ACCOUNTS
of chemical research

Recent Advances in Efficient and Selective Synthesis of Di-, Tri-, and Tetrasubstituted Alkenes via Pd-Catalyzed Alkenylation−Carbonyl Olefination Synergy

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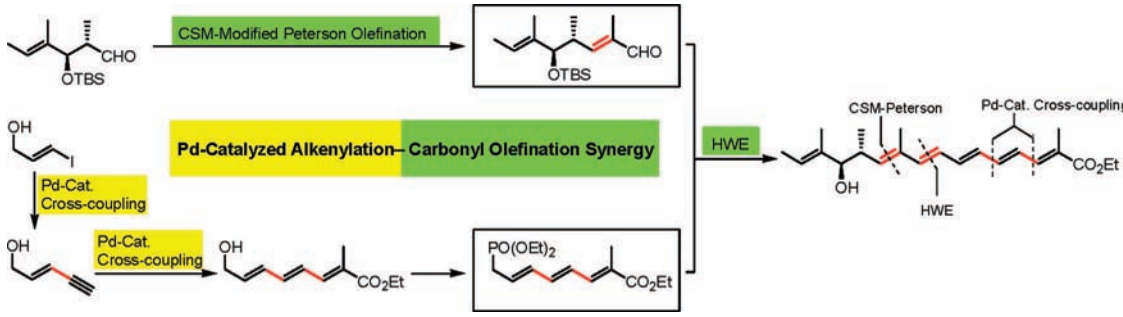
RECEIVED ON FEBRUARY 2, 2008

CONSPECTUS



Although generally considered competitive, the alkenylation and carbonyl olefination routes to alkenes are also complementary. In this Account, we focus on these approaches for the synthesis of regio- and stereodefined di- and trisubstituted alkenes and a few examples of tetrasubstituted alkenes. We also discuss the subset of regio- and stereodefined dienes and oligoenes that are conjugated.

Pd-catalyzed cross-coupling using alkenyl metals containing Zn, Al, Zr, and B (Negishi coupling and Suzuki coupling) or alkenyl halides and related alkenyl electrophiles provides a method of alkenylation with the widest applicability and predictability, with high stereo- and regioselectivity. The requisite alkenyl metals or alkenyl electrophiles are most commonly prepared through highly selective alkyne addition reactions including (i) conventional polar additions, (ii) hydrometalation, (iii) carbometalation, (iv) halometalation, and (v) other heteroatom-metal additions. Although much more limited in applicability, the Heck alkenylation offers an operationally simpler, viable alternative when it is highly selective and satisfactory.

A wide variety of carbonyl olefination reactions, especially the Wittig olefination and its modifications represented by the *E*-selective HWE olefination and the *Z*-selective Still−Gennari olefination, collectively offer the major alternative to the Pd-catalyzed alkenylation. However, the carbonyl olefination method fundamentally suffers from more limited stereochemical options and generally lower stereoselectivity levels than the Pd-catalyzed alkenylation. In a number of cases, however, very high (>98%) stereoselectivity levels have been attained in the syntheses of both *E* and *Z* isomers.

The complementarity of the alkenylation and carbonyl olefination routes provide synthetic chemists with valuable options. While the alkenylation involves formation of a C−C single bond to a C═C bond, the carbonyl olefination converts a C═O bond to a C═C bond. When a precursor to the desired alkene is readily available as an aldehyde, the carbonyl olefination is generally the more convenient of the two. This is a particularly important factor in many cases where the desired alkene contains an allylic asymmetric carbon center, since α-chiral aldehydes can be prepared by a variety of known asymmetric methods and readily converted to allylically chiral alkenes via carbonyl olefination. On the other hand, a homoallylically carbon-branched asymmetric center can be readily installed by either Pd-catalyzed isoalkyl−alkenyl coupling or Zr-catalyzed asymmetric carboalumination (ZACA reaction) of 1,4-dienes.

In short, it takes all kinds to make alkenes, just as it takes all kinds to make the world.

Published on the Web 09/11/2008 www.pubs.acs.org/acr
10.1021/ar800038e CCC: $40.75

1. Introduction and Overview

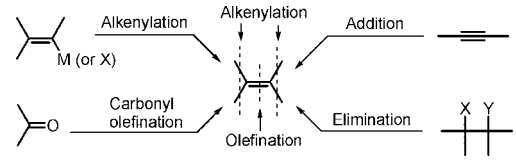
Alkenes represent one of the most widely occurring and important classes of organic compounds. Their efficient, selective, and practical synthesis has provided major challenges to synthetic organic chemists. Even if we limit our consideration to the synthesis of acyclic alkenes, there are close to ten different, basic structural types just for monoalkenes. Our attention here is focused on regio- and stereodefined di- and trisubstituted alkenes, as well as very limited examples of tetrasubstituted alkenes. Even under these restrictions, our synthetic tasks increase exponentially by considering regio- and stereodefined dienes and oligoenes of strictly defined molecular weights. Of particular interest here are those dienes and oligoenes that are conjugated.

2. Alkene Synthesis Methodology

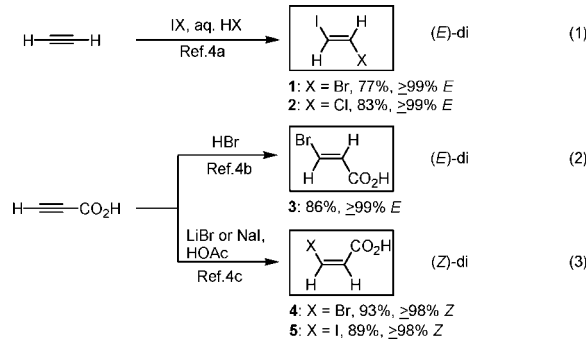
(a) Carbonyl Olefination. Until a few decades ago, regio- and stereodefined alkenes, especially those naturally occurring ones of biological and medicinal interest, were prepared mostly by aldol and related carbonyl olefination reactions,[1] which have been significantly reinforced by the discoveries and development of the P-, S-, and Si-based carbonyl olefination reactions[2] represented by the P-based Wittig olefination and its variants including the Horner−Wadsworth−Emmons (HWE) and *Z*-selective Still−Gennari[2b] modifications, the S-based Julia olefination, and the Si-based Peterson olefination,[2c] as well as their variants. As useful and important as these carbonyl olefination reactions are, they nevertheless are associated with some fundamental difficulties and limitations. Since the very construction of the C=C bond is achieved during any carbonyl olefination reactions, its stereochemical outcome depends on various reaction parameters. Moreover, a successful and selective C=C bond construction means that the reaction as such is not applicable to the synthesis of the opposite stereoisomer unless it is modified. Although not discussed here, the olefin metathesis[3] has emerged recently as a new promising class of olefination, which also appears to share similar difficulties and limitations, as discussed herein.

(b) Alkenylation via Alkyne Addition. As indicated in Scheme 1, there are a few other basic and alternate routes to alkenes. Aside from various elimination processes, some of which also serve as critical steps in the carbonyl olefination, alkyne addition and alkenylation represent two alternate routes to alkenes that are fundamentally discrete from the olefination reactions. In selective alkenylation, regio- and stereodefined alkenyl reagents or intermediates are prepared before

SCHEME 1



SCHEME 2



the critical formation of the desired alkenes. In the required C−C single bond formation, stereochemical outcome is not only governed by a fundamentally different set of parameters but also more readily and predictably achievable. This however mandates the prior synthesis of regio- and stereoisomerically pure alkene intermediates. Generally speaking, this requirement can most conveniently be met by resorting to various alkyne addition reactions. Indeed, it has been known that some pure regio- and stereodefined alkenes are readily and economically preparable by alkyne addition reactions,[4] which are thought to proceed mostly by polar addition mechanisms. Some such examples providing useful alkene "synthons" pertinent to this Account are shown in Scheme 2. Surprisingly, few widely applicable methods for the synthesis of regio- and stereodefined alkenes through the use of these halogenated alkenes had been known before the advent of the Pd-catalyzed alkenylation discovered and developed in the early to mid-1970s, some representative examples of which include the Heck alkenylation[5] and much more widely applicable C−C cross-coupling reactions,[6,7] such as those involving Zn, Al, and Zr (Negishi coupling),[6] and B (Suzuki coupling).[7] Over the past few decades, the Pd-catalyzed alkenylation via cross-coupling has indeed revolutionized the alkene synthesis. In contrast with the Pd-catalyzed alkenylation via cross-coupling with alkenyl metals or alkenyl electrophiles, the Heck alkenylation,[5] which is known to proceed via alkene addition−elimination, is not only more limited in synthetic scope but also more prone to regio- and stereoisomerization and other side reactions. Nonetheless, in cases where the Heck alkenylation proceeds satisfactorily, it can not only be highly competitive but also be nicely comple-

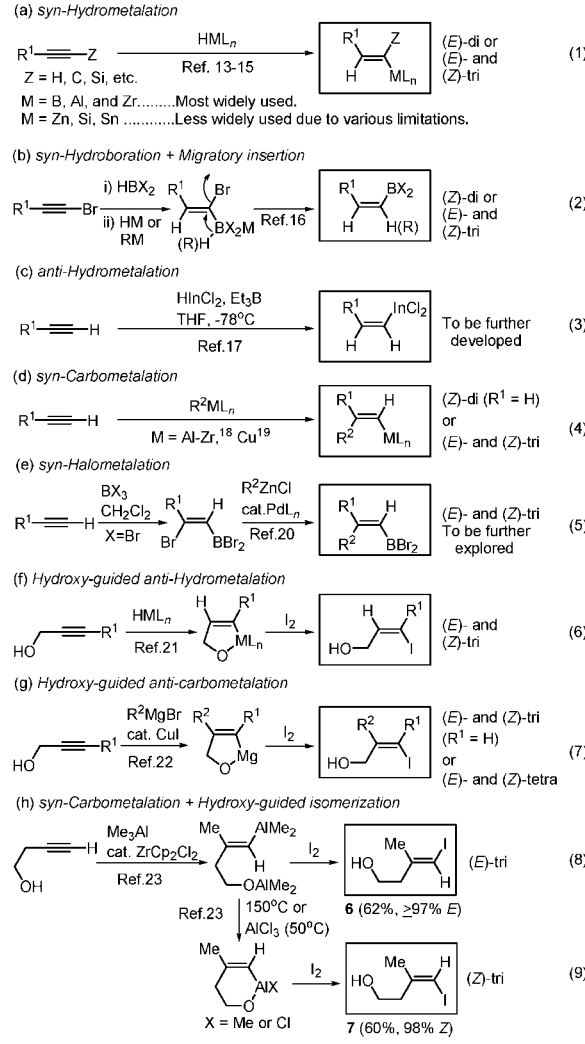
mentary with the Pd-catalyzed alkenylation via cross-coupling. It is also feasible and even satisfactory in many cases to use transition metals other than Pd, including Ni,[8] Cu,[9] and Fe,[10] as catalysts. However, none of them appears to be as widely applicable and generally regio-, stereo-, and chemoselective as that with Pd. It is also appropriate and useful to note that the significantly higher cost of Pd as compared with those of Ni, Cu, and Fe can be largely offset by generally high catalyst turnover numbers (TONs) observed with Pd that can reach desirable levels of 10^3-10^5 or even higher[11] by using bidentate phosphine ligands.

With the development of Pd-catalyzed alkenylation via cross-coupling, efficient and selective preparation of alkenyl intermediates has become critically important. In addition to conventional alkyne addition reactions (Scheme 2), regio- and stereoselective *hydrometalation*, *carbometalation*, *halometalation*, and *metallometalation* have emerged and provided various satisfactory routes to the alkenyl reagents. Although not discussed in detail, it is useful to show metal-promoted regio- and stereoselective addition reactions pertinent to the discussions herein (Schemes 3 and 4). It is also important to note that catalytic hydrogenation provides a widely applicable method for direct conversion of alkynes to mostly *Z*-alkenes.[12]

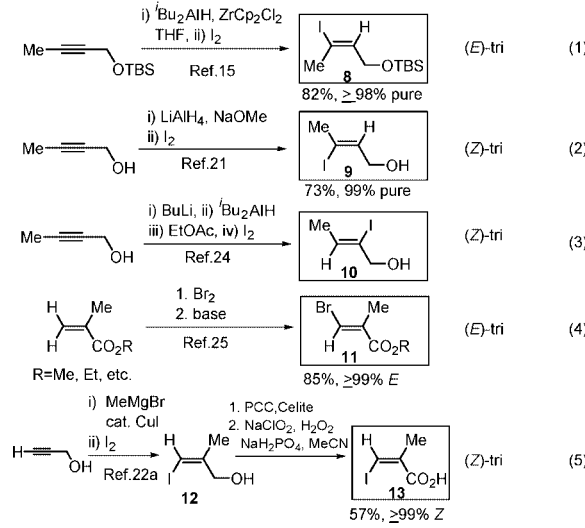
3. Stereo- and Regioselective Synthesis of Monomeric Trisubstituted and Tetrasubstituted Alkenes

With the availability of various selective routes to alkenyl metals and alkenyl halides discussed in the preceding section, it might appear that most of the alkenes can now be synthesized almost at will. This statement is approaching being truthful in the synthesis of mono- and disubstituted alkenes. Despite significant recent advances, however, the selective synthesis of various tri- and tetrasubstituted alkenes can still be very difficult. As discussed above, however, methodological developments over the past few decades have made available a variety of highly (>95%) selective Pd-catalyzed cross-couplings and a few carbonyl olefination methods, notably *E*-selective HWE reaction,[2a] its *Z*-selective Still−Gennari modification,[2b] and the Corey−Schlessinger−Mills (CSM hereafter) modification[2d] of the Peterson olefination.[2c] Among those shown in Schemes 3 and 4, *syn*-carbometalation, that is, item d in Scheme 3, especially the Zr-catalyzed methylalumination of terminal alkynes,[18] has served as a widely applicable tool for the synthesis of naturally occurring (*E*)-trisubstituted alkenes, while carbocupration[19] has been shown to be useful for ethyl and higher alkylmetalation. In the carbometalation and haloboration[20] of terminal alkynes, construction of the disubstituted end of the double bond, which

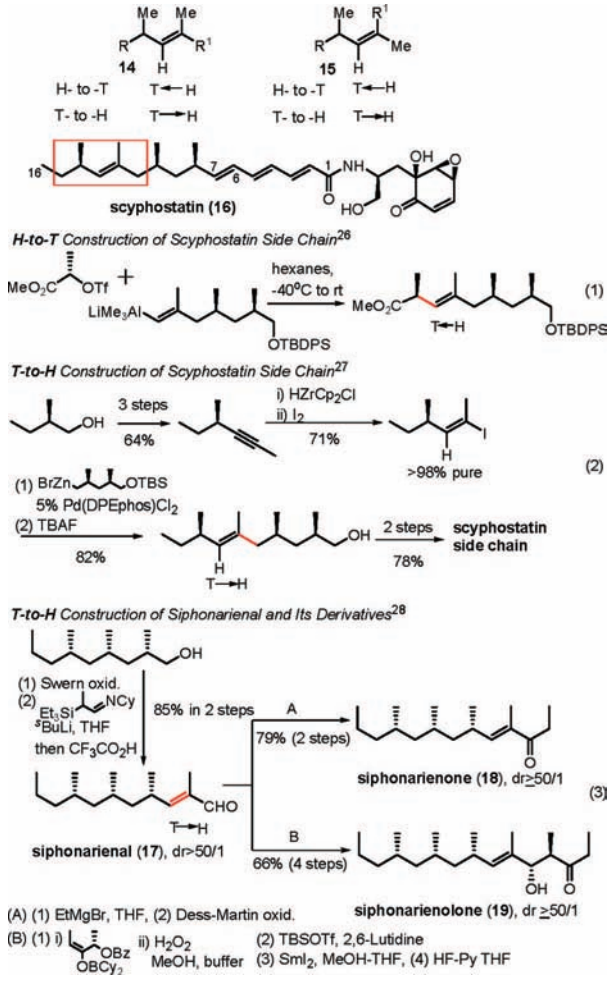
SCHEME 3



SCHEME 4



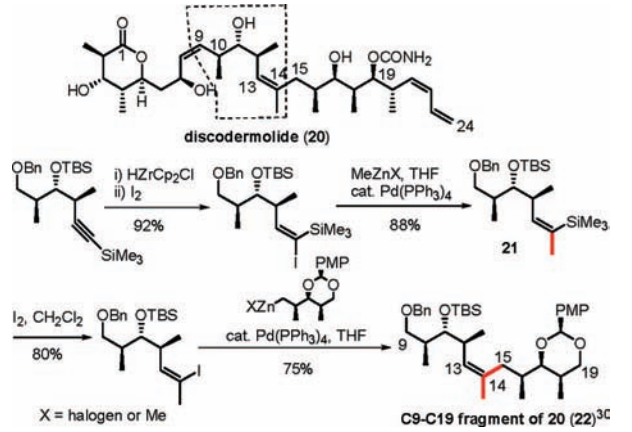
SCHEME 5



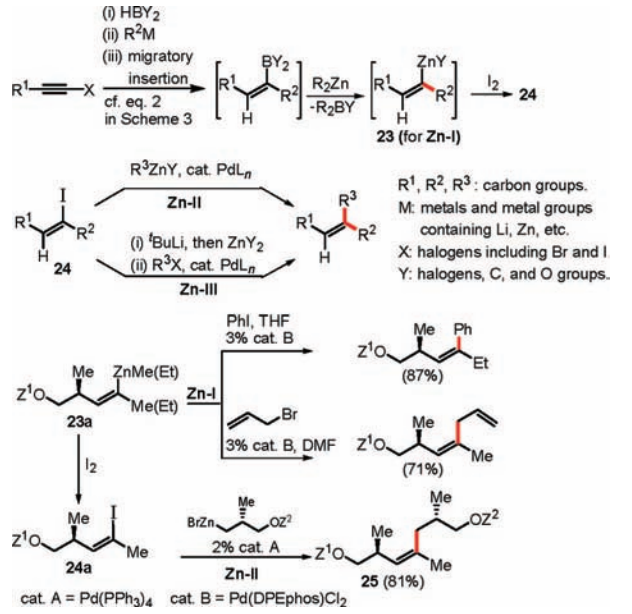
may arbitrarily be termed "head (H)", is achieved first, which may then be followed by the construction of the monosubstituted end, which may be termed "tail (T)", for the "H-to-T" construction of trisubstituted alkenes (Scheme 5).

(a) Proximally Chiral (*E*)-Trisubstituted Alkenes. A large number of polyketides possess those structural units represented by **14** and **15**. The presence of an allylically Me-branched asymmetric carbon center makes it difficult to construct these units in the H-to-T manner, even though a pioneering study by Hoye[26] with a carboalumination-derived alkenylaluminate proceeded with clean stereoinversion to give a side chain precursor to scyphostatin (**16**) (eq 1 of Scheme 5). On the other hand, regio- and stereoselective hydrometalation permits their construction in the T-to-H manner (eq 2 of Scheme 5).[27] Construction of an allylic asymmetric carbon center and an (*E*)-trisubstituted alkene in the T-to-H manner may also be most efficiently achieved by using the highly stereoselective CSM-modification[2d] of the Peterson olefination as exemplified by a recent synthesis of siphonarienal (**17**), siphonarienone (**18**) and siphonarienolone (**19**)[28] (eq 3 of Scheme 5).

SCHEME 6



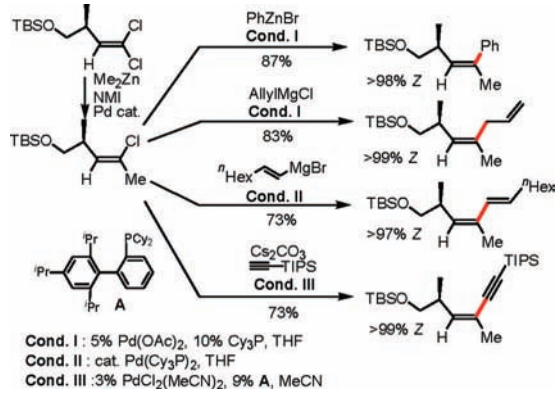
SCHEME 7



(b) Proximally Chiral (*Z*)-Trisubstituted Alkenes. One of the synthetically most demanding monoalkenes has been the (*Z*)-trisubstituted alkene at C13 and C14 of discodermolide (**20**).[29] One approach by Panek[30] that is highly selective, albeit somewhat lengthy, employs hydrozirconation of 1-silyl-1-alkynes. Once the requisite C9−C14 (*Z*)-alkenyl iodide is generated, its isoalkylation with C15−C19 isoalkylmetals seems most satisfactorily achieved by the Pd-catalyzed isoalkyl−alkenyl coupling with isoalkylzincs[29,30] (Scheme 6).

For more efficient constructions, two promising protocols have been developed. One involves the 1-bromo-1-alkyne hydroboration, migratory insertion, and Negishi coupling (Scheme 7).[31] Another is based on a pioneering work of Tamao[32] on Pd-catalyzed stepwise disubstitution of β,β-dichlorostyrene. Significantly, a previously little known second substitution with alkyl, aryl, alkenyl, allyl, and alkynyl groups has

SCHEME 8



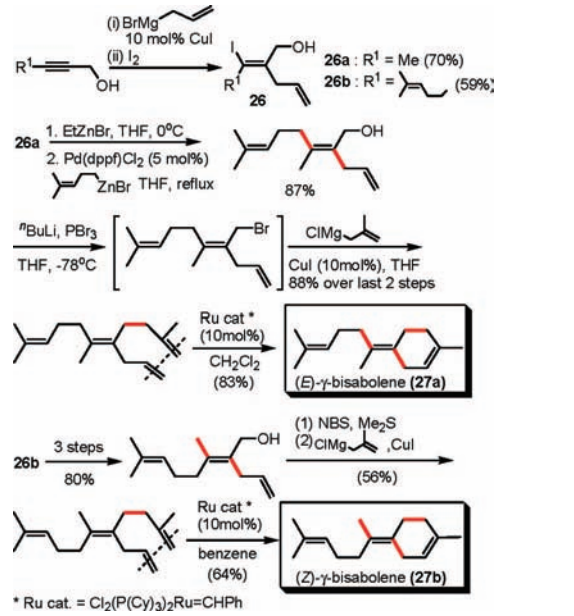
been achieved in good to excellent yields (Scheme 8).[33] Both of these protocols promise to provide satisfactory routes to many demanding (*Z*)-trisubstituted alkenes.

(c) Stereo- and Regioselective Synthesis of Tetrasubstituted Alkenes. Despite major advances discussed in the preceding section, synthesis of acyclic tetrasubstituted alkenes with full control of both stereo- and regiochemistry still remains a difficult and largely unsolved synthetic task. In principle, various selective carbometalation, halometalation, and related heteroatom−metal bond addition reactions of unsymmetrically disubstituted alkynes would provide potentially selective routes to tetrasubstituted alkenes. (*E*)- and (*Z*)-γ-Bisabolenes (**27**) have provided a pair of challenging targets containing an exocyclic tetrasubstituted C=C bond. In their earlier syntheses,[34] the *E* isomer was prepared in 99.6% stereoselectivity, but the stereoselectivity in the synthesis of *Z* isomer was only 83%. On the other hand, application of the Cu-catalyzed *anti*-allylmagnesation (eq 7 of Scheme 3) permitted highly selective syntheses of both isomers via acyclic tetrasubstituted alkene intermediates[35] (Scheme 9).

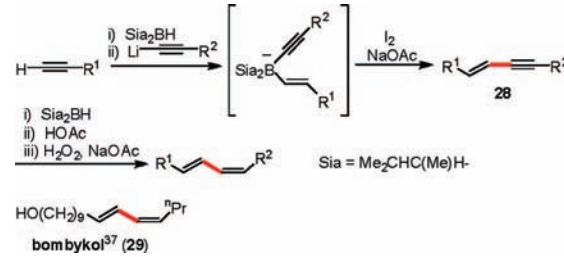
4. Stereo- and Regioselective Synthesis of Conjugated Dienes and Oligoenes

The number of stereo- and regiochemically discrete structural types for conjugated dienes is substantially larger than that for monoenes. Even if we limit our considerations only to those conjugated dienes in which each of the two alkene units is both stereo- and regiodefined, there are 3, 8, and 10 discrete structural types of di-, tri-, and tetrasubstituted dienes, respectively. Stereo- and regiodefined acyclic penta- and hexasubstituted conjugated dienes are still rather rare, and they are not considered here. In this section, some representative examples of the synthesis of di-, tri-, and tetrasubstituted acyclic and conjugated dienes are briefly discussed with emphasis on those present in natural products.

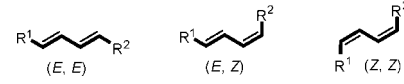
SCHEME 9



SCHEME 10

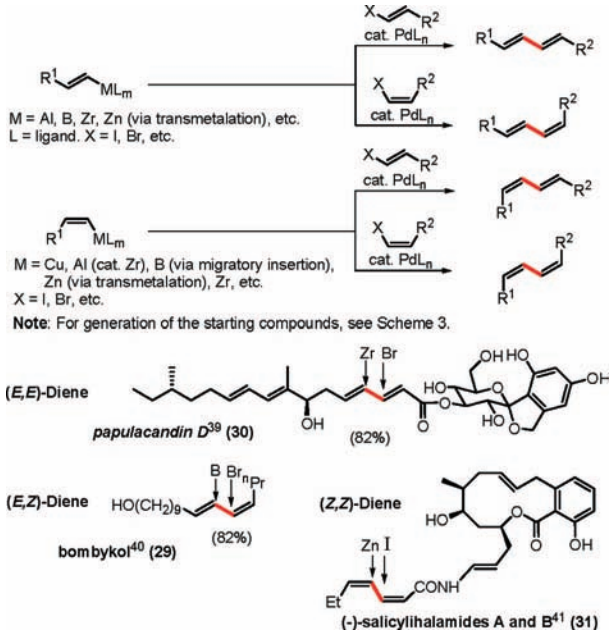


(a) 1,4-Disubstituted 1,3-Butadienes. Iterative hydroboration−protonolysis of unsymmetrically disubstituted 1,3-butadiynes producing (*Z*,*Z*)-1,3-butadienes in 1970 by Zweifel[36] is one of the earliest examples of fully selective syntheses of stereo- and regiodefined conjugated dienes. Inspired by this work, our group developed in 1973 fully selective methods for the syntheses of the (*E*,*Z*)- and (*E*,*E*)-isomers.[37,38]

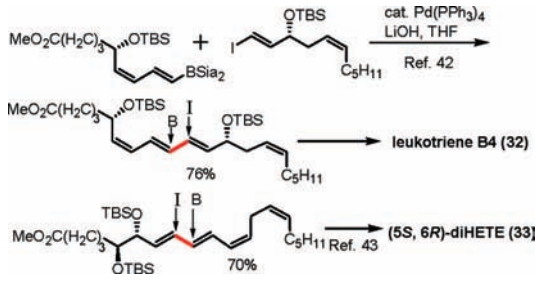


These uncatalyzed organoboron-based methods were soon supplanted by the Pd-catalyzed alkenyl−alkenyl coupling with alkenyl metals containing Al, Zr, and Zn discovered and developed by us during the 1976−1978 period.[6,25] Attempts to use alkenylborons were not successful, but a successful procedure was developed in 1979 by the group of A. Suzuki.[7] Although not widely used, the uncatalyzed alkenylboron route to (*E*,*Z*)-1,3-dienes via (*E*)-1,3-enynes (**28**) (Scheme 10) has been successfully applied to the efficient and selective syntheses of bombykol (**29**).[37] Even today, this must still be con-

SCHEME 11



SCHEME 12

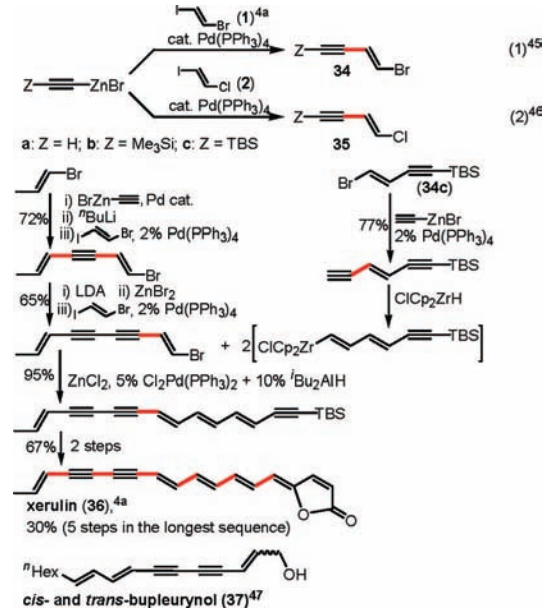


sidered as one of the most efficient and selective routes to 1,4-disubstituted (*E,Z*)-butadienes. Nevertheless, the efficient and selective Pd-catalyzed alkenyl−alkenyl coupling summarized in Scheme 11 is by far the most generally applicable and predictably satisfactory method for the synthesis of all three conceivable types of 1,4-disubstituted 1,3-dienes.

(b) Conjugated Oligoenes and Oligoenynes Containing 1,4-Disubstituted Butadiene Moieties. The Pd-catalyzed alkenyl−alkenyl coupling is readily adaptable to and generally satisfactory for the synthesis of conjugated trienes and higher oligoenes, as well as oligoenynes containing 1,4-disubstituted butadiene moieties. Particularly noteworthy is that many (*Z*)-alkene-containing oligoenes can be synthesized with little or no stereoisomerization, as exemplified in Scheme 12.

As the number of conjugated C=C bonds increases, efficiency of synthesis along with selectivity and other factors becomes increasingly important. In this regard, the use of modular synthons becomes increasingly attractive, and (*E*)-iodobromoethene (**1**)[4a] and (*E*)-iodochloroethene (**2**),[4b] as well as their monoethynylated derivatives, (*E*)-1-bromo-1,3-

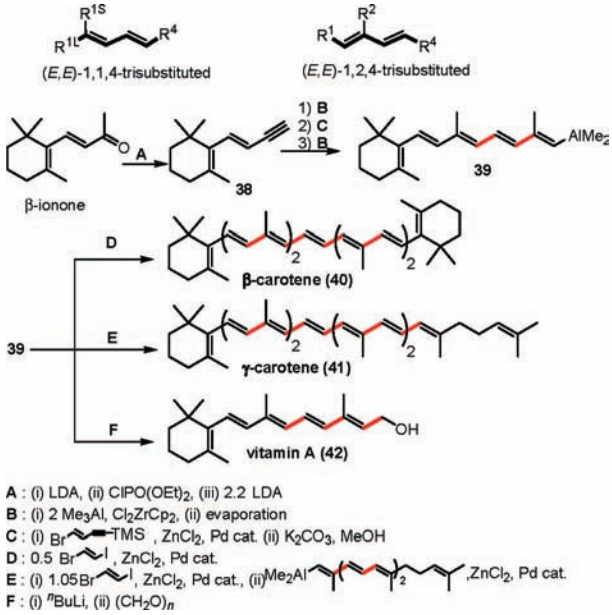
SCHEME 13



butenyne (**34a**)[4a,45] and (*E*)-1-chloro-1,3-butenyne (**35a**)[46] and their silylated derivatives, have been developed as "modular" synthons (Scheme 13). Two-carbon synthons **1** and **2** react well with alkynylzincs, but not under Sonogashira conditions, to give monoalkynylated derivatives, such as **34a** and **35a**, but the reactions of **1** and **2** with alkenyl metals are much less favorable and prone to undesirable side reactions.[6a] But a satisfactory procedure involving the use of 1% of Cl_2Pd(DPEphos), 2% of tris(2-furyl)phosphine, and 2% of $^iBu_2AlH$ as catalysts was developed.[44] Although alkenyl zincs react well with **1**, the corresponding reactions of alkenyl metals of Al or Zr must be cocatalyzed with $InCl_3$ (0.1−0.33 equiv), which was superior to Zn salts as a cocatalyst[44] for this reaction. For these reasons, it is advisable to convert **1** and **2** into **34**[45] and **35**,[46] respectively, and use them as four-carbon synthons. With the incorporation of an alkynyl group, **34** and **35** have proved to be particularly useful synthons for the synthesis of oligoenynes. Highly efficient syntheses of xerulin (**36**)[4a] and bupleurynol (**37**)[47] demonstrate their synthetic utilities (Scheme 13).

Despite its wide applicability, high efficiency, and high stereoselectivity, the Pd-catalyzed alkenylation in the syntheses of dienes, oligoenes, and oligoynes, must still be complemented by other alkenylation reactions, such as the Heck alkenylation,[5] and various carbonyl olefination reactions.[1,2] Efficient and selective construction of the scyphostatin side chain from the C7−C16 chiral isoalkyl alcohol intermediate prepared as shown in Scheme 5 may not be conveniently achieved via Pd-catalyzed alkenylation. In this case, the HWE olefination using (*E,E*)-$(EtO)_2P(O)CH_2(CH{=}CH)_2CO_2Et$ preparable

SCHEME 14

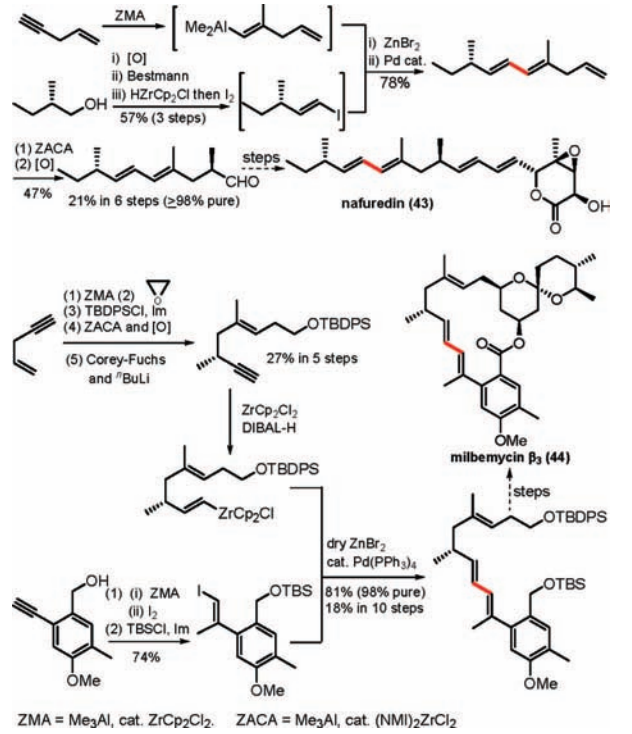


from ethyl 4-bromocrotonate in four steps is an attractive alternative.[26,27] As a rule of thumb, it may tentatively be stated that allylically methyl or other carbon group branched alkenes are more readily prepared via carbonyl olefination, while their homoallylic analogues are more readily accessible via Pd-catalyzed alkenylation. In cases where both types of proximally chiral alkenyl groups are present, both carbonyl olefination and Pd-catalyzed alkenylation are required for their optimal construction.

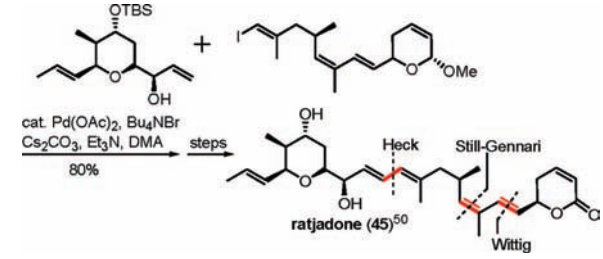
(c) Conjugated Dienes, Oligoenes, and Oligoenynes Containing Tri- and Tetrasubstituted Butadiene Moieties. In this section, only a limited number of representative syntheses of tri- and tetrasubstituted dienes, oligoenes, and oligoenynes will be discussed.

(i) 1,1,4- and 1,2,4-Trisubstituted 1,3-Butadienes. Two most widely encountered and important structural types among the eight possible ones for the indicated classes of dienes are the *trans*,*trans*-butadiene derivatives shown in Scheme 14. In cases where the branching R^{1s} or R^2 group is Me, they are efficiently and selectively obtainable via Zr-catalyzed methylalumination (ZMA), as shown in Schemes 14−16. Those reactions shown in eqs 6−9 of Scheme 3 and all of Scheme 4 should provide useful terminal synthons or alkenylation-to-olefination crossover synthons. It should also be remembered that certain carbonyl olefination reactions including the Corey−Fuchs[48] and other related reactions have served as useful olefination-to-alkenylation crossover reactions in the alkenylation−olefination synergy.

SCHEME 15



SCHEME 16



Carotenoids and retinoids represent some of the most important classes of oligoenes containing (*E*,*E*)-1,2,4-trisubstituted 1,3-butadiene moieties. In cases where they can be prepared from inexpensive β-ionone, it is almost mandatory to use it as the starting compound. And yet, its carbonyl olefination to give trisubstituted alkenes has not been very stereoselective. Moreover, either *Z*-to-*E* isomerization or stereoisomeric purification by isomer fractionation of these trisubstituted alkenes has generally been rather difficult. On the other hand, highly stereoselective (≥98−99%) conversion of β-ionone to β-carotene (**40**), γ-carotene (**41**), and vitamin A (**42**) has been achieved, as shown in Scheme 14.[45] Both 1,2-iodobromoethene (**1**) and 1-bromo-4-trimethylsilyl-1,3-butenyne (**34b**) play crucial roles in these processes. A more recent development of 1,4-pentenyne as a five-carbon modular synthon for the synthesis of various oligoenes containing a homoallylic asymmetric carbon center, such as nafuredin (**43**) and milbemycin β_3 (**44**) (Scheme 15)[49] is also noteworthy.

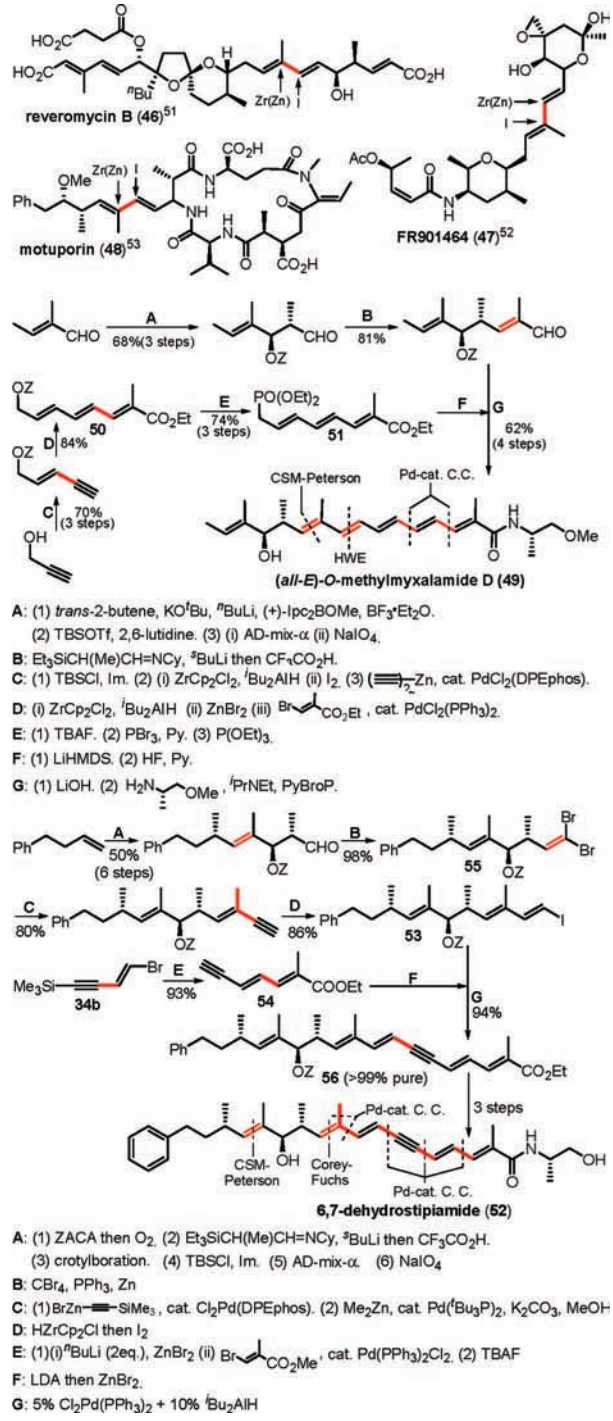
Despite some known limitations and difficulties associated with the Heck reaction, it was recently reported by Kalesse[50] that (*E*,*E*)-1,1,4-trisubstituted-1,3-dienes could be obtained in high yield and in highly stereoselective manner, as exemplified by the synthesis of ratjadone (Scheme 16). It appears very desirable to further delineate the scope and limitations of the Heck reaction.

Construction of (*E*,*E*)-1,2,4-trisubstituted 1,3-dienes may have been most commonly achieved by Pd- and Zn-cocatalyzed alkenylation with (*E*)-2-alkenylzirconium derivatives generated by regioselective hydrozirconation, as exemplified by the synthesis of reveromycin B (**46**),[51] FR901464 (**47**),[52] and motuporin (**48**)[53] (Scheme 17). For generation of $HZrCp_2Cl$, a recently developed procedure involving slow addition of 1 equiv of $^iBu_2AlH$ to $ZrCp_2Cl_2$ in THF[15b] is highly convenient. This protocol can nicely accommodate proximal chiral groups via the T-to-H construction of the (*E*)-2-alkenylzirconium reagents. However, conversion of the aldehyde precursors to the corresponding 2-alkynes typically requires three steps (Scheme 5). In cases where α-chiral aldehydes are used as the starting compound, the use of the CSM modification of the Peterson olefination followed by the HWE reaction (Scheme 17) provides a highly satisfactory synthetic protocol as exemplified in a recent synthesis of (*all-E*)-*O*-methylmyxalamide D (**49**)[54] and 6,7-dehydrostipiamide (**52**).[55] Even so, the synthesis of the requisite oligoene and oligoenyne intermediates **50**, **51**, **53**, and **54** was achieved via Pd-catalyzed cross-coupling.

Interesting and potentially important is that the stepwise double substitution of 1,1-dibromoalkene **55** first with (*all-E*)-BrCH=CHC≡CCH=CHCH=C(Me)CO_2Et obtained from **54** in 82% yield in one step[56] and then with Me_2Zn with Cl_2Pd(DPEphos) as a catalyst gave the 10*Z* isomer of **56**, which amounted to the discovery of inversion of configuration in the Pd-catalyzed cross-coupling of 2-bromo-1,3-dienes.[56] Significantly, this discovery was soon followed by another finding that the use of bulky alkylphosphines or *N*-heterocyclic carbenes can almost fully suppress the configurational isomerization.[57]

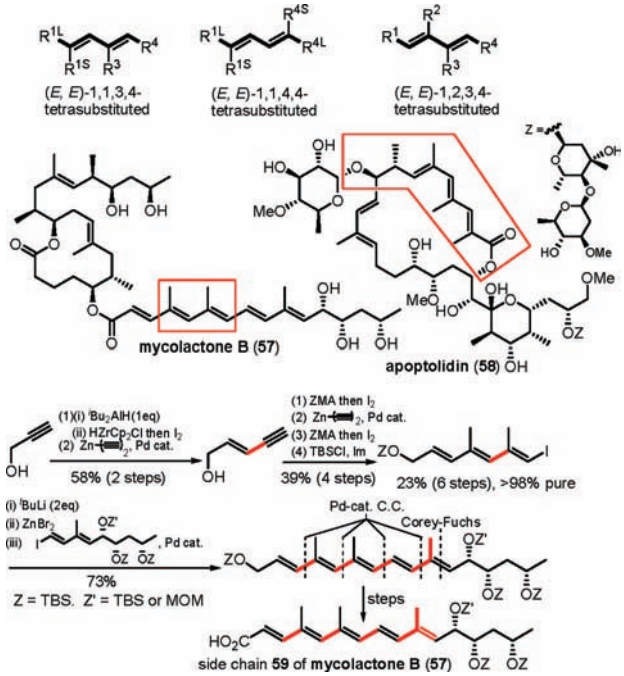
Although much rarer, some naturally occurring *trans*,*trans*-tetrasubstituted 1,3-dienes, mostly *E*,*E* isomers, and related oligoenes are also known,[58] as exemplified by mycolactone B (**57**)[59,60] and apoptolidin (**58**)[61] (Scheme 18). Whereas the C8−C16 fragment of the triprotected mycolactone B side chain **59** containing an allylic asymmetric carbon center was prepared in the T-to-H manner via the stepwise double substitution process with >98% retention[60b] briefly discussed herein, the C1−C7 framework was selectively constructed in the H-to-T manner via iterative ZMA Pd-catalyzed alkenylation.[60] No isomer formation was detected in this synthesis. A convergent assembly was then achieved via Pd-catalyzed alkenyl−alkenyl coupling in 73% yield.

SCHEME 17



(ii) (*Z*)-Trisubstituted Alkene-Containing Tri- and Tetrasubstituted 1,3-Butadienes and Oligoenes Containing Such 1,3-Butadienes. Although far less abundantly occurring, those tri- and tetrasubstituted 1, 3-butadienes that contain one or two (*Z*)-trisubstituted alkenyl groups can exist as configurationally stable species. The significance of the

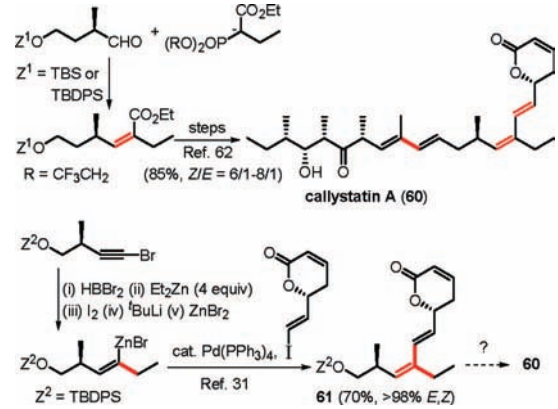
SCHEME 18



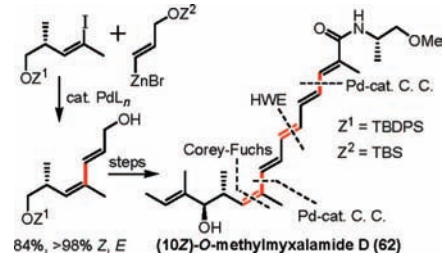
Still−Gennari modification[2b] of the HWE reaction that can, in some cases, serve as a highly (*Z*)-selective carbonyl olefination reaction is well-recognized. Additionally, several promising routes to (*Z*)-trisubstituted alkenyl metals and alkenyl electrophiles have been developed for use in the Pd-catalyzed alkenylation. Only a very limited number of prototypical examples of the syntheses of tri- and tetrasubstituted conjugated dienes and related oligoenes containing (*Z*)-trisubstituted alkenes are discussed below.

Ratjadone[50] (45), Callystatin A[62,63] (60) and (10*Z*)-*O*-Methylmyxalamide D[54] (62). These compounds contain both (*E*,*E*)-1,1,4- or 1,2,4-trisubstituted and (*Z*,*E*)-1,2,4-trisubstituted 1,3-diene moieties. In Kalesse's synthesis of ratjadone (**45**),[50] the (*Z*,*E*)-diene fragment was synthesized by using two carbonyl olefination processes, namely, the Still−Gennari modification of the HWE reaction and the Wittig reaction (Scheme 16). Although the Still−Gennari reaction for the construction of the Et-containing alkene of callystatin A (**60**) is significantly less selective, the *Z*/*E* ratio being 6/1−8/1, it has been used in most of the close to 10 syntheses, of which only the first total synthesis by Kobayashi[62] is cited here. Less widely used but more highly (*Z*)-selective (>98−99%) syntheses of (*Z*)-trisubstituted alkenes shown in Schemes 6−8 are also readily applicable to the synthesis of callystatin A[31,63] (Scheme 19). In the first synthesis of (10*Z*)-*O*-methylmyxalamide D (**62**)[54] summarized in Scheme 20, the synthetic value of alkenylation−olefination synergy is vividly seen.

SCHEME 19



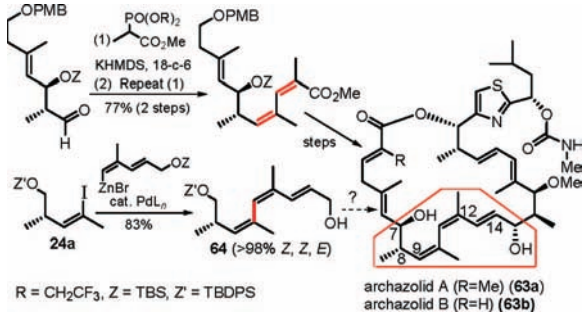
SCHEME 20



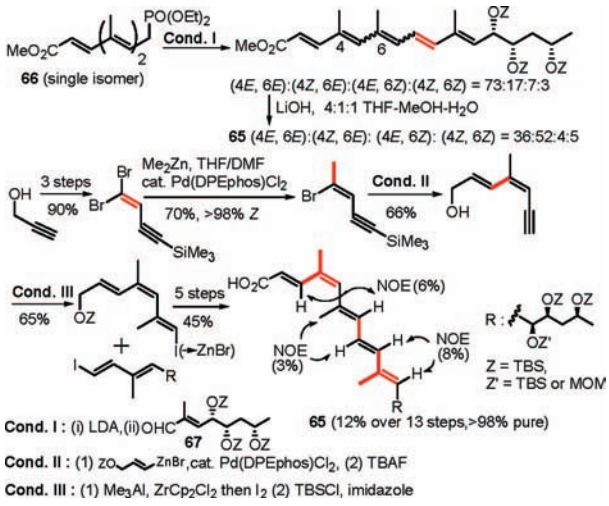
Archazolids A and B[64] (63a and 63b) and Mycolactone A[59,60] (57a). Archazolids (**63**)[64] possess a conjugated triene containing a (*Z*,*Z*)-1,1,3,4-tetrasubstituted-1,3-diene moiety, while the side chain of mycolactone A (**57a**)[59] is a pentaenoic acid containing a (*Z*,*E*)-1,1,3,4-tetrasubstituted-1,3-diene moiety. A highly efficient synthesis of the conjugated triene fragment of **63a** was achieved via a series of two Still−Gennari olefination reactions.[64a] In the synthesis of (−)-archazolid B, Trauner[64b] used a Cu-promoted *trans*-selective monomethylation of a 1,1-dibromoalkene to set up a (*Z*)-2-iodo-2-alkene. Its Pd-catalyzed cross-coupling with a (*Z*,*E*)-1-stanno-2-methyl-1,3-butadiene derivative provided, albeit in low yield, an advanced intermediate to be cyclized via ring-closing metathesis[3] to give, after deprotection, the target compound **63b**. Also very promising is a strictly stereocontrolled Pd-catalyzed alkenylation route[31] (Scheme 21), which involves a Pd-catalyzed alkenylation of **24a**. The triene product **64** was prepared in >98% stereoselectivity. The requisite dienylzinc reagent was prepared via Cu-catalyzed methylmagnesation[22] shown in eq 7 of Scheme 3.

Synthesis of the tris-TBS-protected side chain **65** of mycolactone A (**57a**) by Kishi[59] using the HWE reaction as the key reaction revealed a highly complex stereoisomerism associated with **65**, as indicated at the top of Scheme 22. In marked contrast, the Pd-catalyzed alkenylation provided a strictly

SCHEME 21



SCHEME 22



(>98%) stereoselective route to the tris-TBS-protected side chain **65** of mycolactone A (**57a**)[60b] (Scheme 22).

5. Conclusions

The Pd-catalyzed cross-coupling with organometals containing Zn, Al, and Zr (Negishi coupling), as well as B (Suzuki coupling), provides a highly selective (≥98%) and widely applicable alkenylation route to stereo- and regiodefined alkenes. Although considerably more limited, the Heck reaction provides simpler routes in some cases. Various carbonyl olefination reactions, such as the HWE reaction, provide useful carbonyl olefination routes that are complementary and competitive with the Pd-catalyzed alkenylation. Thus, certain allylically chiral alkenes are most conventionally prepared by the carbonyl olefination (Schemes 5−8 and 15−22), while those with homoallylic chiral centers are efficiently prepared by Pd-catalyzed isoalkylation (Schemes 5−7). As the complexity of the target alkenes increases, synergistic use of various available methods becomes increasingly desirable. Typically, the Pd-catalyzed alkenylation−carbonyl olefination synergy provides widely satisfactory, efficient, and selective routes to various oligoenes (Schemes 16−22).

Support of this work by grants from the National Institutes of Health (Grant GM 36792) and the National Science Foundation (Grant CHE-0309613) is gratefully acknowledged. E.N. thanks his former co-workers whose names and contributions are referenced.

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FOOTNOTES

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