13**) reacted smoothly with the symmetrical acceptor 2-butyne (**83**). When propiolate **84** was reacted with trimethylsilylacetylene (**20**), the coupling was regioselective for the formation of the β-alkynylated product. However, in some instances, mixtures of cross coupling and homocoupling products were obtained: for example, the reaction between phenylacetylene (**16**) and ketone-derived acceptor **85** yielded 44% of enyne **88** but also 41% of the head-to-head homodimer of phenylacetylene.

Table 12: Selective Alkyne Cross Couplings Catalyzed by Ruthenium.



Donor	R_1	Acceptor	R_2	R_3	Product	Yield (%)
13	*t*-Bu	**83**	Me	Me	**86**	87
20	Me_3Si	**84**	Me	CO_2Et	**87**	85
16	Ph	**85**	Et	COMe	**88**	44

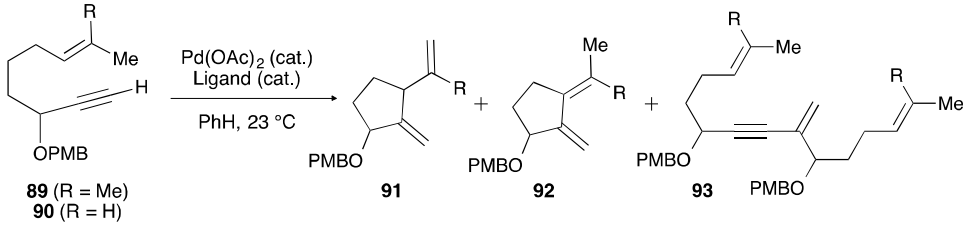
Palladium Catalysis

Palladium occupies a privileged position in the realm of enyne synthesis. A substantial body of research has revealed that palladium complexes can promote the coupling of alkynes to enynes with levels of chemo-, regio-, and stereoselectivity that are unrivaled by any other transition metal. Isolated examples of Pd-catalyzed or co-catalyzed alkyne dimerizations appeared in the mid-to-late 1980s, with Sabourin reporting in 1984 that mixtures of $Pd(OAc)_2$, CuI, and phosphonite ligands effected the head-to-tail dimerization of α-hydroxyacetylenes[28] and with Ishikawa and co-workers disclosing in 1988 that $Pd(PPh_3)_4$ catalyzed the head-to-head coupling of silyl-substituted

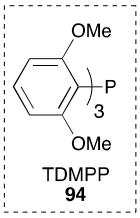
alkynes.[29] Nevertheless, it was a report from Trost and co-workers in 1987 that propelled palladium catalysis to the forefront amongst metal-catalyzed homo- and cross couplings of acetylenes to enynes.[30]

Initially, Pd-catalyzed alkyne homocoupling was observed as a side reaction during cycloisomerization reactions of compounds **89** and **90** (Table 13).[7c,30,31] In the presence of triphenylphosphine-ligated $Pd(OAc)_2$, substrate **89** was converted to a mixture of cycloisomers **91** and **92** along with head-to-tail alkyne dimerization product **93** (entry 1). It was proposed that these different products resulted from competing monodentate coordination of Pd to the alkyne (which effected dimerization to product **93**) and bidentate coordination of Pd to both the alkyne and the olefin of the substrate (which effected the cycloisomerization event). In support of this, the use of the more sterically encumbered ligand tri-*o*-tolylphosphine led to increased selectivity for the homocoupling of substrate **89**. Presumably, this generated a more coordinatively unsaturated palladium complex that favored the monodentate coordination mode (entry 2). When substrate **90**, which bears a disubstituted olefin instead of the trisubstituted olefin of **89**, was reacted using $Pd(OAc)_2$ and either of these ligands, only cycloisomerization products were detected (entries 3 and 4). It was postulated that bidentate coordination was more favorable in this case due to decreased hindrance around the olefin and a more favorable LUMO of the alkene that enhanced coordination. Nevertheless, it was soon discovered that the use of the very sterically encumbered and electron-rich ligand tris(2,6-dimethoxyphenyl)phosphine (TDMPP, **94**) suppressed cycloisomerization and promoted the alkyne coupling of this substrate in high yield (entry 5).

Table 13: Cycloisomerization versus Alkyne Homocoupling in the Reactions of Compounds 89 and 90.

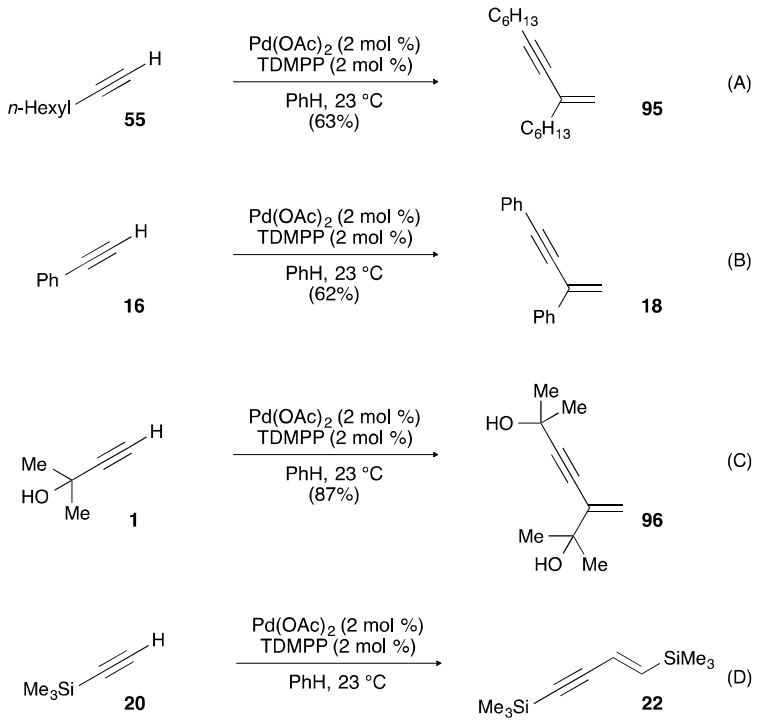


Entry	Substrate	Ligand	Combined Yield of **91** and **92** (%)	**91**:**92**	Yield of Dimer **93** (%)
1	**89**	PPh_3	19	6:1	9-22
2	**89**	P(*o*-tolyl)$_3$	12	2:1	66
3	**90**	PPh_3	41	1:1	N.D.
4	**90**	P(*o*-tolyl)$_3$	33	1:2	N.D.
5	**90**	TDMPP (**94**)	4	0:1	71



These optimized coupling conditions proved extremely general. Upon exposure to 2 mol % each of $Pd(OAc)_2$ and TDMPP, 1-octyne (**55**) and phenylacetylene (**16**) were each smoothly converted to their head-to-tail dimers **95** and **18** (Scheme 7, Eqns. A and B). Free alcohols were tolerated, with propargylic alcohol **1** reacting to give product **96** in

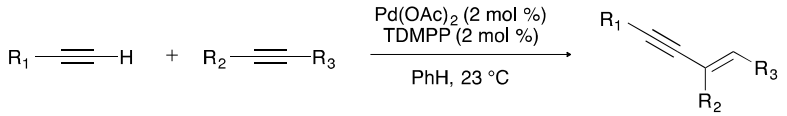
excellent yield (Eqn. C). In these and nearly all other cases examined, the coupling proceeded with complete selectivity for the head-to-tail product, establishing a breadth of scope not previously known for any such alkyne dimerization process and especially not for head-to-tail-selective processes. The only exception came when trimethylsilylacetylene (**20**) was reacted: in this case, (*E*)-head-to-head product **22** was obtained exclusively (Eqn. D).



Scheme 7: Alkyne Dimerizations Effected using Catalytic $Pd(OAc)_2$/TDMPP.

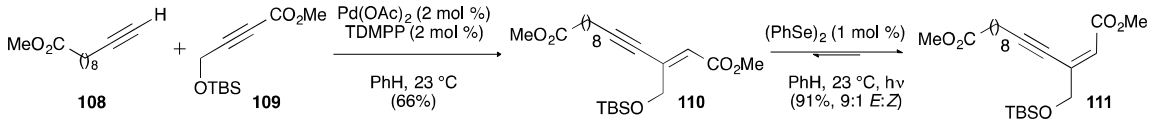
The introduction of one equivalent of an electron-deficient internal alkyne to the same reaction medium was sufficient to suppress homocoupling and promote efficient and selective alkyne cross coupling. To this end, silyl, aryl, and alkyl alkynes were all engaged as donors in couplings with propiolate acceptors (Table 14). Notably, donor alkynes bearing malonate (**97**) and aldehydic (**98**) functionality reacted smoothly. Other electron-deficient functional groups also activated the internal alkyne toward coupling: reactions with acetylenic sulfones (*e.g.*, **100**) and acetylenic ketones (*e.g.*, **101**) were also successful. In addition to being selective for cross coupling over homocoupling, these reactions delivered the indicated enynes with complete regio- and stereoselectivity.

Table 14: Selective Alkyne Cross Couplings Effected using Catalytic $Pd(OAc)_2$/TDMPP.



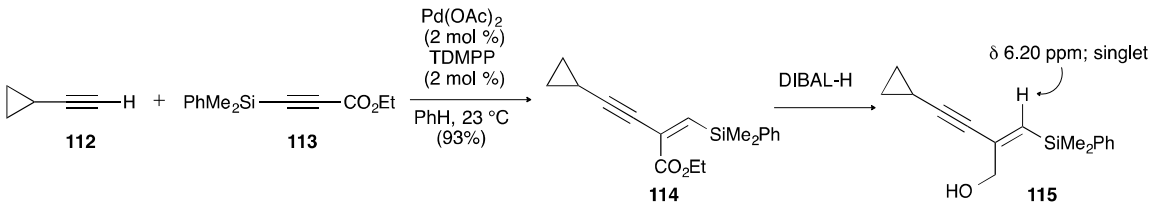
Donor	R_1	Acceptor	R_2	R_3	Product	Yield (%)
20	Me_3Si	**99**	Me	CO_2Me	**102**	95
16	Ph	**99**	Me	CO_2Me	**103**	92
97	$(MeO_2C)_2CH_2$	**84**	Me	CO_2Et	**104**	87
98	$CHO(CH_2)_3$	**99**	Me	CO_2Me	**105**	84
11	*n*-Butyl	**100**	Me	SO_2Ph	**106**	68
16	Ph	**101**	*n*-Hexyl	COMe	**107**	83

While these $Pd(OAc)_2$/TDMPP-catalyzed couplings of terminal alkynes donors with activated alkyne acceptors selectively yielded the indicated *trans*-enynes, these compounds could be converted to their thermodynamically favored *cis*-isomers through a free radical-promoted olefin isomerization.[32] For example, the cross coupling of donor alkyne **108** with propiolate **109** delivered (*Z*)-ynenoate **110**, but the exposure of this compound to diphenyldiselenide (1 mol %) in the presence of visible light furnished a 9:1 mixture that favored (*E*)-isomer **111** (91% combined yield, Scheme 8).



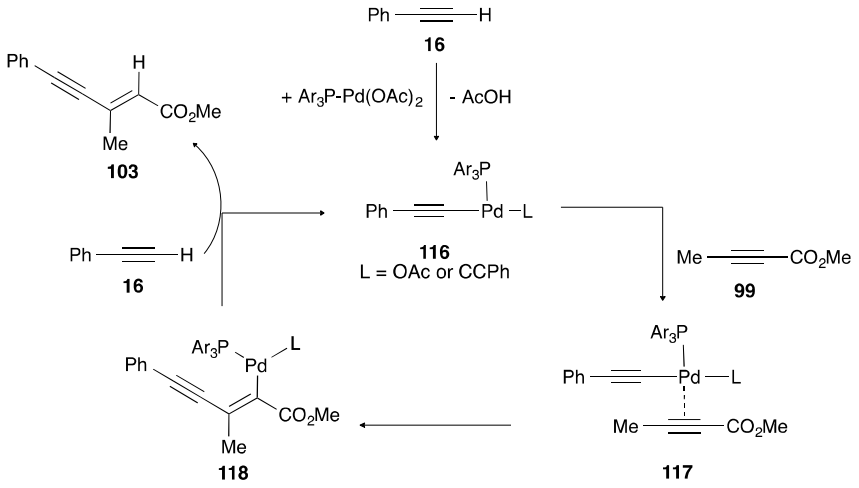
Scheme 8: Access to *cis*-Enynes *via* Sequential Alkyne Coupling and Olefin Isomerization.

A dramatic reversal in the regiochemistry of the alkyne coupling occurred when silyl-substituted alkynoates were reacted. Specifically, the Pd/TDMPP-catalyzed cross coupling of cyclopropylacetylene (**112**) with ethyl 3-dimethylphenylsilylpropiolate (**113**) delivered α-alkynylated compound **114** as the sole product in 93% yield (Scheme 9).[33] Similar results were observed when other alkyl alkynes or phenylacetylene were used as donors. The regiochemical assignment was confirmed upon reduction of ester **114** to primary alcohol **115**. The chemical shift and the multiplicity (*vide infra*) of the vinylic hydrogen were consistent with the contra-Michael, α-alkynylated product; in contrast, the alcohols derived from β-alkynylation products bear vinylic hydrogens that appear as triplets in ^{1}H NMR spectra.



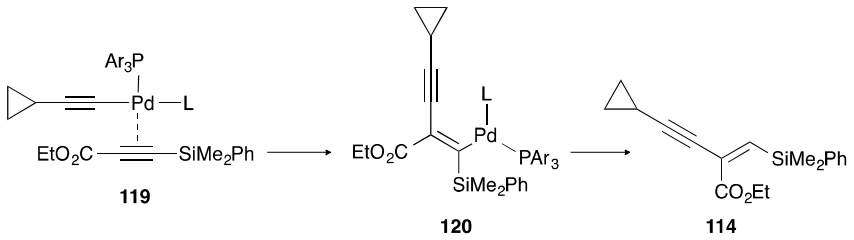
Scheme 4: Reversal of Regioselectivity in the Alkyne Coupling involving Silyl-Derived Acceptor Alkyne 113.

All of these results can be understood in terms of a carbopalladation mechanism that is sensitive to both steric and electronic parameters. A detailed examination of the cross coupling of phenylacetylene (**16**) with methyl 2-butynoate (**99**) is illustrative (Scheme 10). Generation of an alkynylpalladium complex such as **116** may occur either through carboxylate-assisted deprotonation or an oxidative addition-reductive elimination sequence. The use of TDMPP may promote the alkyne coupling by generating a metal complex that is electron-rich enough to insert into the acetylenic C–H yet still sufficiently coordinatively unsaturated enough to ligate an alkyne acceptor. The precise ligand sphere around palladium in complex **116** may vary. While it is plausible that one acetate ligand remains, a dialkynylpalladium species is also possible.[34] The greater electron richness of the latter would explain the high selectivity for cross coupling over homocoupling: such a species would be expected to preferentially coordinate the substrate with the lowest-lying LUMO and the greatest capacity for backbonding; namely, an electron deficient internal alkyne. Such coordination would generate complex **117**, and carbopalladation would yield **118**. The polarization generated in the transition state of the alkyne addition would favor this regiochemistry with an electronically activated acceptor; additionally, this results in the formation of the more stable C–Pd bond. A *syn*-addition event is consistent with the fact that only a single olefin isomer is produced. From **118**, release of enyne product **103** and catalyst regeneration can result upon either protonation by AcOH or metathesis with another molecule of terminal alkyne.



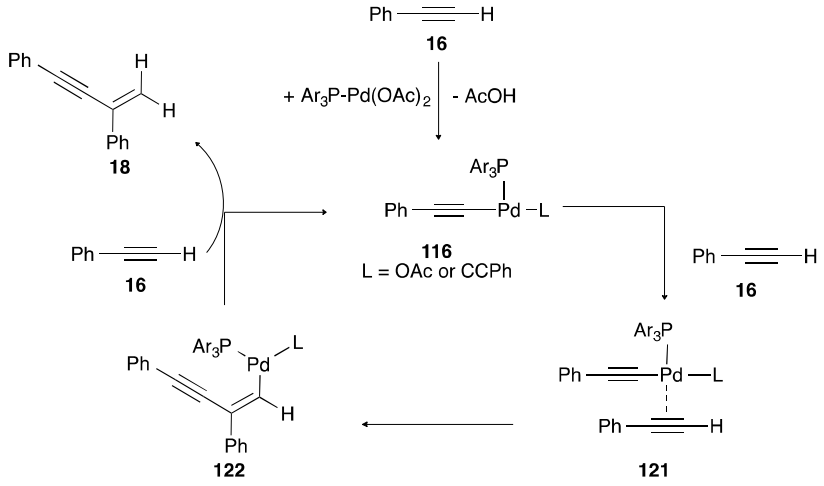
Scheme 10: A Plausible Mechanism for the $Pd(OAc)_2$/TDMPP-catalyzed Alkyne Cross Coupling.

In the case of acceptor **113**, the bulk associated with the dimethylphenylsilyl group appears to disfavor β-addition on steric grounds. Thus, carbopalladation (**119**□**120**, Scheme 11) presumably proceeds with the opposite sense of regiochemistry, leading to α-alkynylation product **114** *via* the intermediacy of enynylpalladium complex **120**. The stabilizing effect of the α-silyl group in this complex may reinforce this steric bias.



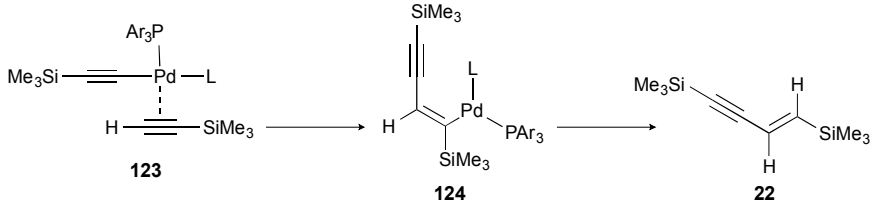
Scheme 11: Reversal of Regioselectivity in the Carbopalladation of Acceptor Alkyne 113.

In the homocoupling process, a comparable sequence of steps may generate complex **121** (Scheme 12). The regioselectivity observed is consistent with formation of enynylpalladium species **122** through a carbopalladation event that places palladium on the less substituted carbon in order to minimize steric interactions. The bulk imparted by the *ortho*-methoxy substituents of TDMPP may reinforce this selectivity.



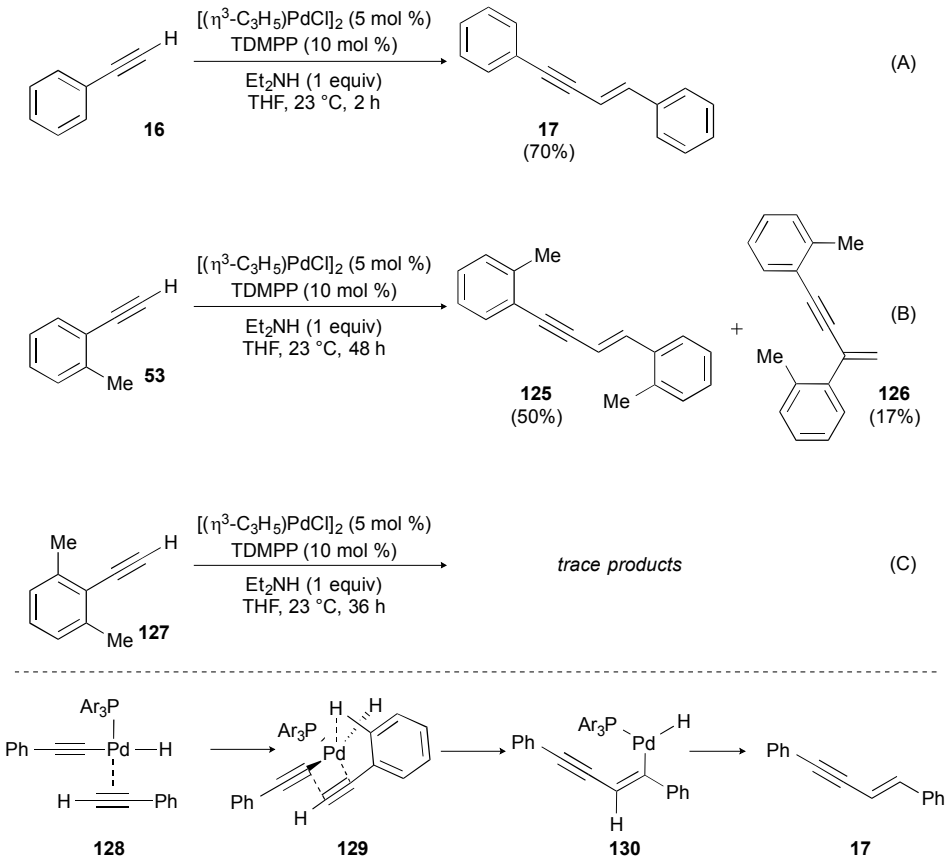
Scheme 12: A Plausible Mechanism for the $Pd(OAc)_2$/TDMPP-catalyzed Alkyne Homocoupling.

Analogously to the reaction of silyl alkyne acceptor **113**, the reversed sense of regioselectivity observed in the homocoupling of trimethylsilylacetylene (**20**) may be due to the stabilizing effect of the α-silicon group. Thus, carbopalladation may generate the sterically less favorable but electronically stabilized enynylpalladium complex **124** (Scheme 13). Catalyst turnover and decomplexation would then deliver the observed product, (*E*)-head-to-head enyne **22**.



Scheme 13: A Mechanistic Rationale for the $Pd(OAc)_2$/TDMPP-catalyzed Homocoupling of Trimethylsilylacetylene to Enyne 22.

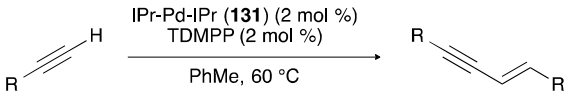
Following this report, other palladium complexes capable of effecting alkyne coupling were identified. In addition to the $Pd(OAc)_2$/P(*o*-tolyl)$_3$ and $Pd(OAc)_2$/TDMPP systems described by Trost and co-workers, Pd_2dba_3•$CHCl_3$/P(*o*-tolyl)$_3$,[35] $Pd(PPh_3)_4$,[35] $PdCl_2(P(OPh)_3)_2$[36], and various complexes of Pd with phosphinooxazoline (PHOX) ligands[37] have all been identified as effective catalysts for head-to-tail alkyne homocoupling and/or cross coupling with activated acceptors. However, it has also been discovered that the regioselectivity of the homocoupling process can vary dramatically depending on the identity of the palladium catalyst. Remarkably, this can be the case even when TDMPP is included as a ligand. In 2001, Gevorgyan and Rubina reported that a mixture of $[(\eta^3\text{-}C_3H_5)PdCl]_2$, TDMPP, and Et_2NH promoted the (*E*)-selective head-to-head dimerization of aryl alkynes (Scheme 14).[38] The process was effective for phenylacetylene and *para*-substituted aryl acetylenes, but it failed when it was applied to alkyl substrates. Interestingly, *ortho*-substituted aryl acetylenes either failed to react or led to mixtures of regioisomeric products, depending on the degree of substitution. For example, while phenylacetylene (**16**) was converted exclusively to dimer **17** (Eqn. A), *o*-tolylacetylene (**53**) afforded a mixture of head-to-head enyne **125** (50% yield) and head-to-tail product **126** (17% yield, Eqn. B), and the reaction of 2',6'-dimethylphenylacetylene (**127**) yielded only trace amounts of dimeric products (Eqn. C). It was postulated that this sense of regioselectivity—which is opposite to that reported by Trost—might have been the result of an anti-Markovnikov carbopalladation process, one that is favored due to a beneficial agostic interaction between the palladium center and an ortho-C–H bond (**128**→**129**→**130**). The potential involvement of such an interaction was supported by the observation of a significant kinetic isotope effect (k_H/k_D = 3.0 ± 0.1 using phenyl-d_5-acetylene). It remains unclear why the Trost $Pd(OAc)_2$/TDMPP system does not promote head-to-head coupling in this manner; however, it is possible that the amine additive and/or the halide or allyl ligands on palladium are also involved in the regiodetermining event in the Gevorgyan process.



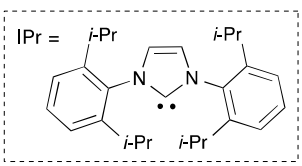
Scheme 14: Pd-catalyzed Head-to-Head-selective Dimerizations of Aryl Alkynes Reported by Gevorgyan.

More recently, Gevorgyan and co-workers developed a general method for Pd-catalyzed (*E*)-selective head-to-head couplings and provided evidence for an alternative reaction mechanism (Table 15).[39] The authors reported that the combination of TDMPP and bis-*N*-heterocyclic carbene palladium complex IPr-Pd-IPr (**131**) promoted the homocoupling of aryl, heteroaryl, and alkyl alkynes. In contrast to the prior report, *ortho*-disubstituted substrate **127** reacted smoothly to yield dimer **137**, a result that suggested that the reaction mechanism did not involve the agostic C–H interaction proposed previously.

Table 15: General Pd-catalyzed Head-to-Head-selective Alkyne Coupling Reported by Gevorgyan.

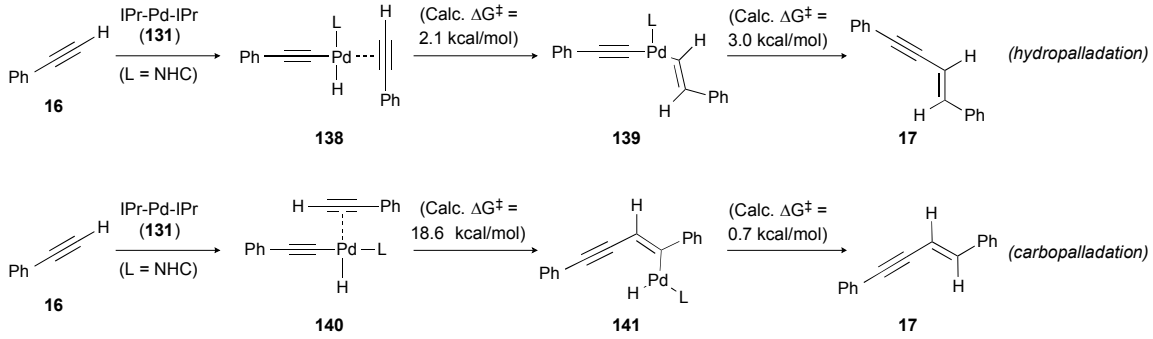


Alkyne	R	Product	Yield (%)
16	Ph	**17**	92
34	*p*-C_6H_4OMe	**134**	81
132	2-pyridyl	**135**	93
133	*n*-decyl	**136**	91
127	2,6-dimethylphenyl	**137**	71



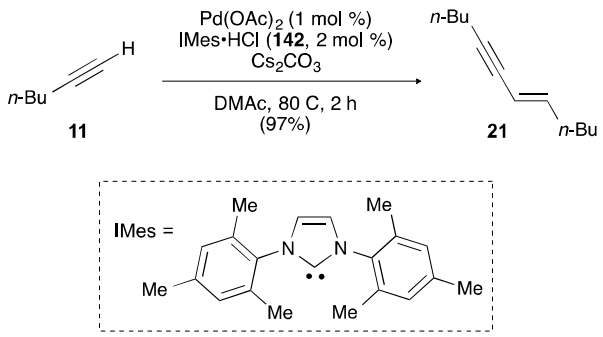
It was instead postulated that the selectivity arose from a hydropalladation mechanism. DFT computational studies were performed on the dimerization of phenylacetylene, and comparisons were made between the energetic barriers involved in the carbopalladation and hydropalladation pathways (Scheme 15). It was determined that insertion of an NHC-ligated palladium complex into an acetylenic C–H was a plausible first step ($\Delta G^{\ddagger}$ = 17.6 kcal/mol) and that the resulting alkynylpalladium hydride could readily coordinate an acceptor alkyne. A square planar geometry was predicted for the adduct, as in **138**. It was calculated that hydropalladation to generate **139** was exergonic (ΔG = – 16.9 kcal/mol) and possessed a low activation barrier ($\Delta G^{\ddagger}$ = 2.1 kcal/mol). C–C bond forming reductive elimination to generate the product (**17**) was also found to have a low energetic barrier (3.0 kcal/mol).

Square planar complex **140** was determined to have the optimal geometry for a carbopalladation pathway. Relative to hydropalladation, this carbopalladation event (**140**□**141**) was calculated to be less exergonic (ΔG = – 13.9 kcal/mol) and to possess a much greater activation energy ($\Delta G^{\ddagger}$ = 18.6 kcal/mol), although the barrier associated with the subsequent C–H reductive elimination step was low ($\Delta G^{\ddagger}$ = 0.7 kcal/mol). Similar trends were observed when the calculations were performed using 1-hexyne as the model alkyne. On the basis of the calculated energetic differences between the two pathways, it was argued that hydropalladation might be the predominant mechanism under these NHC-Pd-catalyzed coupling conditions.



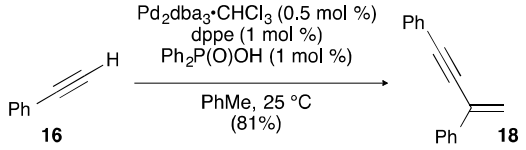
Scheme 15: Computational Analysis of Hydropalladation and Carbopalladation Processess under Pd-NHC Catalysis.

Supporting this assertion is the fact that head-to-head selectivity is observed in other NHC-Pd-catalyzed processes, including those conducted without TDMPP.[40,41] For example, the homocoupling of 1-hexyne (**11**) using $Pd(OAc)_2$ and IMes-HCl (**142**) yielded head-to-head product **21** (Scheme 16).[40]



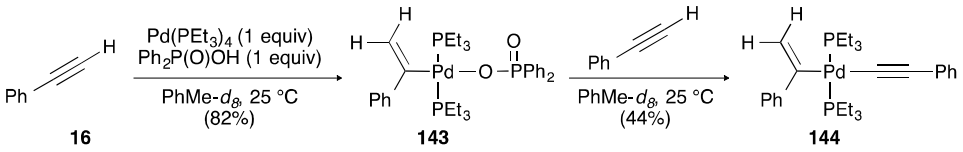
Scheme 16: Pd-NHC-catalyzed Head-to-Head-Selective Alkyne Coupling Reported by Nolan.

Support for a hydropalladation mechanism in head-to-tail-selective alkyne coupling was provided by Han and co-workers who, in 2013, reported an alkyne dimerization reaction catalyzed by Pd_2dba_3•$CHCl_3$, diphenylphosphinoethane (dppe), and diphenylphosphinic acid ($Ph_2P(O)OH$, Scheme 17).[42]



Scheme 17: Head-to-Tail-Selective Coupling under Palladium, Phosphine, and Brønsted Acid Catalysis.

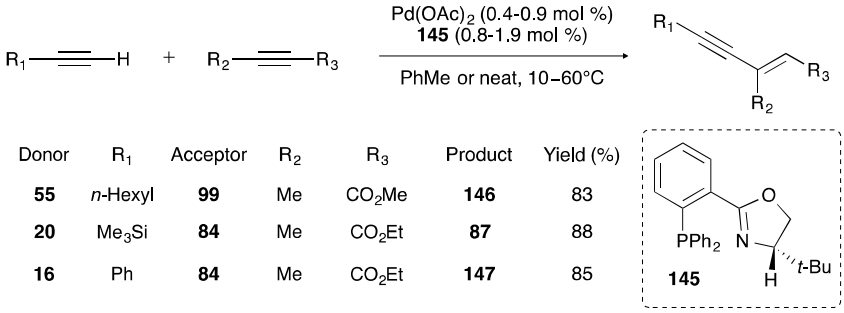
In developing this process, the authors discovered that an equimolar mixture of phenylacetylene, $Pd(PEt_3)_4$, and diphenylphosphinic acid cleanly afforded vinylpalladium complex **143**, putatively as the result of the regioselective hydropalladation of phenylacetylene (Scheme 18). This product was characterized both spectroscopically and by X-ray analysis. When complex **143** was further exposed to phenylacetylene, ligand substitution occurred and vinyl(alkynyl)palladium species **144** was observed. It was discovered that 1 mol % of the phosphinic acid was sufficient to catalyze the direct conversion of equimolar quantities of $Pd(PEt_3)_4$ and various terminal alkynes to structural analogues of **144**, and the *para*-anisyl derivative was isolated and characterized by X-ray crystallography. The facile formation of these complexes under conditions similar to those of the catalytic process led the authors to suggest that a hydropalladation mechanism might be operative in the latter. However, analogous palladium complexes derived from dppe were not reported, nor was it established that complex **144** could directly form enyne **18** *via* reductive elimination. Thus, while the identification of complexes **143** and **144** is consistent with a hydropalladation process, an unequivocal mechanistic assessment is not possible.



Scheme 18: New Palladium Complexes Identified by Han and Co-workers.

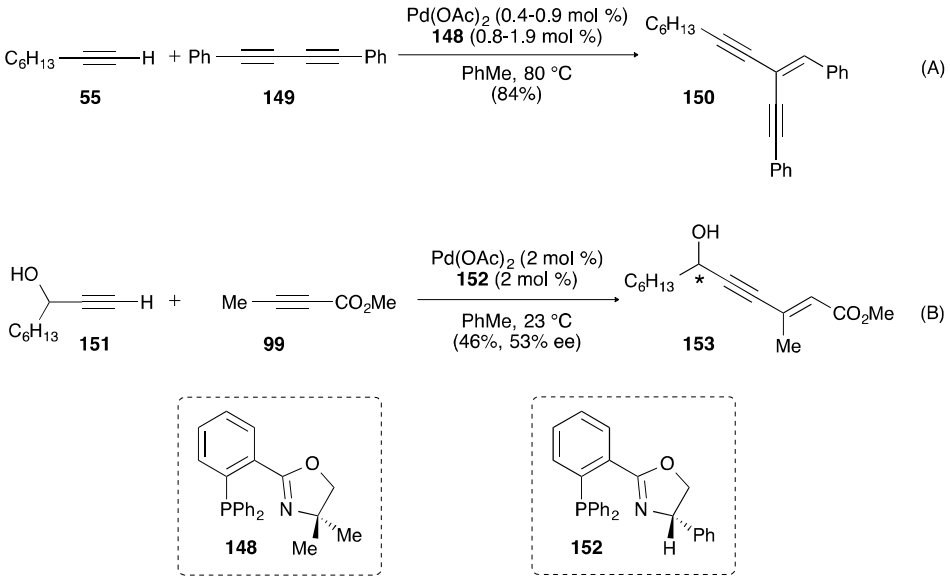
As has been illustrated thus far in this Review, the selective cross coupling of terminal alkynes with internal alkynes constitutes a greater challenge compared to homocoupling, and transition metal catalysts capable of performing such cross couplings are less common. The $Pd(OAc)_2$/TDMPP system stands out as both the earliest example of such a system and the most synthetically versatile, but other palladium catalysts have been identified for this process. Pfaltz and Lücking reported that the combination of $Pd(OAc)_2$ and *t*-Bu-PHOX ligand **145** promoted the coupling of alkyl, silyl, and aryl alkynes with propiolate acceptors in high yield at low catalyst loadings (Table 16).[37]

Table 16: Pd-catalyzed Alkyne Cross Coupling Using PHOX Ligand 145.



Donor	R_1	Acceptor	R_2	R_3	Product	Yield (%)
55	*n*-Hexyl	**99**	Me	CO_2Me	**146**	83
20	Me_3Si	**84**	Me	CO_2Et	**87**	88
16	Ph	**84**	Me	CO_2Et	**147**	85

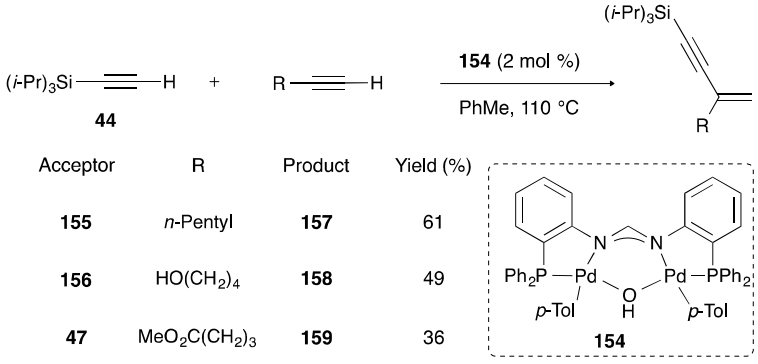
Using dimethyl PHOX ligand **148**, couplings of terminal alkynes with diyne acceptors (*e.g.*, **149**) were also successful (Scheme 19, Eqn. A). When racemic propargylic alcohol **151** was reacted with propiolate **99** using PHOX ligand **152**, a kinetic resolution occurred (Eqn. B). While the ee of adduct **153** was modest (53%), this reaction constituted the first example of a kinetic resolution occurring during an alkyne-alkyne cross coupling. The majority of these couplings were performed in toluene, but excellent results were also achieved under solvent-free conditions. In addition, alkyne cross couplings employing Pd catalysis or Pd and Cu co-catalysis have also been performed in water.[43]



Scheme 19: Pd-catalyzed Alkyne Cross Couplings Using PHOX Ligands 148 and 152.

Chemoselective cross couplings between two different terminal alkynes have also been achieved using palladium catalysis. Tsukada and co-workers reported that dinuclear palladium complex **154** promoted the selective coupling of triisopropylsilylacetylene (**44**) with equimolar amounts of various terminal alkynes, with complete head-to-tail selectivity (Table 17).[44] This sense of regioselectivity complements that obtained using rhodium- or ruthenium-catalyzed reactions involving silyl alkyne donors, which deliver (*E*)- or (*Z*)-head-to-head products, respectively.[14,26]

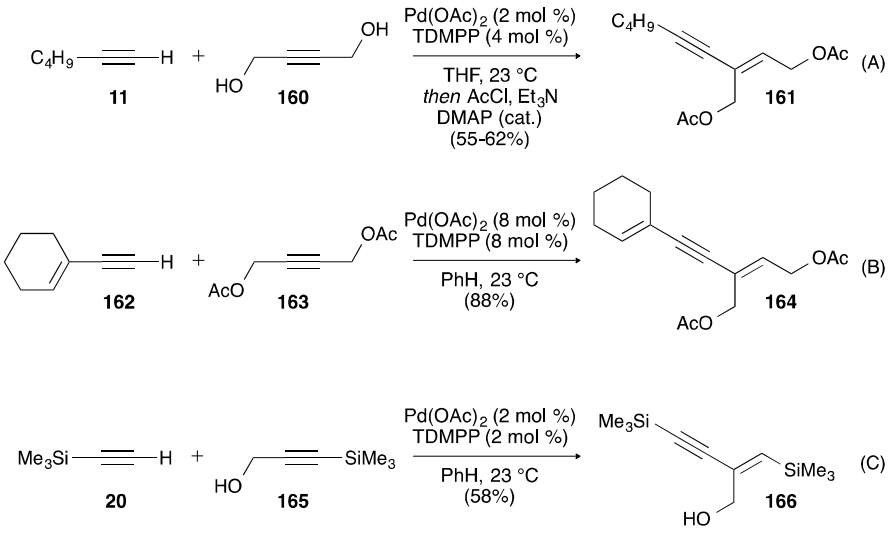
Table 17: Selective Pd-catalyzed Cross Couplings with Triisopropylsilylacetylene.



Acceptor	R	Product	Yield (%)
155	*n*-Pentyl	**157**	61
156	$HO(CH_2)_4$	**158**	49
47	$MeO_2C(CH_2)_3$	**159**	36

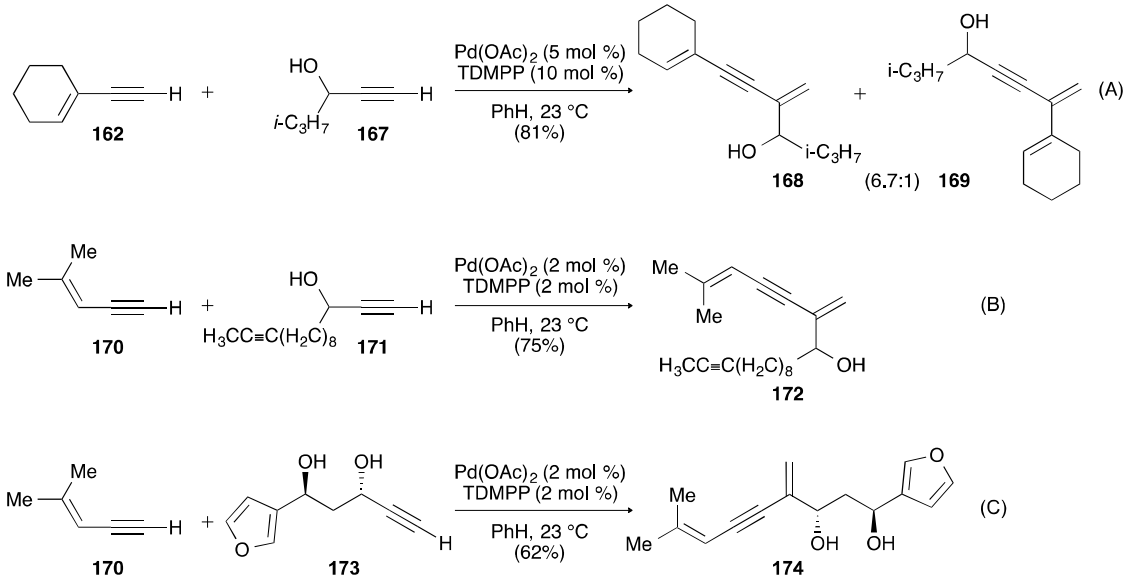
The ability to engage bulky silyl acetylenes selectively as donor alkynes in cross coupling reactions in this manner is well established,[6b,14,26,44] but Trost and McIntosh discovered that highly selective alkyne couplings could be carried out using less biased donors (Scheme 20).[45] Specifically, the $Pd(OAc)_2$/TDMPP-catalyzed coupling of 1-hexyne (**11**) with 2-butyn-1,4-diol (**160**) yielded, after *in situ* acetylation, enyne **161** (Eqn. A). Excellent selectivity was also observed in the reaction of 1-ethynylcyclohexene (**162**) with diacetate **163** (Eqn. B). Trimethylsilylacetylene (**20**) also reacted selectively as

the donor alkyne in the coupling with monoalcohol **165**, furnishing enyne **166** in good yield (Eqn. C).



Scheme 20: Chemoselective Alkyne Cross Couplings Reported by Trost and McIntosh.

The success of the latter reaction suggested that a single propargylic alcohol moiety on a terminal alkyne might provide sufficient activation to induce this substrate to act as the acceptor alkyne in a cross coupling. Indeed, the reaction of 1-ethynylcyclohexene (**162**) with propargylic alcohol **167** furnished a 6.7:1 mixture of products favoring compound **168**, the product that results when the alkyne of the propargyl alcohol acts as the acceptor (Scheme 21, Eqn. A). When enyne **170** was reacted with diyne **171**, the latter of which bears both a propargylic alcohol moiety and an unactivated internal alkyne, the reaction took place selectivity at the alkyne of the propargyl alcohol (Eqn. B). The transformation was also performed using chiral diol **173** as the acceptor, in a synthesis of a caulerpenyne analogue (Eqn. C). The caulerpenynes are a family of cytotoxic, highly unsaturated sesquiterpene constituents isolated from the seaweed *Caulerpa taxifolia.*



Scheme 21: Chemoselective Cross Couplings of Propargylic Alcohol Derivatives under Palladium Catalysis.

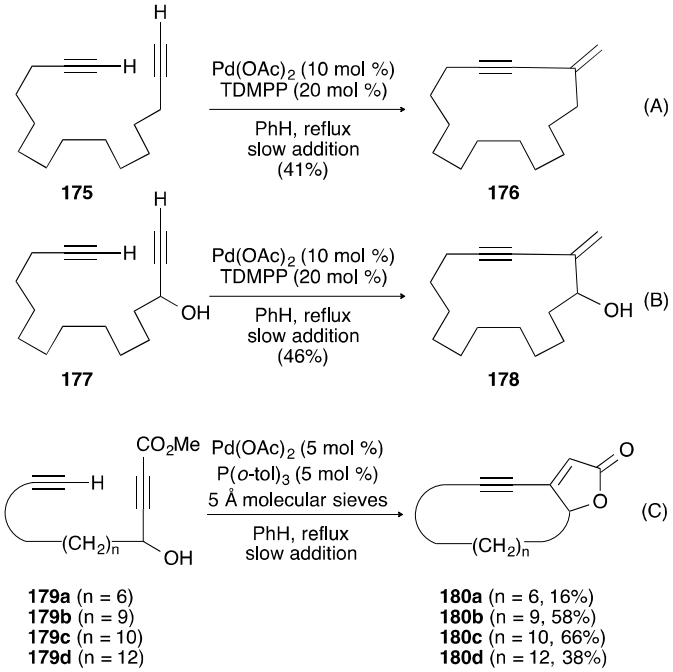
These results revealed that the $Pd(OAc)_2$/TDMPP catalyst system could promote highly selective cross couplings without the need for activation of the acceptor *via* conjugation into a carbonyl or sulfonyl group. It was proposed that the excellent levels of regioselectivity observed with propargyl alcohols were the consequence of electronic effects: specifically, it was postulated that oxygen substitution may act to lower the energy of the alkyne LUMO, which may facilitate the addition of the metal acetylide across the C–C triple bond. Given that propargylic acetates are also competent reaction partners, a hydrogen-bonding interaction between the acceptor and the palladium catalyst was considered unlikely. The fact that enyne donors offer improved performance relative to simple alkyl alkynes may be a consequence of their greater ability to ligate palladium by virtue of a smaller HOMO-LUMO gap. The acidity of the alkyne C–H may also be relevant: the increased acidity of these enyne donors may facilitate the formation of their corresponding palladium acetylides *via* carboxylate-assisted deprotonation,[7c] thus promoting the hydroalkynylation process.

Synthetic Applications of the Palladium-catalyzed Coupling of Alkynes to Enynes

The preceding sections illustrate the capacity for different transition metal catalysts to promote selective couplings of alkynes to various enyne motifs. In terms of the applications of this technology to functionalized molecule and natural product synthesis, the greatest success has been achieved using palladium catalysis. In the following sections, we will discuss the applications of palladium-based catalysts—in particular, the $Pd(OAc)_2$/TDMPP system—in the synthesis of carbocycles, heterocycles, and structurally complex natural products.

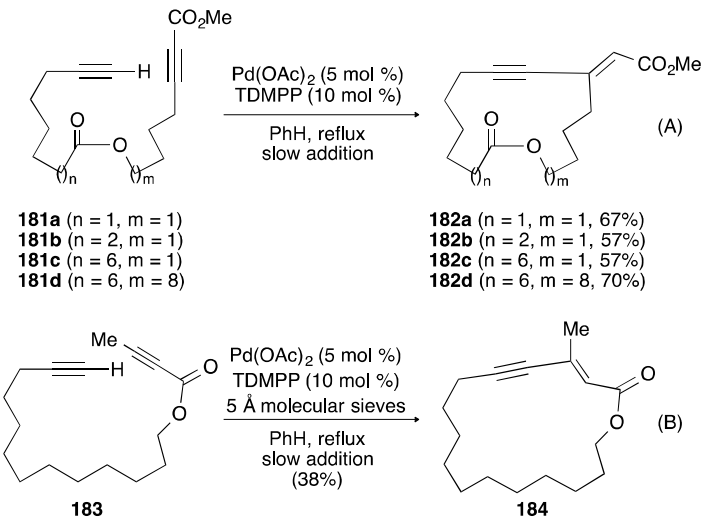
Syntheses of Carbocycles and Heterocycles

Shortly after discovering that the combination of $Pd(OAc)_2$ and TDMPP could catalyze the regioselective homocoupling of terminal alkynes and the chemoselective cross coupling of terminal alkynes with internal alkynes, Trost and co-workers applied both of these protocols to the synthesis of macrocyclic enynes (Scheme 22).[46] Exposure of symmetrical diyne **175** to such a catalyst solution afforded the monocyclic 14-membered ring product **176**, with complete selectivity for head-to-tail coupling (Eqn. A). When unsymmetrical diyne **177** was reacted, the coupling proceeded with complete chemoselectivity for product **178** wherein the propargylic alcohol acted as the acceptor alkyne (Eqn. B). The selectivity presumably results from electronic effects engendered by the hydroxyl group.[45] The introduction of an ester on the diyne substrate (**179a-d**) led to a tandem alkyne coupling-lactonization event, one that directly generated bicyclic lactones **180a-d** (Eqn. C). Tri(*o*-tolyl)phosphine proved to be the optimal ligand for this process, which delivered 10-, 13-, 14-, and 16-membered ring systems.



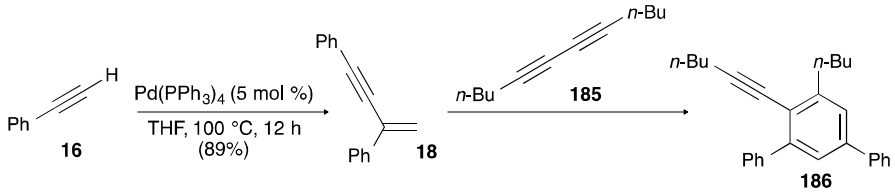
Scheme 22: Synthesis of Enyne-derived Macrocycles and Bicycles *via* Palladium Catalysis.

Excellent selectivity was also obtained in reactions using other propiolate derivatives (Scheme 23). Diynes **181a-d** were smoothly converted to macrolactones **182a-d** in a process that furnished these 14-, 15-, 19-, and 26-membered rings in very good yields (Eqn. A). Diyne **183** was also readily converted into enyne **184**, which contains an endocyclic olefin (Eqn. B). These $Pd(OAc)_2$/TDMPP or $Pd(OAc)_2$/P(*o*-tolyl)$_3$ catalyst systems have proven the most versatile for intramolecular alkyne couplings of this sort, but phosphinooxazoline-ligated palladium has also been shown to be an effective catalyst for the intramolecular head-to-tail coupling of a symmetrical diyne.[37]



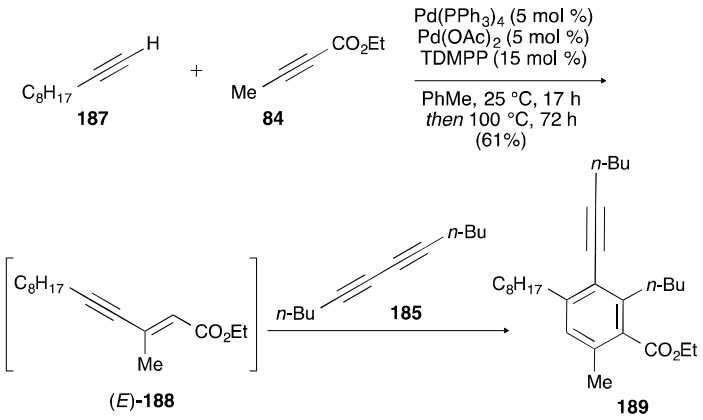
Scheme 23: Further Syntheses of Enyne-derived Macrocycle Bearing Exo- and Endocyclic Olefins.

Other carbocyclic compounds have been prepared through the merger of the Pd-catalyzed intermolecular alkyne-alkyne coupling with cycloaddition chemistry. In 2001, Gevorgyan and co-workers reported one-pot syntheses of tetra- and pentasubstituted benzene derivatives *via* sequential alkyne homocoupling and [4+2] cycloaddition of the enyne products with diynes (Scheme 24).[35] The authors identified $Pd(PPh_3)_4$ as capable of catalyzing both the head-to-tail homocoupling of phenylacetylene and the benzannulation of this dimerization product with diyne **185**.[47] Thus, when all reagents were combined at once in THF and the mixture heated to 100 °C for 12 h, tetrasubstituted benzene **186** was produced as a single isomer in 89% yield. Enyne **18** was identified by GC-MS analysis of the reaction at early time points, providing evidence for the sequential coupling/cycloaddition process depicted. Similar results were obtained with alkyl alkynes, and the combination of Pd_2dba_3•$CHCl_3$ and P(*o*-tolyl)$_3$ was also effective.



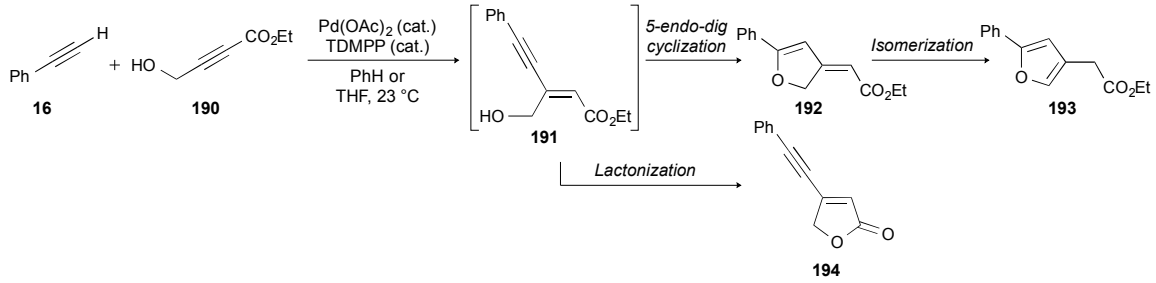
Scheme 24: Sequential Pd-catalyzed Alkyne Homocoupling and [4+2] Cycloaddition.

The use of the $Pd(OAc)_2$/TDMPP catalyst system enabled the assembly of pentasubstituted benzenes from three different alkyne subunits. The reaction of donor alkyne 1-decyne (**187**), acceptor alkyne ethyl 2-butynoate (**84**), and diyne **185** in the presence of $Pd(PPh_3)_4$, $Pd(OAc)_2$, and TDMPP, first at room temperature and then at 100 °C, led initially to enyne **188** and then, upon cycloaddition, to benzene derivative **189** (Scheme 25). The overall process constitutes a formal [2+2+2] trimerization process, but it is one that proceeds with excellent chemo- and regioselectivity and that enables the introduction of a variety of useful functional groups.



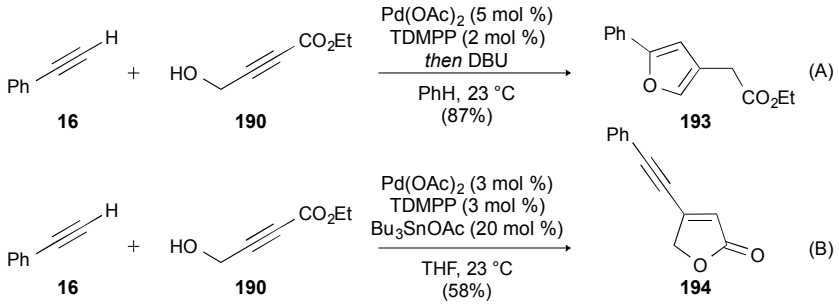
Scheme 25: Synthesis of a Pentasubstituted Benzene Derivative *via* Sequential Catalysis.

The exceptional chemoselectivity and functional group tolerance associated with the palladium-catalyzed alkyne cross coupling has facilitated the synthesis of numerous heterocyclic scaffolds. In 1995, Trost and McIntosh developed protocols for the synthesis of furans and butenolides *via* sequential catalysis involving γ-hydroxyalkynoate alkyne acceptors.[48] In early experiments using 2 mol % each of $Pd(OAc)_2$ and TDMPP, phenylacetylene (**16**) coupled smoothly with acceptor alkyne 190 to give intermediate **191**, but this compound partitioned nonselectively into a mixture of isofuran **192**, furan **193**, and butenolide **194** (Scheme 26).



Scheme 26: Mixtures of Products Obtained in Pd-catalyzed Couplings of γ-Hydroxyalkynoate Acceptors.

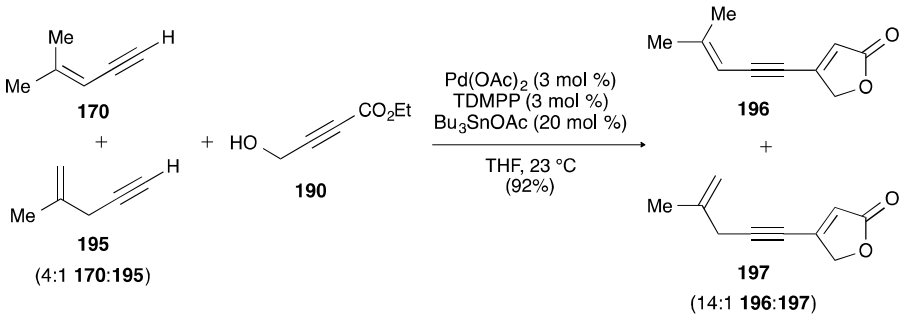
It was proposed that the conversion of hydroxyenynoate **191** to isofuran **192** occurred through a 5-*endo-dig* cyclization promoted by Pd^{II}. Consistent with this, an increase in the $Pd(OAc)_2$ loading to 5 mol % significantly improved the ratio of isofuran to other products. Thus, by performing the coupling with 5 mol % $Pd(OAc)_2$ and 2 mol % TDMPP at room temperature and then treating the mixture directly with DBU to effect isomerization *in situ*, furan **193** was obtained directly in excellent yield (Scheme 27, Eqn. A). On the other hand, the Lewis acidity of Pd^{II}—and, consequently, the degree of 5-*endo-dig* cyclization, and furan formation—were tempered by the addition of triethylamine, with a concomitant increase in the yield of butenolide. Even more effective was the addition of catalytic tributyltin acetate, which promoted the lactonization reaction without inhibiting the alkyne coupling. This enabled a one-pot synthesis of butenolide **194** (Eqn. B).



Scheme 27: Selective Synthesis of Furans and Butenolides *via* Pd Catalysis.

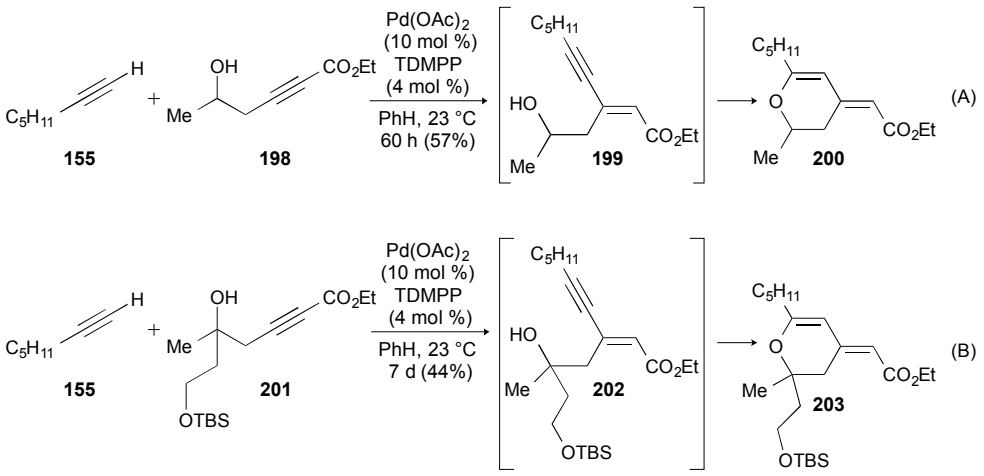
Both methods were compatible with other substrates, including alkyl alkyne donors and acceptors bearing secondary alcohols. In an intriguing competition experiment, a 4:1 mixture of conjugated and unconjugated enyne donors **170** and **195** were reacted with acceptor **190** in the presence of tributyltin acetate (Scheme 28). A kinetic enrichment occurred, with the product mixture containing a 14:1 ratio of products **196** and **197**. These results reflect the greater reactivity of conjugated enyne donors, as described previously (*cf.* Schemes 20 and 21).

Notably, compound **196** is itself a natural product, claviolide, and it is also a known intermediate in the synthesis of the diene natural products (*E*)- and (*Z*)-scobinolide.[49] Its preparation in high yield using the catalytic alkyne coupling process compared favorably to other syntheses reported around the same time, which required the use of stoichiometric quantities of main group and transition metals and which involved a greater number of steps.[49b,c]



Scheme 28: Kinetic Enrichment Using Enynyl Donor Alkynes.

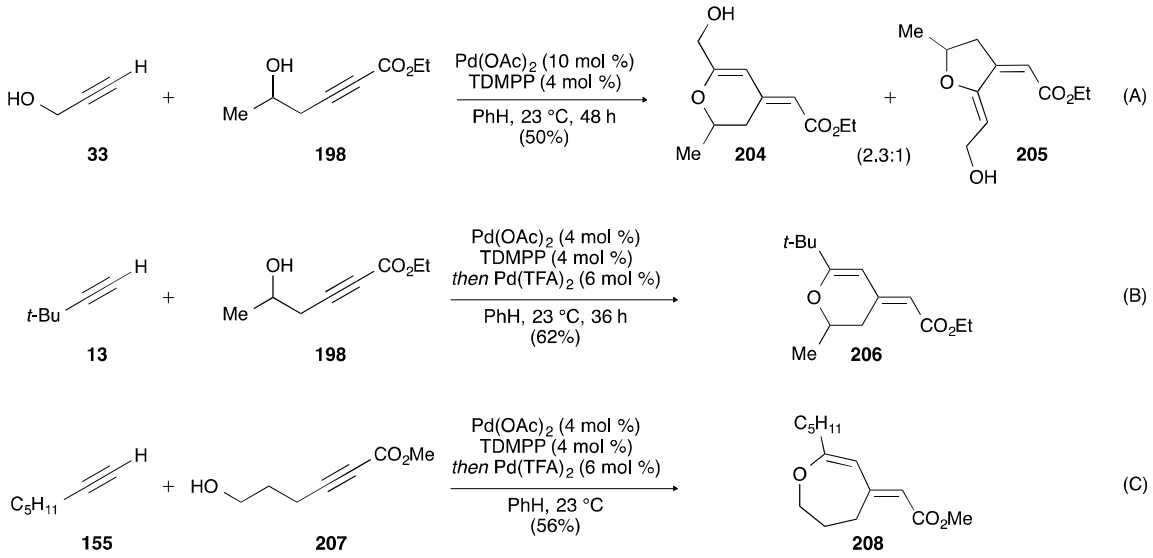
Trost and Frontier subsequently reported syntheses of dihydropyrans from δ-hydroxyalkynoate acceptor alkynes *via* sequential alkyne coupling and 6-*endo*-*dig* cyclization (Scheme 29).[50,51] The cross coupling between 1-heptyne (**155**) and acceptor **198** proceeded smoothly to give enyne **199**, which underwent *in situ* Pd^{II}-catalyzed cyclization to give **200** (Eqn. A). Increased steric encumbrance around the alcohol was tolerated, with acceptor **201** reacting analogously to give dihydropyran **203** (Eqn. B).



Scheme 29: Dihydropyran Syntheses *via* Pd-catalyzed Alkyne Coupling.

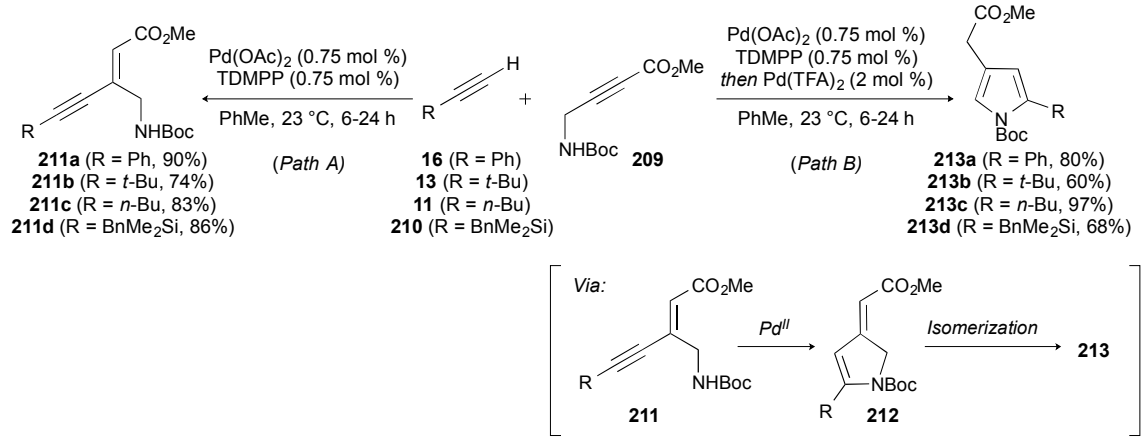
These reactions and others between 1-heptyne and different δ-hydroxyalkynoate acceptors displayed excellent selectivity for the 6-*endo*-*dig* process, as only trace amounts of the corresponding lactone were observed and none of the 5-*exo*-*dig* product was detected. However, experiments involving other donor alkynes revealed that the steric and electronic properties of the donor impacted both reactivity and selectivity (Scheme 30). Propargyl alcohol (**33**) reacted successfully in both stages to furnish dihydropyran **204** in good yield, but it was accompanied by a minor amount of diene **205** resulting from 5-*exo*-*dig* cyclization (Eqn. A). Presumably, the electron-withdrawing nature of the hydroxyl group disfavored the build up of positive charge on the proximal alkyne carbon atom that occurred during the 6-*endo* process, allowing the 5-*exo*-pathway to compete. Consistent with this, higher levels of 6-*endo* selectivity were observed when the hydroxyl group was placed further away from the reactive site on the donor alkyne.

Conversely, the reaction with the more sterically encumbered *tert*-butylacetylene (**13**) was completely selective for the formation of dihydropyran **206**, but the cyclization was slow, and the product was obtained in only 25% yield after 14 days. It was soon discovered that the addition of catalytic palladium trifluoroacetate dramatically increased the rate of cyclization. These two Pd-catalyzed reactions could be performed in one pot: when the alkyne coupling was carried out to completion using $Pd(OAc)_2$/TDMPP and then $Pd(TFA)_2$ was added, **206** was obtained in 62% yield in only 36 h (Eqn. B). This sequential catalysis procedure also enabled the synthesis of larger ring systems such as **208** (Eqn. C), a product that could not be accessed using $Pd(OAc)_2$ and TDMPP alone.



Scheme 5: Further Syntheses of Six- and Seven-membered Oxygen Heterocycles.

Trost and co-workers also discovered that activated propargylic amines could serve as competent acceptor alkynes in the $Pd(OAc)_2$/TDMPP-catalyzed cross coupling, setting the stage for the efficient synthesis of nitrogen heterocycles from the corresponding enynes.[52] Specifically, couplings between carbamate acceptor **209** and phenylacetylene (**16**), *tert*-butylacetylene (**13**), 1-hexyne (**11**) and benzyldimethylsilylacetylene (**210**) all occurred smoothly in the presence of only 0.75 mol % each of $Pd(OAc)_2$ and TDMPP, providing ynenoates **211a-d** (Scheme 31, Path A).

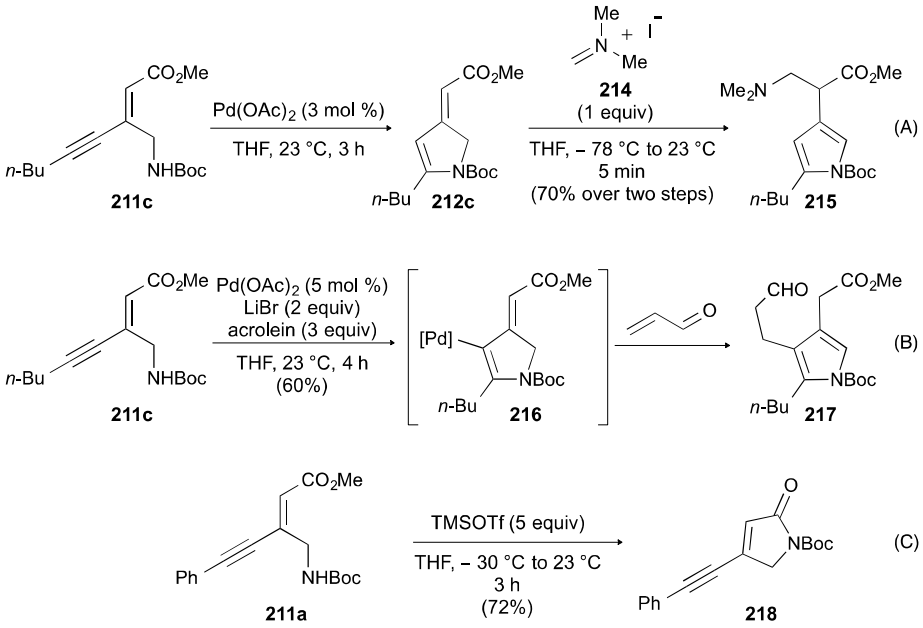


Scheme 31: Pd-catalyzed Alkyne Cross Coupling in the Service of Pyrrole Synthesis.

Under these reaction conditions, 5-*endo*-*dig* cyclization was not observed (*cf.* Scheme 26). This cyclization—and the concomitant formation of isopyrroles **212**—could be induced by performing the alkyne coupling using excess $Pd(OAc)_2$ relative to ligand, and it could also be promoted thermally (100 °C, 48 h). However, the best results were achieved by treating ynenoates **211** with catalytic $Pd(TFA)_2$, which promoted both cyclization to the isopyrroles and the isomerization of the latter to pyrroles **213**. A one-pot protocol was developed wherein the coupling was carried out to completion using $Pd(OAc)_2$ and TDMPP and then $Pd(TFA)_2$ was introduced to trigger the 5-*endo*-*dig* event

(Path B). Under these conditions, a range of 2,4-disubstituted pyrroles **213** was prepared in high yields.

Ynenoates **211** could be converted into more densely substituted heterocycles *via* addition or isomerization reactions (Scheme 32). Exposure of compound **211c** to catalytic $Pd(OAc)_2$ in THF promoted its cyclization to isopyrrole **212c**, which was isolated and then reacted with Eschenmoser's salt (**214**) to deliver aminomethylated compound **215** in very good yield (Eqn. A). Performing the 5-*endo-dig* cyclization in the presence of LiBr and acrolein generated, presumably *via* vinylpalladium species **216**, conjugate adduct **217** (Eqn. B). Moreover, ynenoate **211a** was converted to pyrrolidinone **218** upon treatment with TMSOTf (Eqn. C). Thus, multiple different heterocyclic scaffolds were accessed from simple alkyne precursors *via* efficient isomerization and/or C–C bond forming reactions.



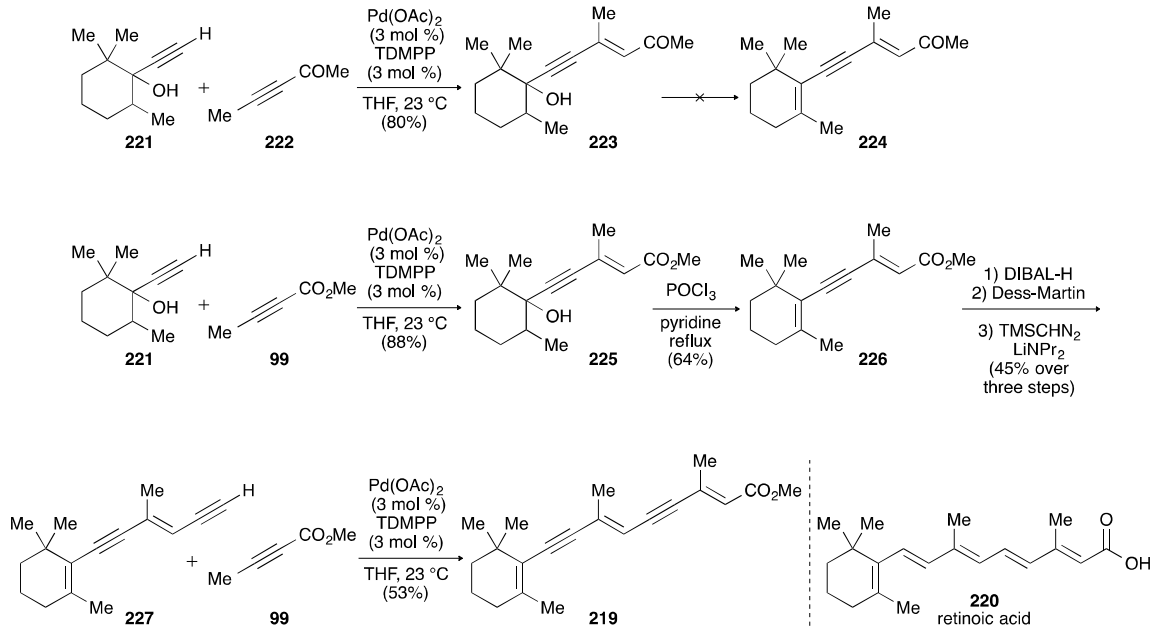
Scheme 32: Synthesis of Substituted Heterocycles from Ynenoates 211.

Natural Product Synthesis

The impressive level of chemoselectivity associated with the $Pd(OAc)_2$/TDMPP catalyst system renders it well suited for the synthesis of complex natural products. Recognizing the biological importance of both natural retinoids and their synthetic analogues, Trost and Harms targeted methyl 7,8,11,12-tetradehydroretinoate (**219**), an unnatural congener of retinoic acid (**220**) wherein the carbon framework has been rendered more rigid by the replacement of two *trans*-olefins with acetylenes (Scheme 33).[7c,53,54]

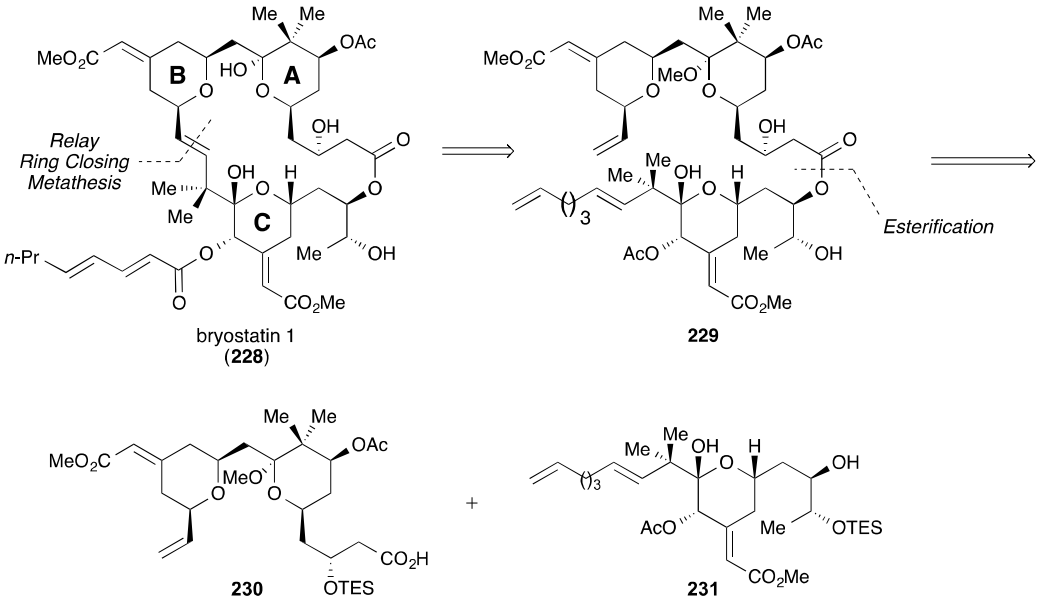
An iterative sequence of Pd-catalyzed cross couplings enabled a short and efficient synthesis of the target. In the first generation strategy, tertiary alcohol **221** was coupled with ynone **222** under standard conditions to give enyne **223**, with the intention of converting the ketone moiety to a terminal alkyne *via* dehydration.[55] However, the need for an alternative strategy arose when it was discovered that it was not possible to dehydrate tertiary alcohol **223** to dienyne **224**. The coupling was instead performed using

methyl 2-butynoate (**99**) as the acceptor, an event that delivered enyne **225** in excellent yield. Dehydration in this case proceeded smoothly by the action of $POCl_3$ in pyridine, generating dienyne **226**. DIBAL-H reduction, alcohol oxidation, and olefination using lithiated trimethylsilyldiazomethane delivered diyne **227**. Despite the presence of multiple alkynes and the potential for olefin isomerization to occur, a second Pd-catalyzed cross coupling between this substrate and acceptor alkyne **99** proceeded smoothly and selectively to deliver the target in good yield.



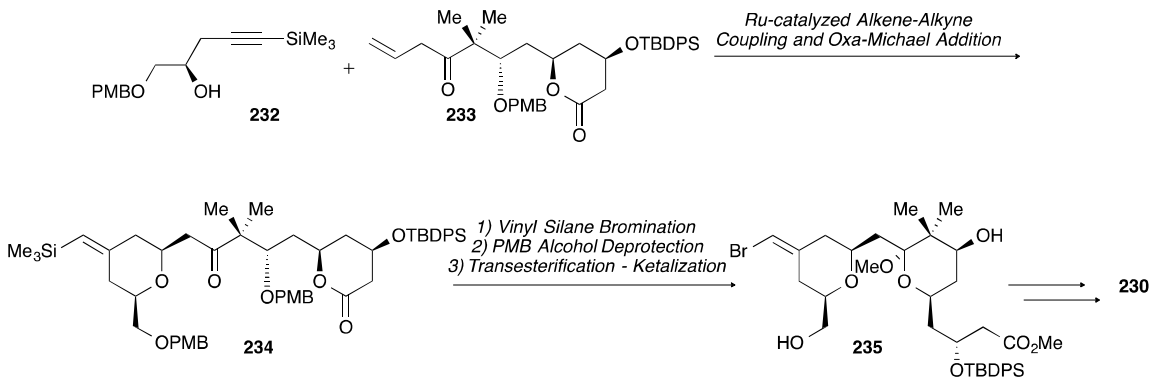
Scheme 33: Synthesis of a Retinoid Analogue *via* Iterative Alkyne Cross Coupling.

The $Pd(OAc)_2$/TDMPP-catalyzed alkyne coupling has proven exceptionally powerful for the synthesis of marine macrolides. Trost and co-workers employed the transformation during synthetic efforts toward bryostatin 1 (**228**, Scheme 34).[56,57] Retrosynthetically, it was imagined that the sterically hindered *trans*-olefin of the target might be forged *via* a relay ring closing metathesis reaction of compound **229**. This intermediate would be accessible through esterification of carboxylic acid **230** with the secondary alcohol of compound **231**.



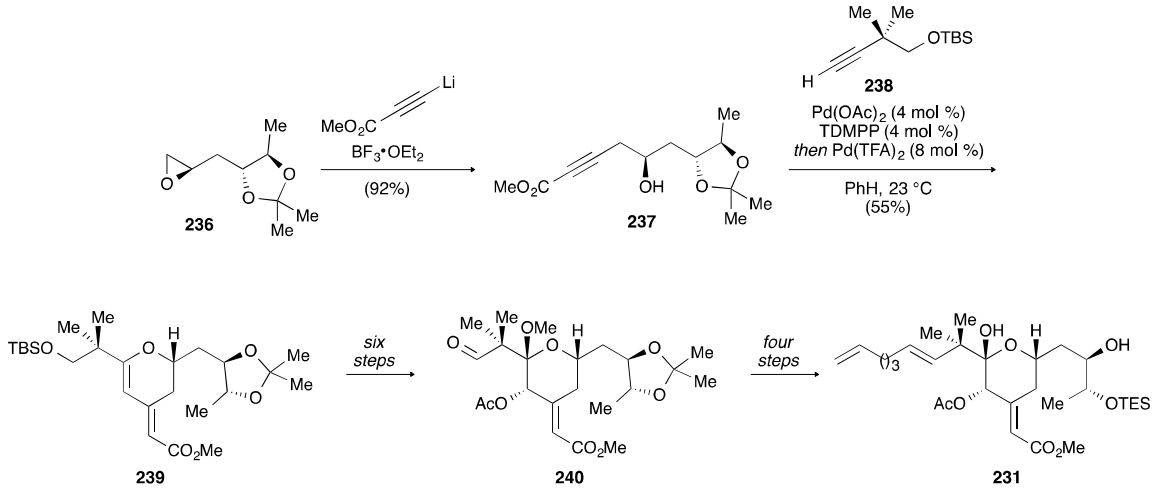
Scheme 34: Retrosynthetic Analysis of Bryostatin 1 (228).

Fragment **230** contains the A and B rings of the natural product. Its synthesis has been described in detail elsewhere,[58] but we highlight here key steps (Scheme 35). A ruthenium-catalyzed alkene-alkyne coupling between silyl alkyne **232** and γ,δ-unsaturated ketone **233** was followed by a spontaneous oxa-Michael addition,[59] which yielded vinyl silane **234**. After conversion of the vinyl silane moiety to a vinyl bromide and removal of the PMB protecting groups, an acid-catalyzed transesterification-ketalization sequence delivered bispyran **235**. This compound was readily advanced to desired acid **230**.



Scheme 35: Key Steps in the Synthesis of Bryostatin1 Fragment 230.

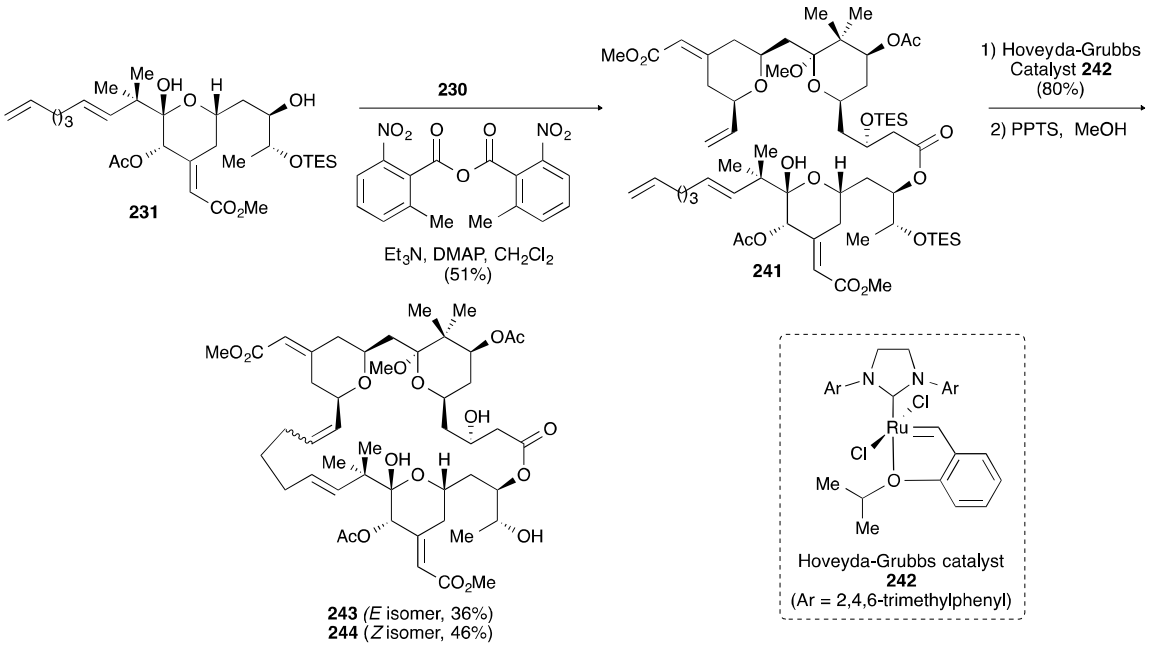
Fragment **231** was prepared using the tandem Pd-catalyzed alkyne coupling/6-*endo-dig* cyclization process (Scheme 36). To this end, epoxide **236**, which is available in six steps from D-galactonic acid 1,4-lactone, was reacted with lithiated methyl propiolate and BF_3•OEt_2 to afford acceptor alkyne **237** in high yield (92%). Alkyne coupling with donor alkyne **238** proceeded smoothly using 4 mol % $Pd(OAc)_2$/TDMPP, and the subsequent introduction of 8 mol % $Pd(TFA)_2$ to the reaction mixture triggered the 6-*endo-dig* cyclization to forge dihydropyran **239** in 55% yield.[56]



Scheme 36: Synthesis of Key Fragment 231 *via* Pd-catalyzed Alkyne Coupling.

The team discovered that this protocol was effective on scales up to 0.3 mmol. On larger scales, more reproducible results were obtained when the sequence was performed over two steps, using $Pd(OAc)_2$/TDMPP to effect the alkyne coupling and then using the combination of $PdCl_2(MeCN)_2$ and TDMPP to catalyze the cyclization (89% yield for alkyne coupling and 62% yield for oxycyclization, the latter on 7 mmol scale; 55% overall yield).[51] Over six steps, the vicinal oxygens of the pyran were installed stereoselectively, and the silyl ether was converted to an aldehyde; these transformations yielded compound **240**. Olefination, ketal removal, and monoprotection of the diol moiety then delivered fragment **231**.

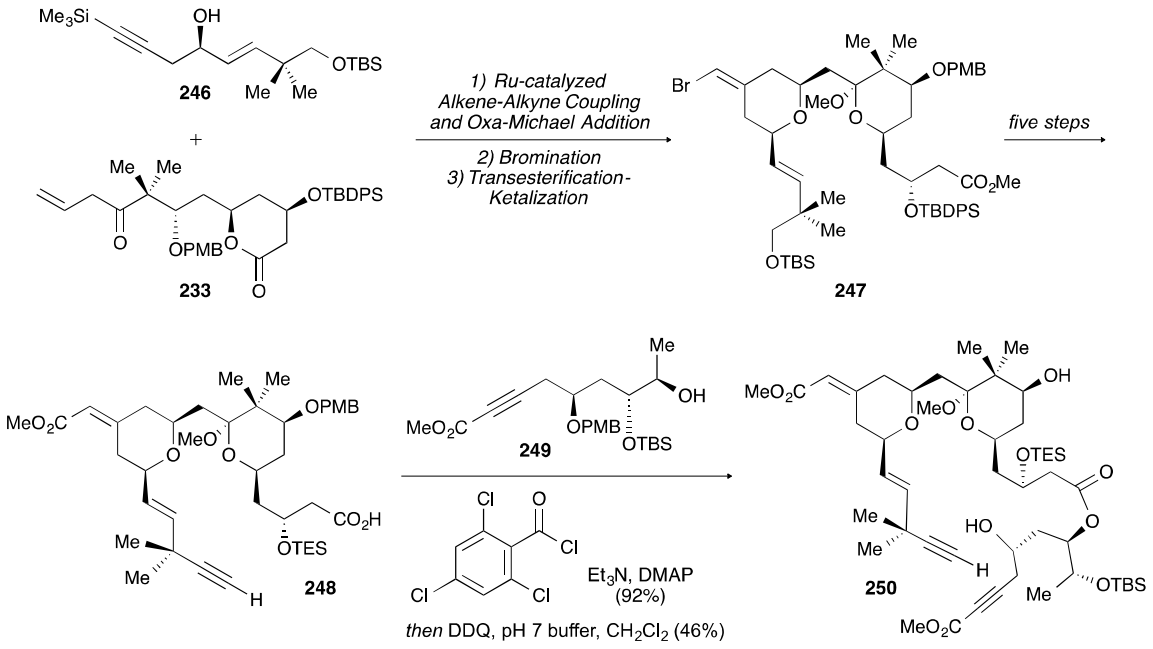
This alcohol was united with acid **230** using the Shiina esterification conditions (Scheme 37). Thus, after activation of the acid fragment with 2-methyl-6-nitrobenzoic anhydride in methylene chloride, introduction of the alcohol component and 4-dimethylaminopyridine delivered ester **241**. Surprisingly, exposure of this polyene to the Hoveyda-Grubbs catalyst (**242**) did not deliver the product of relay ring closing metathesis but, instead, that of direct ring closing metathesis. Following silyl ether deprotection, 31-membered rings **243** and **244** ((*E*)- and (*Z*)-olefin isomers, respectively), were isolated in very good yields.



Scheme 37: Synthesis of Bryostatin 1 Analogues 243 and 244.

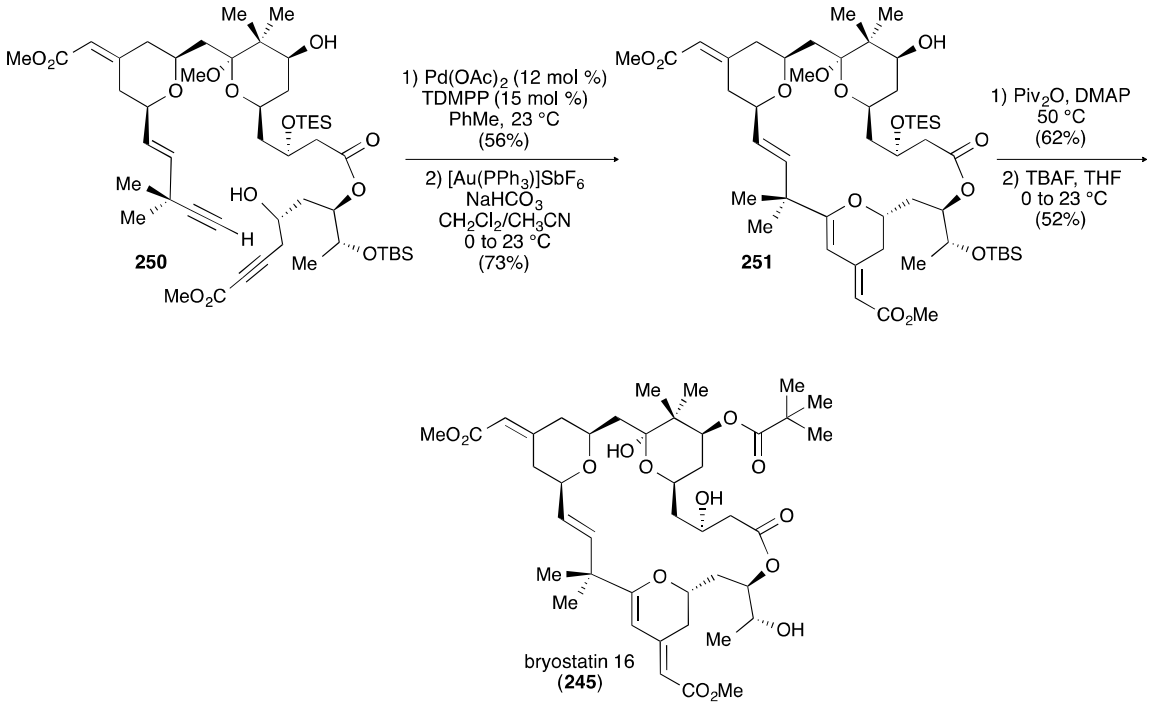
These unusual products, which otherwise bear all of functionality of the target natural product except the α,β,γ,δ-unsaturated carboxylate side chain, were assayed for biological activity. While related open chain intermediates in the synthetic sequence were found to be devoid of biological activity, compounds **243** and **244** were both active against breast and ovarian cancers, with the former demonstrating nine-fold greater potency than the latter.

Trost and Dong applied a late-stage intramolecular alkyne coupling-oxycyclization sequence to the total synthesis of bryostatin 16 (**245**).[60] As in the bryostatin 1 synthesis, a fragment containing both the A and B rings was efficiently prepared *via* the ruthenium-catalyzed alkene-alkyne coupling/oxa-Michael reaction between compounds **246** and **233** (Scheme 38). Bromination of the resulting vinyl silane and a similar one-pot transesterification-ketalization event delivered bispyran **247**. This product was then taken into a five-step sequence involving vinyl bromide carbonylation, primary alcohol oxidation, homologation of the resulting aldehyde into a terminal alkyne, and ester hydrolysis. This furnished acid **248**. A Yamaguchi esterification between this acid and alcohol **249** proceeded in high yield. Following PMB deprotection, diyne **250** was obtained, and the stage was set for the intramolecular alkyne-alkyne coupling.



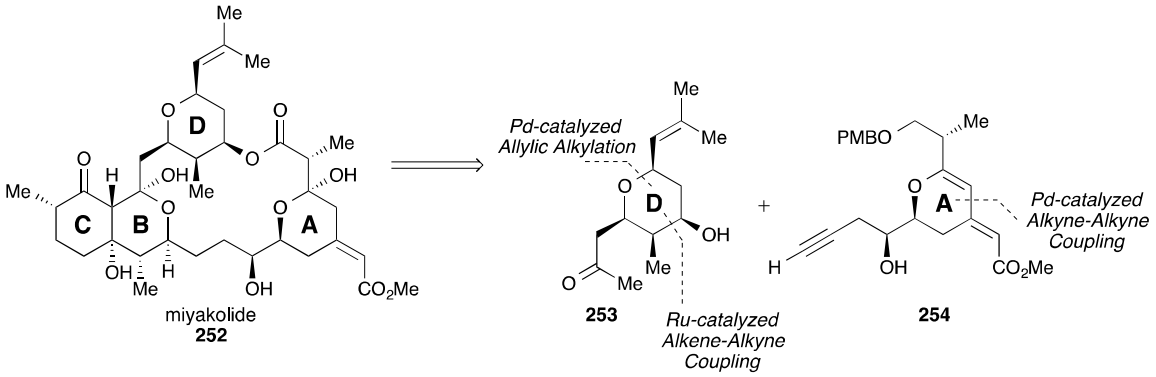
Scheme 6: Synthesis of a Diyne Precursor to Bryostatin 16.

The optimal parameters for the event were determined to be the use of a slight excess of TDMPP relative to $Pd(OAc)_2$ (15 mol % and 12 mol %, respectively) in toluene at room temperature (Scheme 39). Under these conditions, palladium-catalyzed macrocyclization occurred to deliver the desired ynenoate in 56% yield, marking the first time that the process had been applied in such a complex molecular environment. From a survey of transition metal species, $[Au(PPh_3)]SbF_6$ emerged as ideal for the 6-*endo*-*dig* cyclization, which proceeded in 73% yield. In a testament to their synthetic power, this combination of transformations enabled the synthesis of dihydropyran **251** in only 24 steps, with little work remaining to complete the synthesis. Indeed, installation of the pivaloyl group present in the natural product and global deprotection occurred without incident, completing this concise synthesis of bryostatin 16 (**245**).



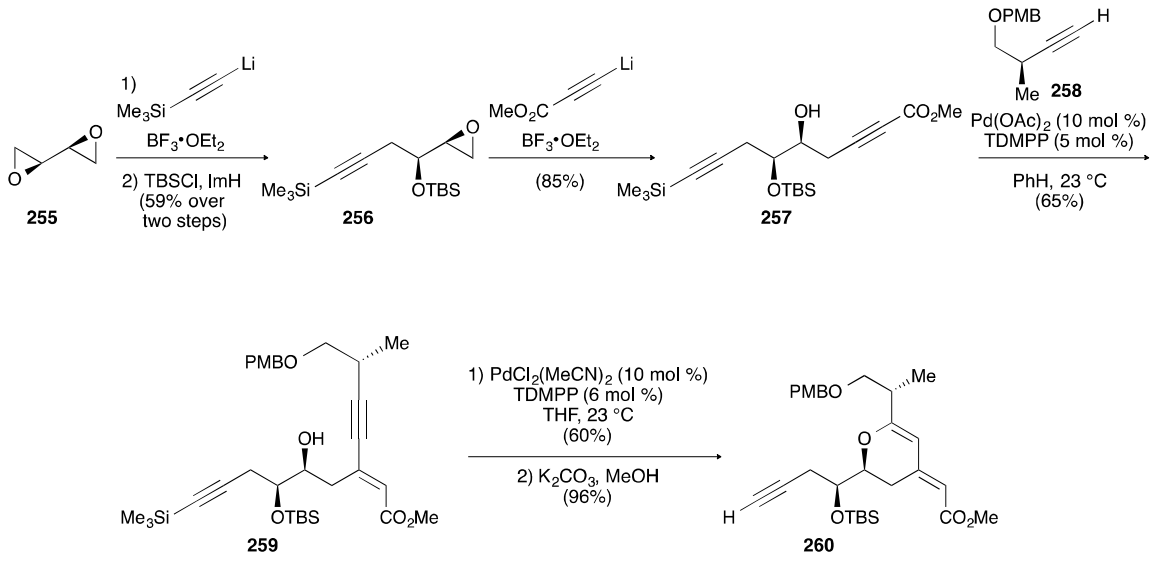
Scheme 39: Completion of the Total Synthesis of Bryostatin 16.

The Pd-catalyzed tandem alkyne cross-coupling-6-*endo-dig* cyclization has proven useful in syntheses of other macrolides. Along with a number of other catalytic and atom-economic reactions, Trost and Ashfeld utilized it in their studies toward miyakolide (**252**, Scheme 40).[61] The all-*cis* D ring pyran (**253**) was prepared in enantioenriched form *via* sequential Ru-catalyzed alkene-alkyne coupling and Pd-catalyzed intramolecular allylic alkylation, and the synthesis of A-ring glucal **254** was enabled by the alkyne coupling.



Scheme 40: Retrosynthetic Analysis in the Synthesis of Miyakolide (252).

To this end, enantiopure bisepoxide **255**, which is readily prepared from L-dimethyl tartrate, was reacted first with lithiated trimethylsilylacetylene and, then, after silyl protection of the resulting secondary alcohol, with lithiated methyl propiolate (Scheme 41). Diyne **257** was thus prepared in good yield in three steps. Chemoselective alkyne coupling between the propiolate moiety of compound **257** and terminal alkyne **258**, itself readily accessed from the Roche ester, furnished enyne **259** in good yield. Despite the presence of two alcohol derivatives and two different acetylene units, each of which was suitably disposed for different oxycyclization events, the desired 6-*endo-dig* reaction proceeded smoothly. After straightforward alkyne desilylation, the A-ring component **260** was isolated in high yield.



Scheme 7: Miyakolide A-Ring Synthesis *via* Sequential Pd-catalyzed Alkyne Coupling and Oxycyclization.

Conclusions

The transformations described herein illustrate the potential associated with the selective coupling of alkynes to various enyne structures. The utility of transition metal catalysis in this regard has focused on the use of simple rhodium, ruthenium, or palladium salts to effect alkyne homo- and/or cross coupling. The preparation of new, specialized transition metal complexes led to increases in catalytic efficiency and to the development of numerous selective and potentially broadly applicable methods. Control over the regio- and stereoselectivity has been exercised through the judicious choice of metal catalyst, phosphine ligand, and/or reaction solvent. Moreover, intrinsic differences in the reactivity of different alkynes have been exploited for the development of chemoselective cross coupling reactions.

The discovery that combinations of simple, readily available palladium salts and phosphine ligands—most notably palladium acetate and tris-(2,6-dimethoxyphenyl)phosphine (TDMPP)—could promote either regioselective alkyne homocoupling or regio- and stereoselective cross couplings of terminal alkyne donors with internal alkyne acceptors led to the development of a remarkable number of new and highly atom-economic synthetic methods. Using palladium catalysis, efficient syntheses of 1,3-enynes, carbocycles, oxygen and nitrogen heterocycles, and highly complex natural products have been demonstrated. These examples showcase not only the versatility but also the chemoselectivity of this catalytic process. Given the remarkable selectivity displayed by this and other systems, there can be no doubt that transition metal-catalyzed alkyne coupling reactions holds much promise in complex molecule synthesis.

Acknowledgements

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