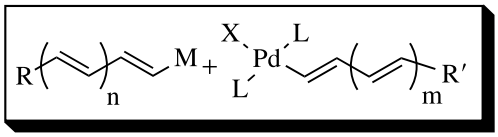

III.2.17 Synthesis of Conjugated Oligomers and Polymers via Palladium-Catalyzed Cross-Coupling

III.2.17.1 Synthesis of Conjugated Oligomers for Applications in Biological and Medicinal Areas

BRUCE H. LIPSHUTZ

A. INTRODUCTION

Construction of polyenes containing three or, in particular, more conjugated olefinic units of defined geometries present special synthetic challenges. Only recently have there been developments in methodology that offer direct and relatively general solutions. Extensive earlier efforts tended to rely on time-honored, inveterate approaches based on phosphorus chemistry, most notably Wittig and Horner–Emmons–Wadsworth conversions. Further processing *in situ* or via eventual manipulations allowed for enhanced *E* or *Z* stereoselectivities.[1] Still, although variations that retain the ylide or phosphonate strategy continue to appear, stereospecificity remains an elusive goal in the polyene arena. While advances in organic synthesis have been exponential during the past two decades, so has there been an explosion in transition metal organometallic chemistry. One outgrowth of major consequence for polyene synthesis is the anticipated maintenance of stereochemical integrity in vinyl halide cross-couplings with sp^2-stereodefined organometallics.[2],[3] Although various transition metals, most prominently copper, have been and continue to be of extraordinary service in planning synthetic strategies,[4] it is the chemistry of palladium[5] that has emerged as the metal of choice for realizing conjugated polyenes.

The incentive for developing organometallic solutions to highly conjugated polyenes lies both in their value as reactive intermediates (e.g., in electrocyclizations) as well as in the vast array of natural and unnatural targets that bear this type of key subunit. Extensive conjugation can be found in such critical biomolecules as retinoids[6] (e.g., all *E*-retinoic acid, **1**) with roles not only in the chemistry of vision but as potent antitumor agents; arachadonic acid cascade derivatives[7] (e.g., leukotriene B_4, **2**), which are local hormones involved in numerous bioresponses; and polyene macrolide antibiotics[8] (e.g., amphotericin B, **3**), which are clinically valued antifungals, especially for those with weakened immune systems brought on by HIV.

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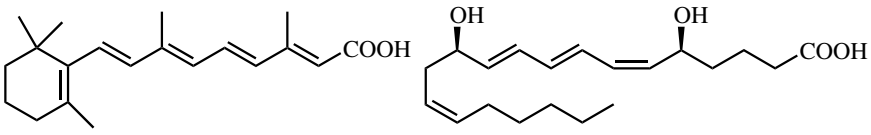
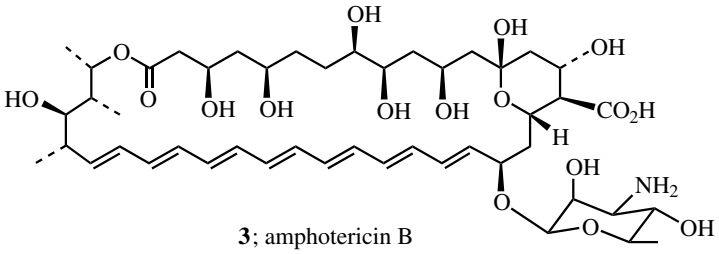


1; all *E*-retinoic acid

2; LTB_4

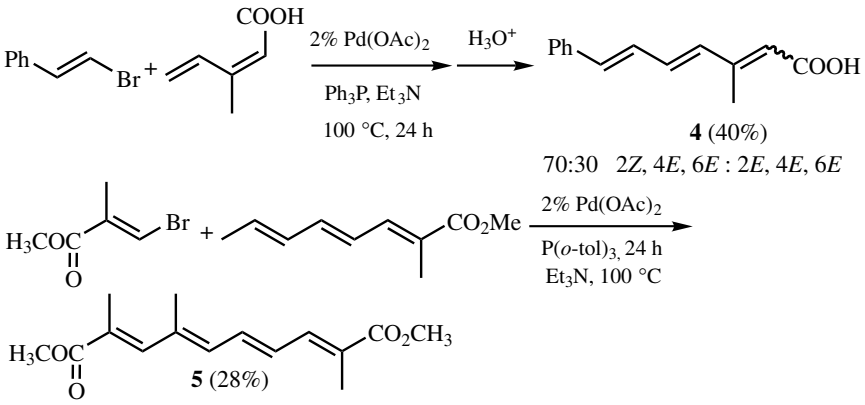


3; amphotericin B

B. STRATEGIES FOR PALLADIUM-CATALYZED POLYENE CONSTRUCTIONS

B.i. Heck Couplings

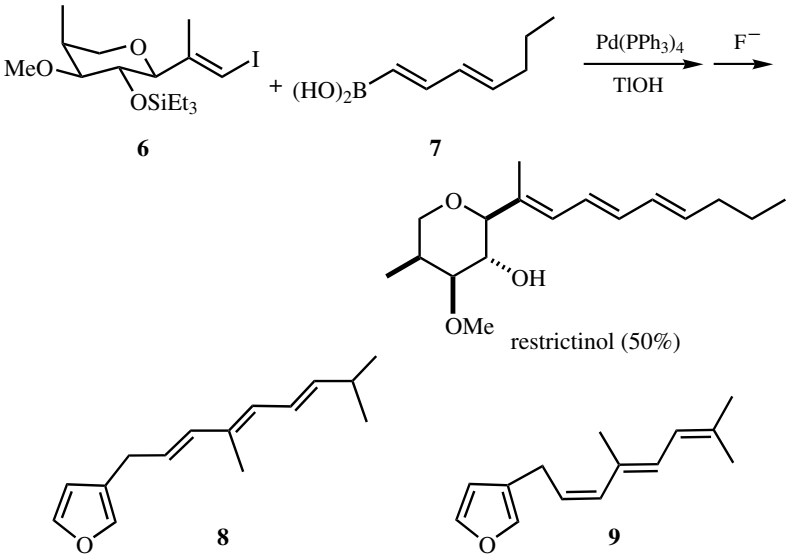
Early work on Heck reactions of conjugated acids and esters with vinylic halides provided modest inroads to trienic and tetraenic frameworks. Losses in stereochemical integrity are commonplace, usually in the dienic fragment, given the likelihood of π-allyl-palladium intermediates. Representative examples of a conjugated triene[9],[10] and tetraene[9],[10] (**Scheme 1**) involving couplings between a vinyl bromide and either a dienic or trienic acid or ester in the presence of triethylamine afford products **4** and **5**, respectively. Best results are obtained when one or both components bear a conjugated ester or acid residue. The high temperatures required may be responsible for the limited stereoselectivity oftentimes obtained when *Z*-bromides are involved. These representative cases provide foreshadowing for the shift away from this particular method of polyene formation and toward methods that do not involve equilibrating π-allyl-palladium species as reaction intermediates.



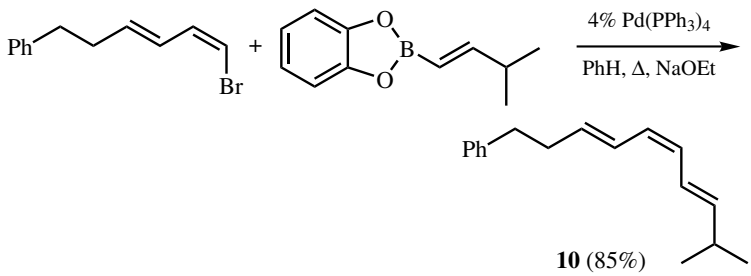
Scheme 1

B.ii. Pd(0)-Mediated Couplings: Trienes via Suzuki, Negishi, and Sonogashira Reactions

Couplings of *E*-vinyl boronic acids or esters with *E*-vinylic halides in the presence of base and catalytic quantities of Pd(0) result in all *E*-trienic products. Iodide **6** has been used together with boronic acid **7** in the presence of aqueous TlOH to afford the desired triene in good yield (**Scheme 2**).[11] The product requires a simple desilylation to reveal restrictinol. Similar couplings based on catecholborane derivatives have been applied to syntheses of furanosesquiterpenoids, in particular dendrolasin-related natural products **8** and **9** isolated from marine sponges.[12] Catechol boranes can also be employed for triene synthesis, in this case involving coupling with a *Z*-vinyl bromide (**Scheme 3**).[13] The resulting conjugated *E*,*Z*,*E*-triene **10** was obtained in high yield, reflecting retention of stereointegrity in each reaction partner, as expected.[2],[3]



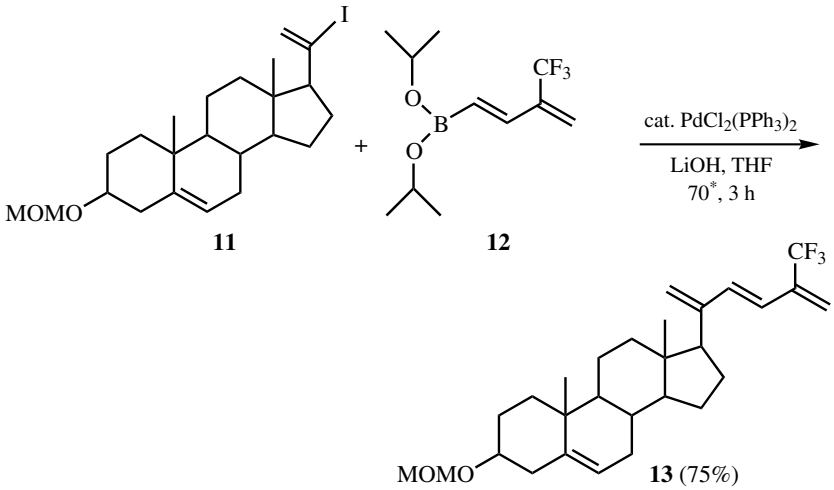
Scheme 2



Scheme 3

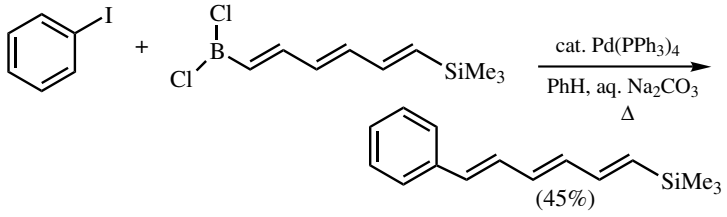
Fluorine-modified steroids (e.g., of vitamin D_3) oftentimes show unique biological activities.[14] Trifluoromethylated trienic steroids have been prepared using dienylboronate

12 in THF with aqueous LiOH present (2 equiv).[15] Thus, steroidal vinyl iodide **11** reacted with **12** under the influence of 3 mol % $PdCl_2(PPh_3)_2$ to give the desired product **13** (**Scheme 4**).



Scheme 4

Vinylic boranes utilized in these couplings are usually formed via hydroboration or quenching of lithiated intermediates with trialkylborates [$B(OR)_3$]. One alternative approach relies on ligand exchange between a polyenic silane and BCl_3.[16] Although the resulting dichloroboranes could be converted to their catechol derivatives in benzene, more expedient was their direct coupling with vinyl or aryl iodides (**Scheme 5**). The process calls for 2–4 equiv of aqueous Na_2CO_3, which presumably generates *in situ* the corresponding boronic acid.

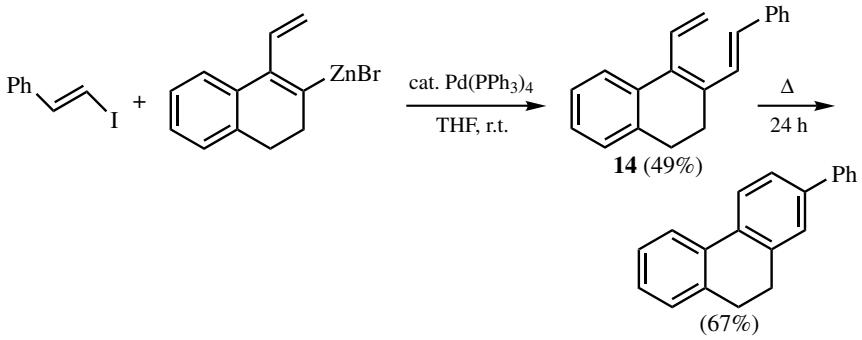


Scheme 5

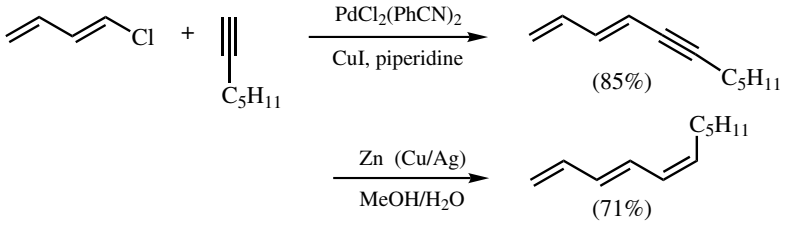
An alternative route to conjugated trienes includes use of vinylzinc halides, together with haloalkenes receptive toward insertion by Pd(0). Such Negishi couplings have successfully produced conjugated trienes,[17] with products of type **14** being susceptible to subsequent electrocyclic ring closure upon heating in xylene (**Scheme 6**).

Sonogashira couplings between terminal alkynes and vinyl halides set up polyenyne networks,[18]–[22] which are usually followed by Boland reduction[18],[23] using zinc under aqueous conditions (**Scheme 7**). This sequence necessarily affords a *Z*-olefin-containing

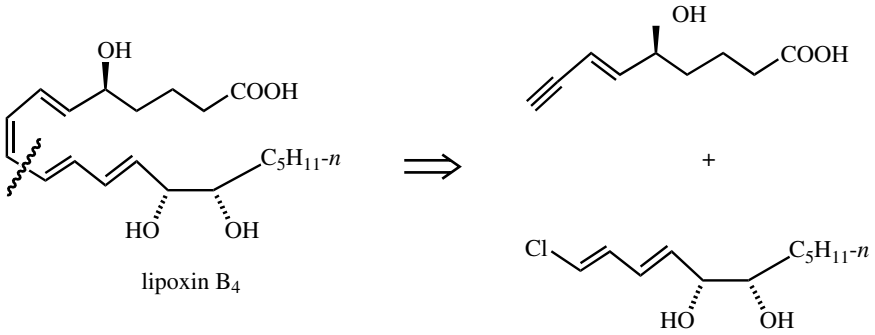
unit, as used to advantage in a recent synthesis of lipoxin B_4 (**Scheme 8**).[19] In more highly conjugated systems, however, isomerization to the all-*E* polyene can be achieved (*vide infra*).



Scheme 6



Scheme 7

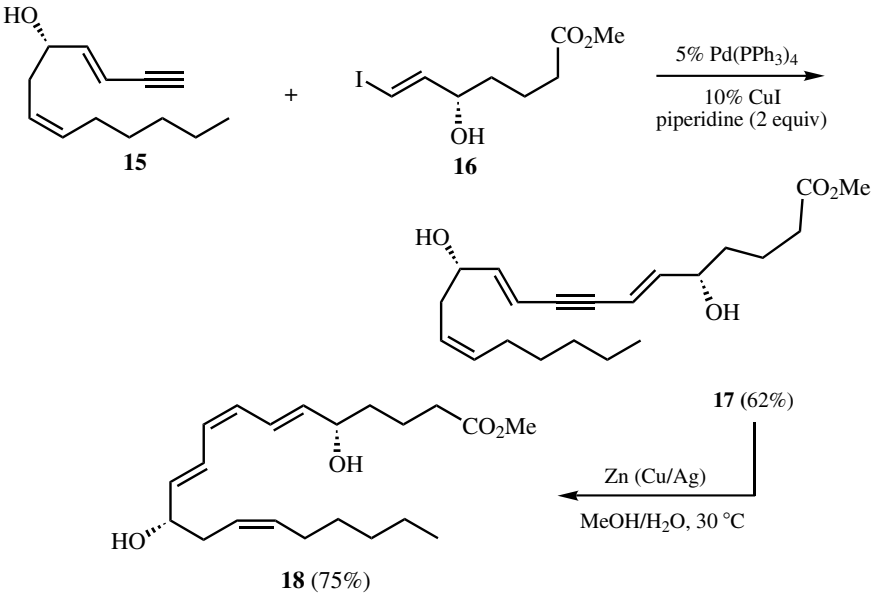


Scheme 8

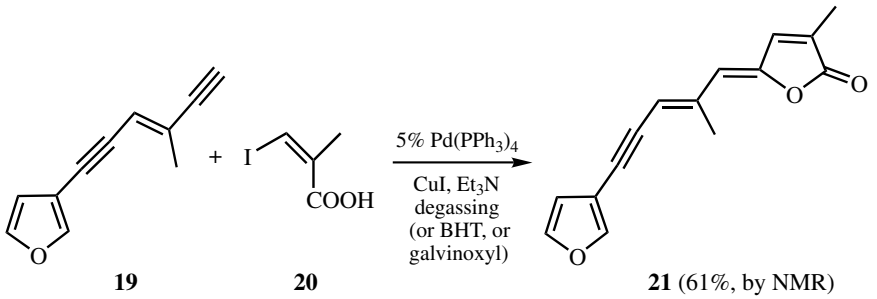
A synthesis of (5*S*,12*S*)-diHETE (**18**) relies on such a key Sonogashira coupling–Boland reduction sequence, with subunits **15** and **16** as reaction partners.[24] The initially isolated trienyne **17** is then smoothly converted to the target in 75% yield (**Scheme 9**).

A tandem cross-coupling–lactonization between terminal alkyne **19** and *Z*-iodo acid **20** was anticipated to afford freelingyne, a sesquiterpene from *Eremophilia freelingii*.[25] Curiously, presumed free-radical involvement prevented the desired course of reaction,

with mainly homocoupling of endiyne **19** being observed (**Scheme 10**). Only through the agency of several cycles of freeze-degassing, or addition of BHT or galvinoxyl, was success ultimately achieved. The stereopurity of **21** was >98%, while prior syntheses were less stereoselective.[26]



Scheme 9



Scheme 10

C. TETRAENES AND BEYOND

In order to synthesize conjugated polyenes at the tetraene stage, and certainly for pentaenes and higher vinylogs, challenges not normally encountered with simpler polyenes must be met in addition to the usual search for optimum coupling conditions. Most notably, extended polyenes tend to be highly sensitive to light and heat, easily oxidized at allylic sites, and oftentimes susceptible to both acid- and base-catalyzed polymerization. Isolation, therefore, can be very costly, yield-wise. To make matters worse, reactivity patterns may be grossly altered as the

length of the polyenic organometallic increases, thereby placing increased demands on catalyst activity as well as other reaction variables (e.g., nature of the base in a Suzuki coupling). These patterns of reduced reactivity with increasing length of polyene chain, first noted by Negishi and Owczarczyk,[27] may be anticipated from theory as indicated by very recent *ab initio* calculations, performed at UCSB in collaboration with Professor Don Aue, allowing for comparisons between simple vinylboronic acid and its higher homologues up to the decapentenyl array (**Table 1**).[22] Immediately apparent is that coefficients for the LUMOs at boron drop precipitously with increasing conjugation. These data suggest that, even for the derived *ate* species, far less electron density at boron (and at C-1) is to be expected and available for participation in the transmetallation step with a Pd(II) intermediate, thereby potentially accounting for the experimentally observed significant decrease in reaction rate.

One approach to all *E*-tetraenes, also applicable to pentaenes, relies on conjunctive reagent **23**, readily available in gram quantities from acetylene acetal **22** via a three-step procedure (**Scheme 11**).[28] Transmetallation of **23** to the vinyllithium followed by conversion to the corresponding diorganozinc affords a species that readily couples with vinylic halides to give either trienynes or tetraenynes upon removal of the acetylenic TMS moiety (**Scheme 12**). The terminal alkyne can then be hydrozirconated, although the resulting polyenic zirconocene does not participate in Pd(0)-mediated couplings with vinylic halides or triflates.[27] Upon transmetallation to aluminum,[29] however, it can be acylated to arrive at oxopolyenes, subsections characteristic of several polyene macrolide antifungal agents, as exemplified by the mycoticins.[30],[31]

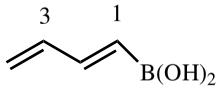
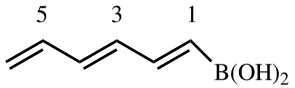
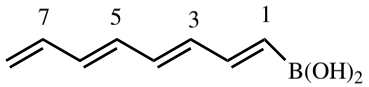
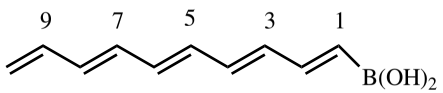
Using an *E*-vinyl zirconocene of type **25**, a *trans*-selective cross-coupling with 1,1-dibromo alkene **24** can be effected in the presence of 5 mol % of DIBAL-reduced $PdCl_2(PPh_3)_2$ (**Scheme 13**).[32] Curiously, the corresponding olefinic zinc bromide of **25** was completely unreactive toward **24**, attributed to potential *E*-to-*Z* isomerization driven by internal chelation to oxygen. The newly formed trienyne **26** could then be carboxylated and lactonized via catalytic Ag(I). Removal of the two TBS protecting groups gave lissoclinolide, **27**, an agent active against Gram negative bacteria.

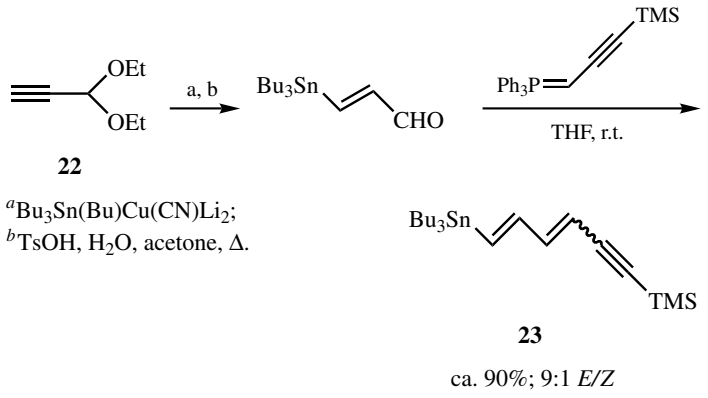
The pentaene portion of the multidrug resistance reversing agent (−)-stipiamide (**28**), first synthesized in 1997, relies on a Stille coupling between *E*-dienyl iodide **30** and *Z*-vinylstannane **31** in the final step, thereby establishing the C-7 to C-8 linkage (**Scheme 14**).[33] The coupling takes place in only 15 minutes at ambient temperature, being run in *N*-methylpyrrolidinone with a close to 1:1 stoichiometry of reactants. Although the central olefin of *Z* constitution is initially maintained in the coupling, some loss of stereochemistry occurs during workup and isolation (i.e., to the all *E* form, along with lesser amounts to the 4*Z* isomer).

Akin to (−)-stipiamide (**28**) is (−)-myxalamide A (**29**), the *E*,*E*,*Z*,*E*,*E*-pentaene portion having been fashioned via the alternative Suzuki process between a vinyl catecholborane (formed *in situ* via hydroboration of alkyne **33**) and *Z*-vinyl iodide **32** (**Scheme 15**).[34] Using catalytic $Pd(OAc)_2$ and the water-soluble phosphine ligand TPPTS, coupling in aqueous CH_3CN at room temperature gave the desired natural product in 44% isolated yield as a pure isomer.

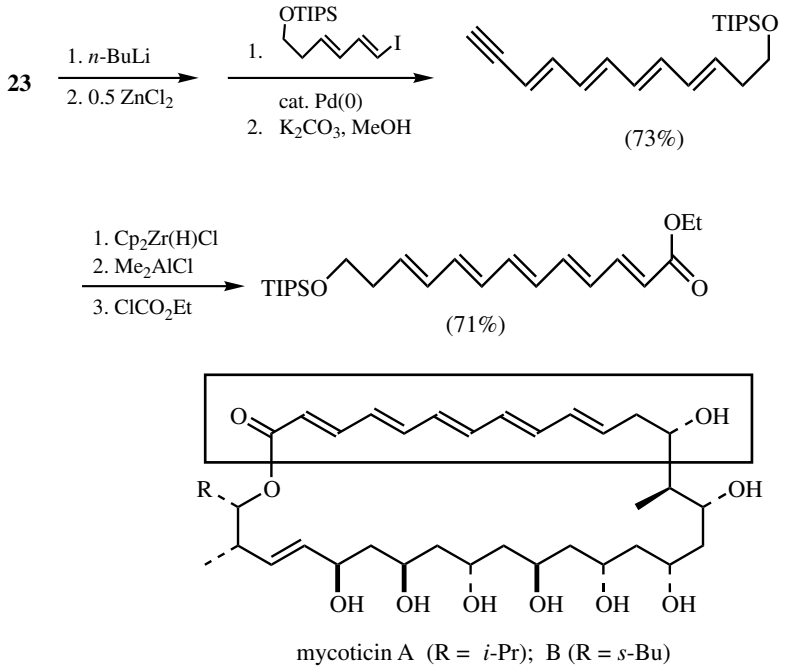
More highly conjugated polyenes, such as hexa- and heptaenes, have been made in a number of ways that rely on Pd-catalyzed chemistry as the key C—C bond-forming step. In one route to all *E*-hexaenes, the new conjunctive reagent **34**, a bromotrienyne, serves as a masked vinyl anion at one end and vinyl cation at the other.[35],[36] Coupling of **34** with vinylic or polyenic zinc reagents **35** in the presence of Pd(0) leads to tetra- or pentaenynes, which are subject to further elaboration at the alkyne terminus (**Scheme 16**).

TABLE 1. ***Ab initio*** **Calculations Using Spartan Modeling Software at the HF//3-21G/3-21G* Level**

	LUMO Coefficients										
	B	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
	**0.347**	0.704	0.586								
	**0.233**	0.517	0.484	0.366	0.536						
	**0.174**	0.434	0.353	0.429	0.476	0.244	0.416				
	**0.138**	0.366	0.273	0.415	0.399	0.335	0.423	0.176	0.332		
	**0.114**	0.313	0.221	0.381	0.336	0.359	0.390	0.266	0.365	0.134	0.270



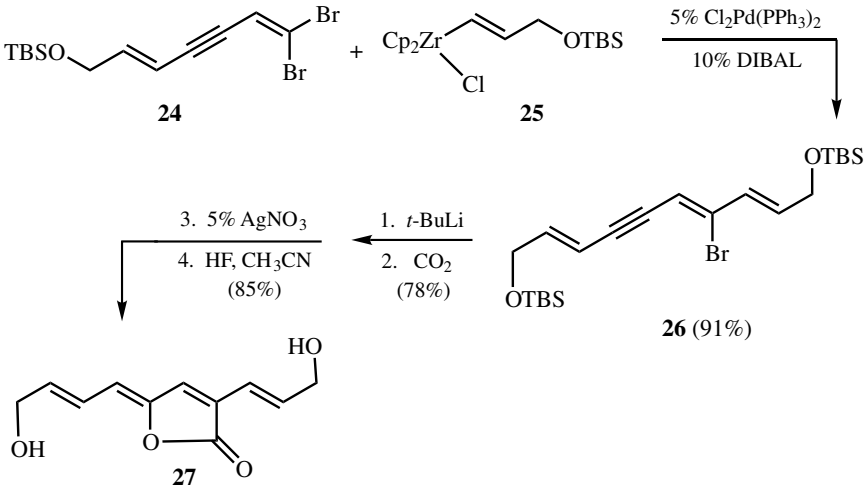
Scheme 11



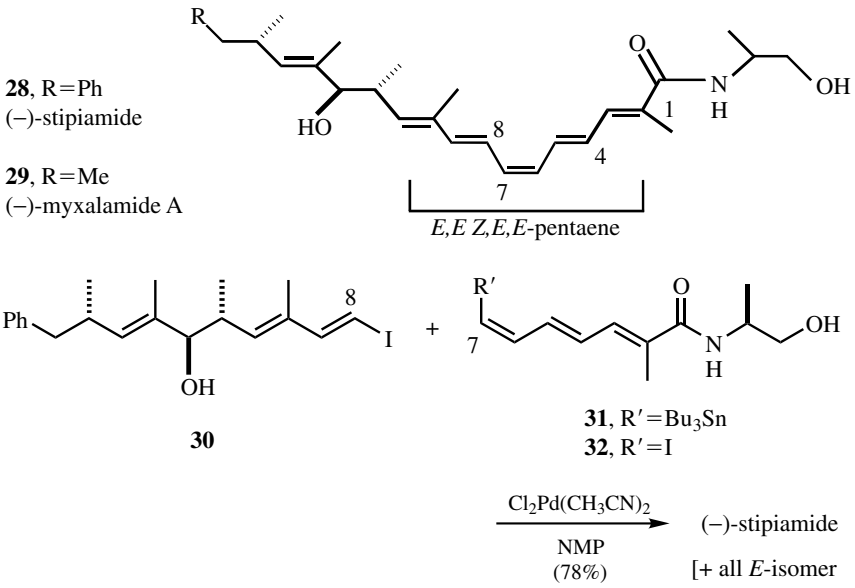
Scheme 12

Thus, as previously demonstrated with stannyl reagent **23**,[28] hydrozirconation–transmetallation of initial product **36** to the corresponding vinylalane[29] imparts sufficient reactivity for acylation with chloroformates (or acid chlorides). In applying this strategy to the all *E*-hexaene portion of the dermastatins,[37] fragment **37** could be constructed in a minimum number of operations in good overall yield (56%).

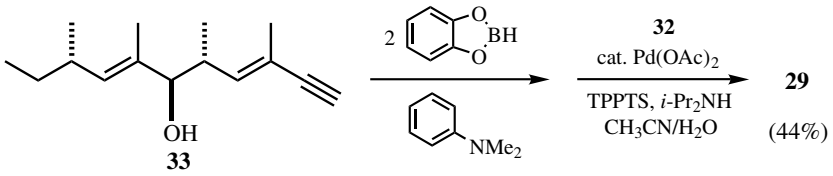
Extensive studies on Sonogashira couplings between substituted enynes and vinyl chlorides have documented the unexpected facility, and therefore significant utility, of these efficient processes. Inherent to these schemes, as true with less highly conjugated products (*vide supra*), is the requirement that the internal alkyne generated be reduced,



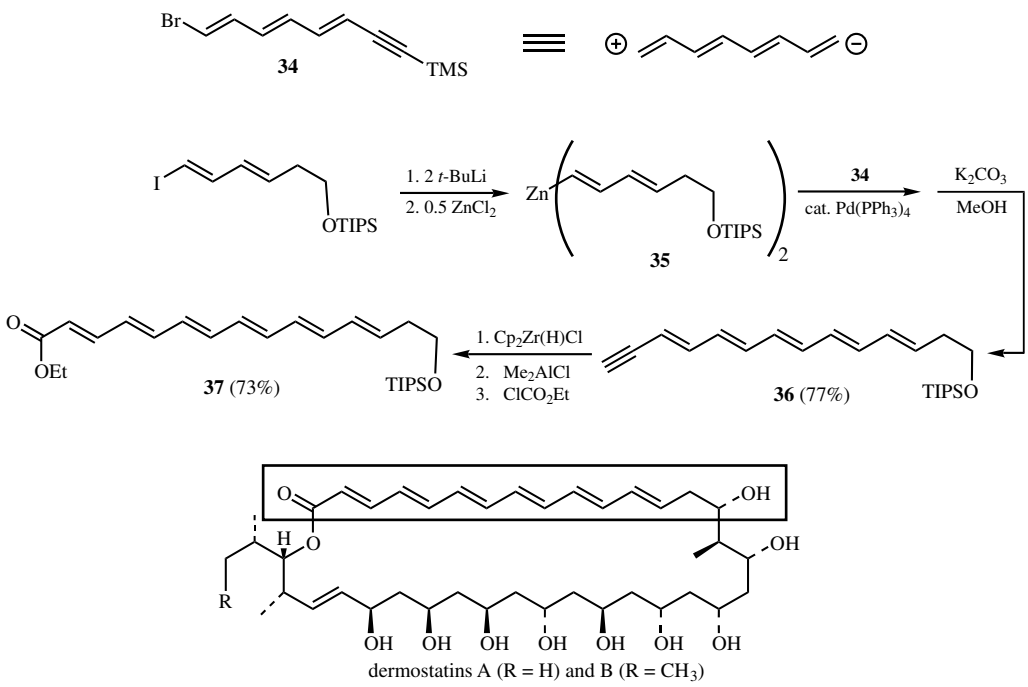
Scheme 13



Scheme 14

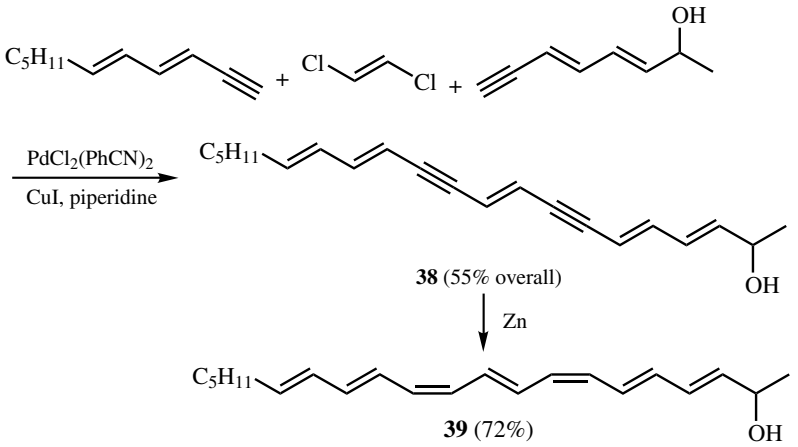


Scheme 15



Scheme 16

initially affording a *Z*-olefin. When multiple acetylenic sites are present, such as with pentaendiyne **38**, Boland reduction[23] affords the corresponding heptaene **39** bearing two *Z*-olefins (**Scheme 17**).[38] In the presence of only one internal *Z*-alkene, isomerization at room temperature occurs to the all *E* heptaene network.[39],[40] This particular product type highlights the potential of *E*-1,2-dichloroethylene[41] to serve as a "linchpin," each terminus undergoing sequential Pd(0)-mediated coupling in the presence of CuI and a base.[22]

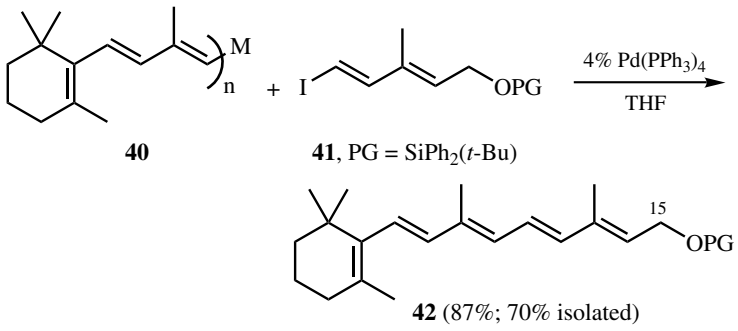


Scheme 17

D. RETINOIDS

Aside from the well-recognized role of retinoids in the chemistry of vision,[42] they bind to, and therefore activate, up to six intracellular retinoid receptors (the RARs and RXRs).[43] In doing so they serve as modulators of nuclear transcription, which impacts numerous cellular events (e.g., reproduction, immune function, and development). Such actions have consequences for treatment of certain cancers, including leukemia, melanoma, Kaposi's sarcoma, and squamous cell carcinoma. Several approaches to both natural and unnatural retinoids, which make use of a Pd(0)-induced vinyl–vinyl cross-coupling, have appeared over the last decade, with extensive work ongoing given the connection to oncology.

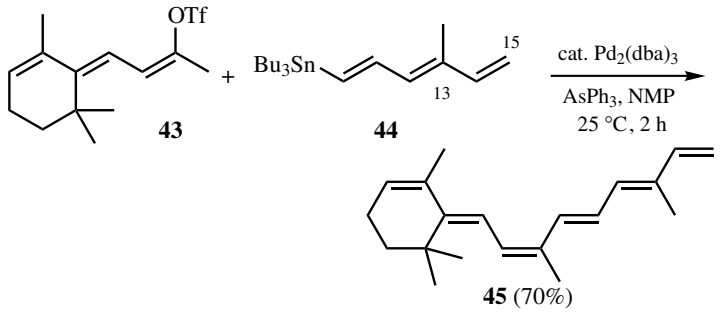
An early, highly stereoselective synthesis of vitamin A (i.e., retinol; **42**, PG = H) made use of a Negishi coupling between trienylzinc **40** (M = Zn; $n = 2$) and dienyl iodide **41** (**Scheme 18**).[44] Several other organometallic partners (M in **40**) were considered, including $AlMe_2$, $Mg_{1/2}$, $SnMe_3$, $Cu{\cdot}MgX_2$, $BO_2C_6H_4$, and Cp_2ZrCl. Not one of these alternatives afforded a yield close to that obtained with the corresponding divinyl zinc species (i.e., from a trace of product being formed with either the borate or zirconocene, to a maximum of 60% with the alane). The nature of the protecting group in **41** was also influential, with the *t*-$BuPh_2Si$ moiety imparting the greatest element of stability.



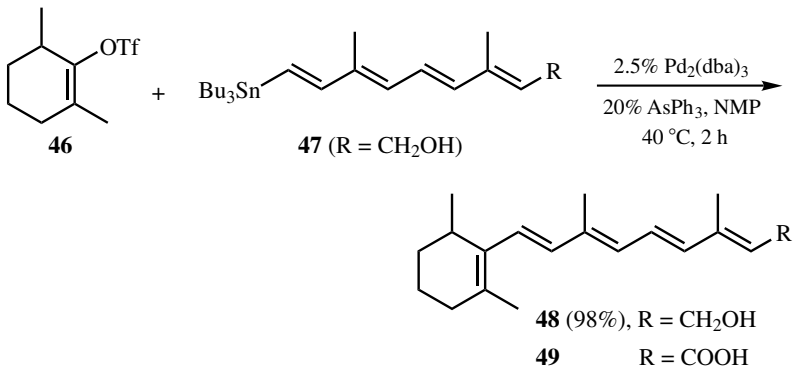
Scheme 18

Although the Stille coupling version of this reaction was low yielding, this appears to be related to the nature of the fragments and polarities of the subunits involved. Thus, a Stille coupling approach could successfully be applied to a synthesis of both all *E*-, and 8*Z*-anhydroretinol **45** (compare **40** n = 1, M = $SnBu_3$ versus **44**, and **41** versus **43**; **Schemes 18** and **19**).[45] In **44**, the natural (protected) C-15 alcohol is no longer present (cf. **42**). In addition, these couplings now share in the benefits associated with more modern conditions and insights regarding leaving group abilities, involvement of ligand(s), polarity of solvent(s), and so on.[46]

Ring-modified analogs have also been tailored using a Stille coupling, such as that formed from reaction between racemic dimethylated cyclohexenyl triflate **46** and tetraenylstannane **47** (**Scheme 20**).[47] The decreased steric hinderance due to the 2,6-dimethyl-, rather than 2,6,6-trimethyl-, cyclohexenyl pattern in **46** allows for a very efficient route to the observed pentaene **48**, which was ultimately parlayed to acid **49** in three additional operations.

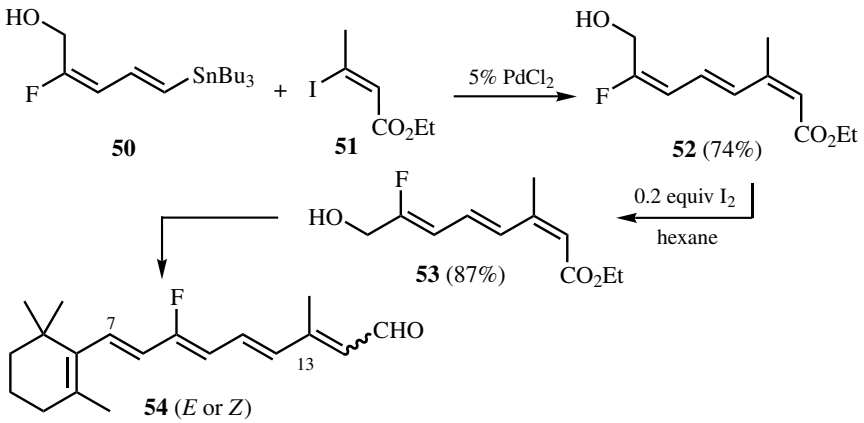


Scheme 19



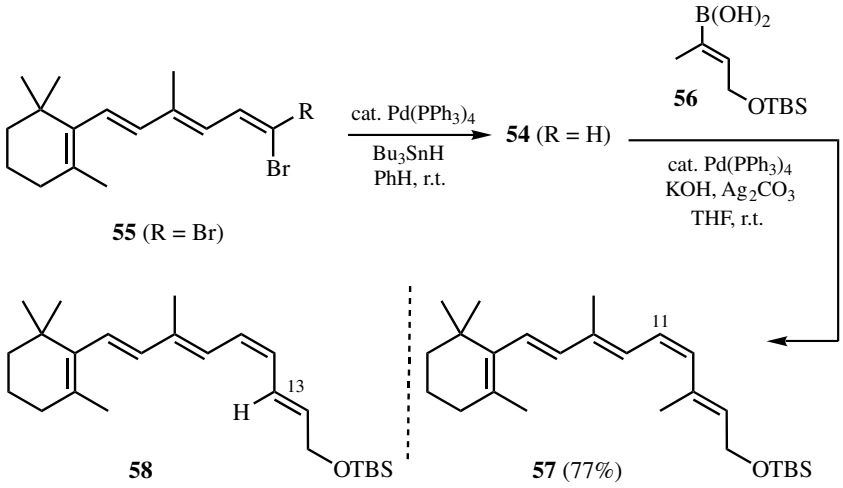
Scheme 20

The 9-fluoro analog of all *trans*-retinal, *E*-**54**, has been constructed with the aid of a Pd(0)-catalyzed Stille coupling between fluorodienylstannane **50** and the *Z*-β-iodo ester **51** (**Scheme 21**).[48],[49] Subsequent isomerization of adduct **52** to **53** was effected with catalytic I_2, obtained as a single isomer. Oxidation with MnO_2 set the stage for Wittig elaboration to the target pentenals **54**.



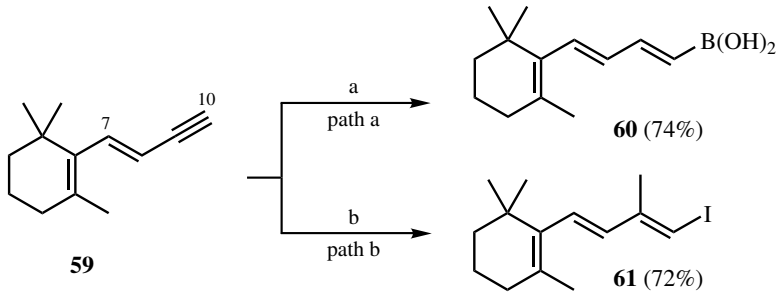
Scheme 21

Suzuki couplings have figured prominently in retinoid synthesis as well, with both the natural series and several analogs having been formed using slight variations in substrate structures. For example, 11*Z*-retinol has been configured via dibromide **55** (R = Br), which can be selectively dehalogenated to *Z*-**54** (R = H) using a Pd(0)-catalyzed reduction in the presence of Bu_3SnH (**Scheme 22**).[50] Upon exposure of the monobromide to vinylboronic acid **56**, protected 11*Z*-pentaenol **57** was formed in 77% yield. In a similar way, the corresponding 13-desmethyl-(11*Z*)-retinol (**58**) was prepared.

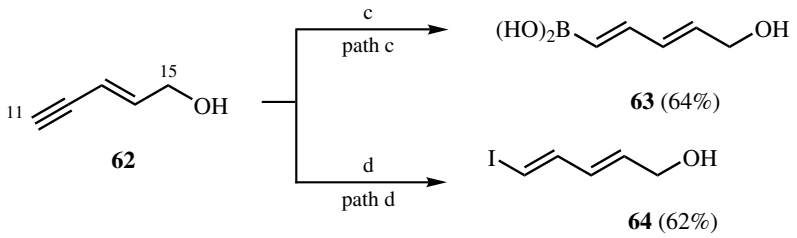


Scheme 22

Several other retinol analogs, as well as the parent system, have been made using dienyne **59** and enynol **62** as the Cl-10 and C11–15 fragments, respectively (**Scheme 23**).[51] The former serves as precursor to either boronic acid **60** (path a) or vinyl iodide **61** (path b), while the latter can be converted to dienylboronic acid **63** (path c) or dienic iodide **64** (path d). Combinations involving **60**, **61**, **63**, and **64** provided, for example, the 13-desmethyl retinol **65**, while Pd(0)-mediated coupling of **60** and **64** gave the 9,13-didesmethyl analog **66** (**Scheme 24**). An identical route using **61** and the methylated version of boronic acid **63** (i.e., **67**), or coupling between **60** and methylated **64** (i.e., **69**), led to all *trans*-retinol **68** and the 9-desmethyl analog **70**, respectively.



Scheme 23



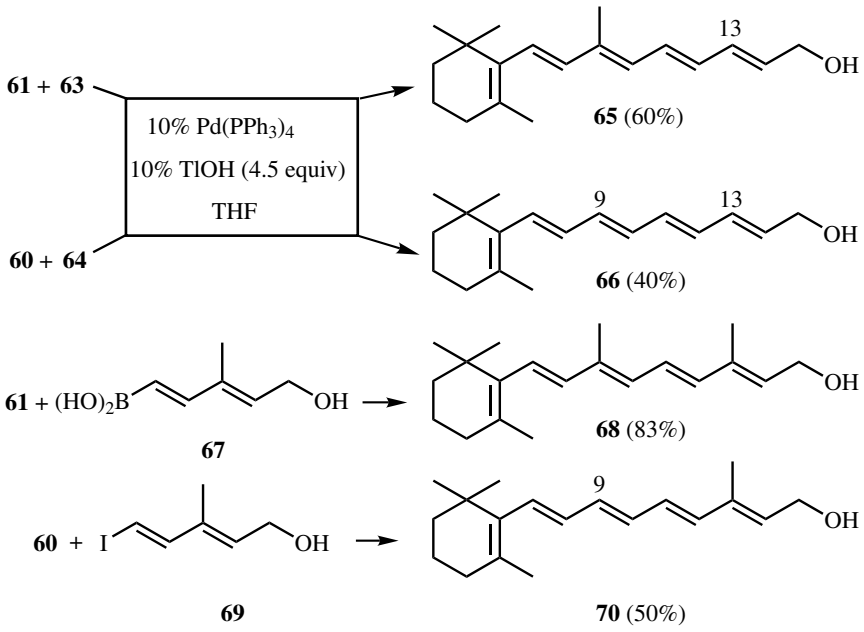
[a] Catecholborane, BH_3, *N*,*N*-diethylaniline (10%), PhH, r.t., 9 h.

[b] Me_3Al, Cl_2ZrCp_2, CH_2Cl_2, 0 °C to r.t., 12 h; then ICN, THF, 0 °C.

[c] Catecholborane (2 equiv), 0 °C to r.t., 2 h; then H_2O, r.t., 2.5 h.

[d] As in c, then I_2, NaOH, Et_2O, 0 °C.

Scheme 23 (*Continued*)



Scheme 24

E. SUMMARY

Several very effective methods now exist for preparing highly conjugated networks ranging from trienes to heptaenes. The common denominator that provides opportunities for realization of these highly sensitive materials is Pd(0). The mild conditions that suffice, together with remarkable functional group tolerance, combine to offer an especially effective catalytic tool for vinyl–alkynyl or vinyl–vinyl cross-couplings. Organometallic reaction partners tend to involve the elements of boron, tin, zinc, and zirconium, while electrophiles are mainly vinylic halides or pseudohalide derivatives. The extent of

conjugation in the nucleophilic subunit can dramatically affect the extent of coupling, with higher levels leading to reduced efficiencies. Steric effects in the electrophilic portion have also been found to influence the extent of cross-coupling. As more information on these fundamental Pd(0)-catalyzed processes becomes available, there is every reason to anticipate further experimental and theoretical refinements. From the synthetic perspective, there is certainly no shortage of valued and challenging targets to which such advances could immediately be applied.

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