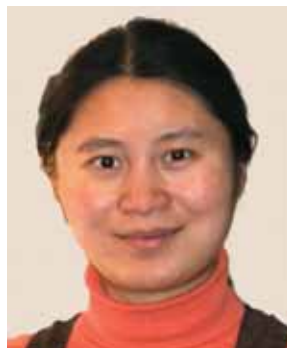


Palladium-Catalyzed Alkenylation by the Negishi Coupling



Professor Ei-ichi Negishi

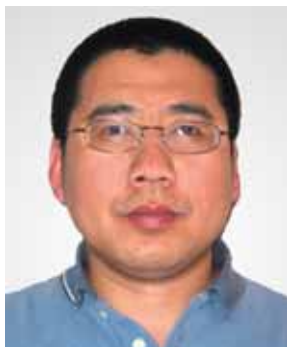


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1. Introduction

The palladium-catalyzed cross-coupling of an organometal (R^1M) with an organic electrophile (R^2X) has emerged over the past thirty years as one of the most general and selective methods for carbon–carbon-bond formation (eq 1). Currently, it appears to be generally superior to related methods involving the use of Ni, Cu, or Fe catalysts in its scope and stereo-, regio-, and chemoselectivities.¹ The R^1 group of R^1M can be aryl, alkenyl, alkynyl, allyl, benzyl, propargyl, alkyl, cyano, or enoxy; while the R^2 group of R^2X can be aryl, alkenyl, alkynyl, allyl, benzyl, propargyl, alkyl, or acyl. Use of other related carbon groups as R^1 and/or R^2 is not only conceivable, but also known in the literature. Even if only those nine types of organometals (R^1M) and eight types of organic electrophiles (R^2X) mentioned above are considered, their binary combinations lead to 72 different types of cross-coupling reactions, and most of these reactions have indeed been developed. Until recently, the use of alkyl electrophiles lacking proximal π bonds had been considered to be categorically very difficult, and the task of Pd-catalyzed alkylation had been achieved by using alkylmetals. The latter is still of much broader synthetic applicability. However, some recent developments suggest that this generalization may have to be significantly modified in the future, as discussed in Section 2.6. Another group of categorically difficult Pd-catalyzed cross-coupling reactions are those involving cross-coupling between allyl, benzyl, and/or propargyl groups.^{1a} In addition, a more promising, direct, and selective α alkenylation and α alkynylation of metal enolates^{1a,2–4} need to be further developed.

The Pd-catalyzed cross-coupling can be performed with organometals containing any of ten or more different metals including Zn, Al, or Zr (Negishi coupling),¹ B (Suzuki coupling),^{1,5,6} Sn (Stille coupling),^{1,7} as well as Li,⁸ Mg,^{9,10} In,¹¹ Si,^{1,12} Cu,¹³ and Mn.¹⁴ This review will briefly discuss the Pd-catalyzed alkenylation involving Zn-, Al-, or Zr-containing organometals and leading to the direct formation of a carbon–carbon single bond to alkenyl groups. Its application to the synthesis of alkenes of biological, medicinal, and materials science interest will also be briefly discussed. To indicate various types of cross-coupling, compound adjectives, such as alkenyl–aryl and aryl–alkenyl, are used. In these words, the first and second terms indicate the R^1 and R^2 groups of R^1M and R^2X , respectively. Recent advances in the development of (i) hydrometallation–cross-coupling and carbometallation–cross-coupling tandem processes, and (ii) the

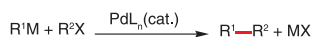
selective disubstitution of 1,1- and 1,2-dihaloalkenes will be emphasized. The Pd-catalyzed alkenylation via cross-coupling may be classified into 16 types. Most of these types and results that had been reported prior to 1998 have been comprehensively reviewed elsewhere.^{1a} It is worth mentioning, however, that two recent reviews of the Pd-catalyzed alkynylation^{1,15} contain many new examples of the Pd-catalyzed alkenyl–alkenyl coupling.

2. The Pd-Catalyzed Alkenylation with Zn, Al, and Zr Organometals

2.1. Early Findings

Between 1976 and 1978, Negishi's group published close to ten seminal papers on the Pd- or Ni-catalyzed cross-coupling,^{16–24} disclosing, for the first time, the following findings pertinent to this review.

- i. The Pd- or Ni-catalyzed reaction of alkenylalanes with aryl halides represents the first set of examples of the Pd- or Ni-catalyzed organoalane cross-coupling, and of the Pd- or Ni-catalyzed hydrometallation–cross-coupling tandem reaction.¹⁶
- ii. The alkenyl–alkenyl couplings of *cis*- or *trans*-1-iodo-1-hexene with *trans*-1-(diisobutylaluminum)-1-hexene represent the earliest examples of the Pd- or Ni-catalyzed “pair-selective” and stereoselective synthesis of conjugated dienes.¹⁷
- iii. These reactions also demonstrated, for the first time, some distinct advantages of Pd over Ni, e.g., superior stereospecificity: $\geq 98\%$ (Pd) vs $\geq 90\%$ (Ni).¹⁷
- iv. The reaction of (*E*)-3-bromo-2-methylacrylic ester provided the first example of generally favorable Pd-catalyzed conjugate substitution.^{17,18,22–25}
- v. The Pd-catalyzed reaction of alkynylzinc chlorides with alkenyl halides¹⁸—along with the related alkynyl–aryl,¹⁹ aryl–aryl,²⁰ and benzyl–aryl²⁰ coupling reactions—not only provided some of the earliest examples of the Pd-catalyzed cross-coupling of organozincs, but also indicated the superior reactivity of organozincs under the Pd-catalyzed cross-coupling conditions relative to the ten or so other types of organometals mentioned earlier.
- vi. Following the discovery of the Ni-catalyzed cross-coupling reaction of alkenylzirconiums with aryl halides in 1977,²¹ the Pd-catalyzed alkenyl–alkenyl coupling of alkenylzirconium derivatives with alkenyl halides was reported in 1978.²²
- vii. The first examples of the Pd-catalyzed carboalumination–cross-coupling tandem reaction were also reported in 1978.²³ The use of Zn salts, such as $ZnCl_2$ or $ZnBr_2$, as additives or cocatalysts in the coupling step of this tandem reaction was shown to be highly desirable or even essential to observing satisfactory results. This study demonstrated, for the first time, the concept of double metal catalysis and the favorable effects of additives on the Pd- or Ni-catalyzed cross-coupling.²³
- viii. The findings reported in references 16–23 established that the Pd- or Ni-catalyzed cross-coupling can be achieved with organometals containing various metal counterions other than Mg, which had previously been used almost exclusively. A systematic screening of metal counterions was conducted for the first time for the Pd-catalyzed reaction of alkynylmetals with *o*-tolyl iodide.^{24–26} This study indicated that, in addition to alkynylzincs, organometals containing B and Sn were superior reagents, and these were subsequently developed as the Suzuki^{1,5,6} and Stille^{1,7} coupling reactions, respectively. The reaction of *n*-PentC \equiv CB(*n*-Bu)₃Li with *o*-tolyl iodide, producing the desired *n*-PentC \equiv C(*o*-Tol) in



eq 1

92% yield, was the first example of the Pd-catalyzed cross-coupling of organoboron compounds. Further details of the early developments of the Negishi coupling and related cross-coupling reactions are discussed in the pertinent reviews.^{25,26}

2.2. Summary of Current Status

2.2.1. Metal Counteractions

The Pd-catalyzed cross-coupling has proved to be of wide scope with respect to metal counteractions.¹ In many less demanding cases, all or most of the ten or more metals that have been used as counteractions may work satisfactorily. In other more demanding cases, however, critical differences among them have been observed. It is therefore desirable to be familiar with the pros and cons of the various available counteractions. In view of the multimechanistic and multifaceted nature of the Pd-catalyzed cross-coupling, however, it is not practical to compare and rank them on one scale. From a practical viewpoint, synthetic chemists are generally seeking those methods and reactions that satisfy some or most, if not all, of the following criteria: (i) predictably general applicability, especially with respect to the R¹ and R² groups to be coupled, (ii) high product yield, (iii) high regio-, stereo-, and chemoselectivities minimizing the need for separation and purification, (iv) high efficiency including step-economy as well as operational simplicity and convenience, (v) low costs of reagents, catalysts, other materials, and of other aspects of operation, and (vi) high level of safety especially with regards to toxicity as well as explosion and fire hazards.

A priori, organometals containing highly electropositive metals, such as Li and Mg, which are normally considered to be “highly nucleophilic”, would be desirable from a reactivity point of view. Conversely, organometals containing highly electronegative metalloids, such as B and Si, might be expected to be of limited reactivity. Under conditions that are stoichiometric in Pd, highly electropositive metals, such as Li and Mg, are at least as reactive as Zn.²⁷ Under Pd-catalyzed conditions, however, the reactivity order of Zn > Mg >> Li has been observed more often than not.^{1,24,27,28} This unexpected order of reactivity has been tentatively interpreted in terms of catalyst poisoning by highly nucleophilic organometals containing Li and Mg. On the other hand, there have also been indications that Grignard reagents display a significantly higher catalytic reactivity than the corresponding organozincs in some cases, such as those involving organic chlorides.²⁹ Therefore, in cases where Grignard reagents and organolithiums are generated first, they should also be tested in the cross-coupling reaction before converting them into other organometals.

At the end of the nucleophilicity scale lie highly electronegative metals and metalloids, such as B and Si. Organoboranes, as opposed to borates, and organosilanes are as such of very low reactivities at best. In fact, silyl groups are often used as protecting groups. As noted in the first successful Pd-catalyzed organoboron cross-coupling^{24–26} vis-à-vis earlier failures with alkenylboranes,^{16,17} the reactivity of organoboranes can be substantially increased through ate complexation.^{1,5,6} Similar activations of organosilanes with fluorides have also made organosilanes useful in the Pd-catalyzed cross-coupling.¹² Generally speaking, however, it has become increasingly clear that Zn displays the highest reactivity under the Pd-catalyzed conditions, and that its catalytic reactivity is followed by those of several metals of intermediate electronegativity including Al,^{16,17,25} In,¹¹ Sn,^{30–32} Zr,³³ and Cu³⁴ (**Scheme 1**).^{1a} Thus, one can expect that high reactivity with respect to the desired cross-coupling—relative to other undesired processes including regio- and stereoisomerizations and catalyst poisoning—should lead to high product yields, a wider scope of cross-coupling,

higher selectivities, higher catalyst turnover numbers, and lower cost of operation.

The selection of metal counteractions, of course, involves some other factors, such as chemoselectivity, operational convenience including compatibility with water and air, economy, safety, and others. Some of these factors must undoubtedly be responsible for the current widespread use of B and Sn. For toxicity related reasons, however, the use of Sn might be projected to be increasingly limited. On the other hand, it appears that Si might be used more extensively in the future. Along a more scientific line, the facile and convenient preparation of stereo- and regio-defined alkenylmetals and the corresponding halides or related electrophiles is one of the most critical factors in selecting counteractions for the Pd-catalyzed alkenylation. Several metals and metalloids such as B, Al, In, Zr, Cu, Si, Sn, and Zn have been used for forming the first-generation alkenylmetals directly from alkynes, rendering these metals attractive counteractions in Pd-catalyzed alkenylations.^{5,6,34–47} On the other hand, alkenylmetals containing Li and Mg have been prepared mostly from alkenyl halides rather than alkynes. In many cases, the methods of converting alkynes to alkenylmetals are also applicable to the preparation of alkylmetals from alkenes.^{48–50} Various types of hydrometallation, carbometallation, and heterometallation including metallometallation have been employed for the Pd-catalyzed alkenylation often in conjunction with the use of Zn or In salts as cocatalysts.

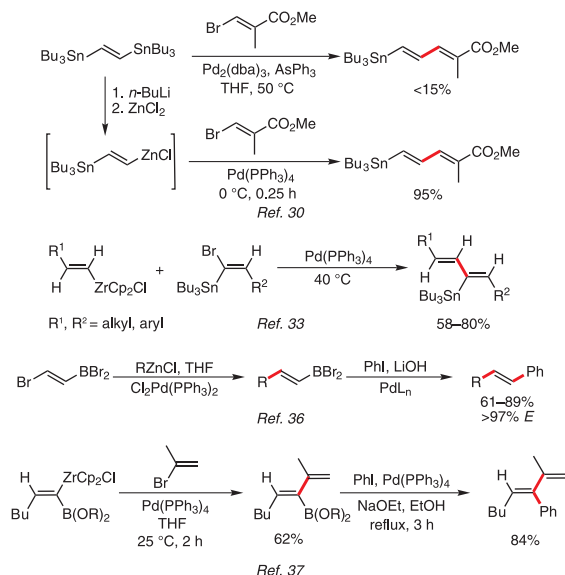
2.2.2. Leaving Groups

Other parameters influencing the Pd-catalyzed alkenylation reaction include the nature of the leaving group (X) in the electrophilic partner (R²X), the Pd catalyst, cocatalyst or other additive, and solvent. In cases where R²X represents alkenyl electrophiles, the X group is usually I, Br, Cl, or some oxygen-containing group, such as OTf and OPO(OR)₂. For a given R² group, the generally observed order of reactivity of halogens is I > Br > Cl. Unfortunately, the generally least expensive, and hence most desirable, Cl-containing electrophile is the least reactive. Therefore, a reasonable course of action might be to choose first the most reactive I- or Br-containing electrophile and see if the desired cross-coupling can be satisfactorily achieved. If the coupling reaction is thus achievable, one may then attempt to use the less expensive Cl or other leaving groups. In this context, a recent report of the reactions of aryl and alkenyl chlorides with aryl- and alkynylzinc chlorides in THF–NMP at 100 °C in the presence of 2 mol % of Pd[(*t*-Bu)₃P]₂ is noteworthy.^{51b}

2.2.3. Pd Catalysts, Cocatalysts or Other Additives, and Solvents

Three other chemical parameters are available for optimizing the reaction conditions: (i) phosphines and other ligands in the Pd catalysts, (ii) cocatalysts and other additives, and (iii) the solvents used. In recent years, some significant advances have been made in the first two categories, especially in ligands. These topics have very recently been discussed in some detail.^{1b} Ligands, additives, and solvents specifically utilized in the Pd-catalyzed alkenylation with Zn, Al, and Zr organometals are presented in **Figure 1**.^{51–60}

In summary, the selection of an optimal set of parameters for a given Pd-catalyzed cross-coupling is becoming increasingly more involved and at times confusing. Until recently, the combination indicated as *Procedure 1* (*Conventional Standard Conditions*) and employing PPh₃ as the ligand, had been most widely utilized (**Figure 2**). In many less demanding cases, it has worked satisfactorily, and it should still be one of the first-round options.



Scheme 1. The Higher Reactivities Displayed by Zn and Zr Relative to Other Metals in the Pd-Catalyzed Alkenylation.

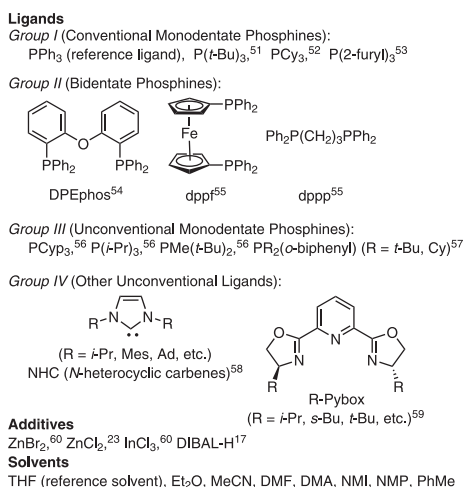


Figure 1. Ligands, Additives, and Solvents Commonly Used in the Pd-Catalyzed Alkenylation with Zn, Al, and Zr Organometals.

Procedure I (Conventional Standard Conditions):

Catalyst: 1–5 mol % of $\text{Pd}(\text{PPh}_3)_4$, or several variants of $\text{Pd}(\text{PPh}_3)_2\text{L}_n$ including $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ with or without DIBAL-H; $\text{Pd}_2(\text{dba})_3$ or $\text{Pd}(\text{dba})_2$; $\text{Cl}_2\text{Pd}(\text{MeCN})_2$; and Li_2PdCl_4 in the presence of PPh_3

Additive: ZnBr_2 or ZnCl_2 , as needed
Solvent: THF and/or DMF

Procedure II (Modern Standard Conditions):

Catalyst: $\text{Cl}_2\text{Pd}(\text{DPEphos})$, $\text{Cl}_2\text{Pd}(\text{dppf})$, or $\text{Cl}_2\text{Pd}(\text{dppp})$

Catalyst Loading: Initial screening at 1–5 mol % then consider $\leq 10^{-1}$ – 10^{-3} mol %

Additive: ZnBr_2 , ZnCl_2 , or InCl_3 , as needed
Solvent: THF and/or DMF

Figure 2. Conventional and Modern Standard Conditions for the Pd-Catalyzed Alkenylation with Zn, Al, and Zr Organometals.

On the other hand, it has become increasingly clear in recent years that some bidentate ligands, such as DPEphos⁵⁴ and dppf,⁵⁵ are very frequently superior to simple monodentate phosphines. In less demanding cases, their differences may not be readily noticeable or hardly significant, but in other more demanding cases, these differences become significant. *Procedure II (Modern Standard Conditions)*, employing bidentate ligands, should be considered as needed. Yet other procedures may be considered for solving even more difficult problems.

Even in cases where the differences among two or more procedures seem very minor at high catalyst loadings (1–5 mol %), they usually become more noticeable and significant at lower catalyst loadings. The catalyst loading level or catalyst turnover number (TON) is a potentially very significant issue in the practical application of the Pd-catalyzed cross-coupling. For example, even if a Pd catalyst costs \$10,000/mol, it would effectively cost a mere \$1–10/mol at a TON level of 10^3 – 10^4 . Since the overall cost of operation also depends on the costs of other reagents, the practical value of attaining extremely high TONs ($>10^6$) may be questioned. Nevertheless, the currently prevalent level of $\text{TON} \leq 10^2$ should be elevated to 10^3 – 10^5 in most cases. Recent studies indicate that the use of some chelating ligands, such as DPEphos and dppf, in conjunction with organometals containing Zn, B, and In, as well as Al–Zn and Zr–Zn combinations, can readily achieve $\text{TONs} > 10^4$.⁶¹

2.3. Alkenyl–Aryl, Aryl–Alkenyl, and Alkenyl–Alkenyl Coupling Reactions

2.3.1. Alkenyl–Aryl and Aryl–Alkenyl Couplings

Both of these reactions produce aryl–substituted alkenes or styrene derivatives. Both protocols involving the Negishi coupling are generally satisfactory, but the following considerations might be important in choosing one over the other: (i) In cases where the required alkenyl reagents are readily accessible via hydrometallation or carbometallation, first consideration should be given to generating the alkenylmetals in situ and carrying out the alkenyl–aryl cross-coupling in the same pot. (ii) On the other hand, many readily available alkenyl electrophiles, such as vinyl bromide, vinylidene chloride and bromide, and (*E*)-3-bromo-2-methylacrylic acid derivatives, favor the aryl–alkenyl coupling protocol. (iii) In some cases, alkenyl electrophiles are most readily accessible from the corresponding carbonyl compounds in the forms of alkenyl triflates or phosphates. In these cases, the aryl–alkenyl coupling protocol would be favored.

Since Al, Zr, and Zn offer a wide range of hydrometallation and carbometallation reactions, and since Zn along with Al–Zn and Zr–Zn combinations are among the most favorable metals in the Pd-catalyzed cross-coupling, both alkenyl–aryl and aryl–alkenyl Negishi cross-coupling reactions rank among the most satisfactory methods for forming the required C–C bonds. Although the number of applications to the synthesis of natural products is still rather limited, the examples reported thus far point to the potential utility and versatility of these reactions (Scheme 2).^{62–64} A recent application of the Pd-catalyzed reaction of an alkenylzirconium derivative with a bromoxazole to the synthesis of (–)-diazonamide A is especially noteworthy.⁶⁴ Other notable examples include the synthesis of alkenyl-substituted nucleosides⁶⁵ and a phorbaxazole A model.⁶⁶

2.3.2. Alkenyl–Alkenyl Coupling

Mainly during the past decade, the Pd-catalyzed alkenyl–alkenyl coupling involving Al and Zr has been extensively applied to the synthesis of conjugated dienes and oligoenes (Table 1).^{67–88} In many of these reactions, ZnBr_2 or ZnCl_2 was utilized as a promoter or cocatalyst. In some cases where the Al–Zn or Zr–

Zn combination proved to be less than satisfactory, the use of preformed alkenylzincs derived from the corresponding Li or Mg precursors was demonstrated to be generally superior to them. In some cases, however, a useful synergism was observed between Al or Zr and In, which rendered InCl_3 superior to ZnBr_2 or ZnCl_2 as a cocatalyst.⁶⁰ Overall, the Pd-catalyzed alkenyl–alkenyl coupling involving Al, Zr, and Zn represents one of the most generally applicable and satisfactory protocols for the synthesis of conjugated dienes and oligoenes. Nevertheless, it should not be overlooked that several other metals and metalloids including Mg, B, Sn, Si, and Cu have also been employed satisfactorily in many cases.^{1,5,6,7,9–13}

2.4. Alkynyl–Alkenyl and Alkenyl–Alkynyl Coupling Reactions

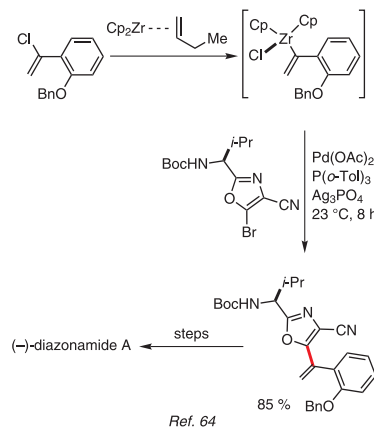
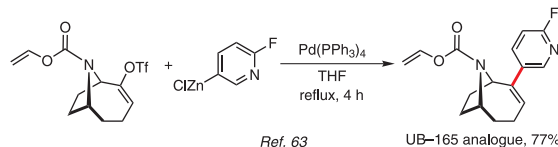
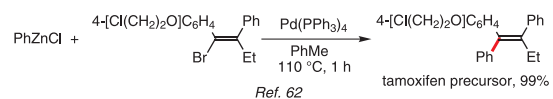
Although the Pd-catalyzed reaction of alkenylmetals containing Al or Zr with 1-iodo-1-hexyne in the presence of ZnCl_2 was reported as early as 1978,²³ the alkenyl–alkynyl coupling protocol has not been widely used for the synthesis of conjugated enynes. A notable exception is the synthesis of enediyne by the reaction of (*Z*)-1,2-bis(trimethylstannyl)ethylene with α,ω -diiododiyne.¹⁵ It is generally more convenient to use the alkynyl–alkenyl coupling protocol for the synthesis of conjugated enynes. This reaction utilizes alkynylzincs and provides one of the most satisfactory, generally applicable, and convenient routes to conjugated enynes (Table 2).^{80,85,87,89–94} In many less demanding cases, the Sonogashira coupling^{1a} has probably been most widely used. However, it has recently been shown that its scope is significantly more limited than the alkynylzinc protocol. Thus, for example, it has often been problematic to use alkynes containing electron-withdrawing groups, such as an ester, in the Sonogashira coupling.¹⁵ Direct synthesis of terminal alkynes without protection–deprotection by this reaction has not been practical either. As discussed earlier, it is also possible to use several other classes of alkynylmetals and metalloids containing Mg, B, Al, In, Si, Sn, and others. In cases where alkynylmetals containing Mg are satisfactory, their use should be considered before converting them into other alkynylmetals. Since alkynylmetals containing B, Al, In, Si, and Sn are prepared mainly from alkynylmetals containing Mg, Li, or some other alkali metal, and since they are generally less reactive than alkynylzincs, their use in place of Mg or Zn should be well justified.^{1a,15,95}

2.5. Benzylolation, Allylation, and Propargylation of Alkenylmetals and Alkenyl Electrophiles

In this section, six types of cross-coupling reactions are discussed. These lead to three types of products: allylarenes (or benzylalkenes), 1,4-dienes, and 1,4-enynes. Relevant findings reported prior to 1998 have been comprehensively reviewed.^{1a}

2.5.1. Alkenyl–Benzyl and Benzyl–Alkenyl Coupling Reactions for the Synthesis of Allylarenes

Benzylolation by the Pd-catalyzed cross-coupling is a generally favorable process that can be achieved satisfactorily via either alkenyl–benzyl or benzyl–alkenyl coupling. If alkenylmetals are more readily accessible than the corresponding halides, the alkenyl–benzyl coupling may be considered first. If, on the other hand, alkenyl electrophiles are more readily available than the corresponding alkenylmetals, the benzyl–alkenyl coupling should be considered first. It is also important to note that benzylzincs can usually be more cleanly and readily prepared than the corresponding Li- or Mg-containing benzylmetals by direct metallation of benzyl bromides or chlorides with Zn metal with minimum complications arising from homocoupling and other



Scheme 2. Synthesis of Natural Products and Related Compounds via the Negishi Alkenyl–Aryl or Aryl–Alkenyl Coupling.

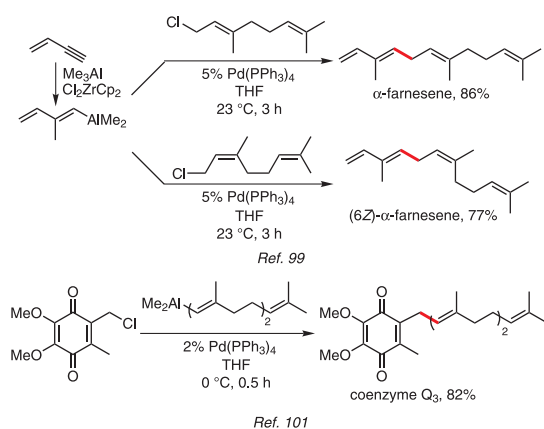
Table 1. The Pd-Catalyzed Alkenyl–Alkenyl Coupling with Al, Zr, and Zn Organometals in Natural Product Synthesis

Year	Natural Product or Related Compound	Major Author	Ref.
1987	Piperovatine	Crombie, L.	67
1991	Methyl dimorphecolate	Duffault, J. M.	68
1991	Vitamin A	Negishi, E.	69
1995	Papulacandin D	Barrett, A. G. M.	70
1996	Discodermolides	Schreiber, S. L.	71
1996	Zaragozic acid C	Paterson, I.	72
1996	Nakienone B	Negishi, E.	73a
1997	Nakienone A	Negishi, E.	73b
1997	Gadain and Savinin	Rossi, R.	74
1998	Okinonellin B	Romo, D.	75
1998	(±)-Carbacyclin	Negishi, E.	76
1999	Lissoclinolide	Negishi, E.	77
1999	Reveromycin B	Theodorakis, E. A.	78
2000	Pitiamide A	Wipf, P.	79
2000	Xerulin	Negishi, E.	80
2001	β- and γ-Carotenes	Negishi, E.	81
2001	Eunicenone A	Corey, E. J.	82
2001	FR901464 (antitumor antibiotic)	Jacobsen, E. N.	83
2002	Motuporin	Panek, J. S.	84
2004	cis- and trans-Bupleurnol	Organ, M. G.	85
2004	(–)-Callystatin A	Panek, J. S.	86
2004	6,7-Dehydrostipiamide	Negishi, E.	87
2004	Xerulinic acid	Brückner, R.	88

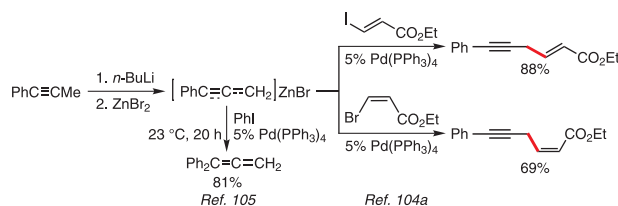
Table 2. The Pd-Catalyzed Coupling between Alkynylmetals Containing Zn or Mg and Alkenyl Electrophiles in Natural Product Synthesis

Year	Natural Product or Related Compound	Major Author	Ref.
1982	Octa-2,3-dien-5,7-diyne-1-ol ^a	Vermeer, P.	89
1988	Marasin	Boersma, J.	90
1997	Freelingyne	Negishi, E.	91
2000	Xerulin	Negishi, E.	80
2000	(±)-Harveynone	Negishi, E.	92
2000	(±)-Tricholomenyn A	Negishi, E.	92
2001	(-)-Salicylihalamides A and B	Fürstner, A.	93
2004	Ant venom	Organ, M. G.	94
2004	<i>cis</i> - and <i>trans</i> -Bupleurynol	Organ, M. G.	85
2004	6,7-Dehydrostipiamide	Negishi, E.	87

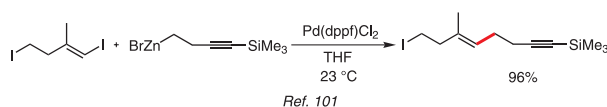
^a A metabolite of *Cortinellus berkeleyanus*.



Scheme 3. The Pd-Catalyzed Alkenyl–Allyl Coupling in the Synthesis of Natural Products.



Scheme 4. The Pd-Catalyzed Coupling of Allenylzinc Derivatives.



eq 2

side reactions.²⁰ This usually makes Zn the metal of choice in the Pd-catalyzed benzyl–alkenyl coupling.

2.5.2. Allyl–Alkenyl and Alkenyl–Allyl Coupling Reactions for the Synthesis of 1,4-Pentadienes

Despite the fact that the reaction of allyl(tributyl)stannane with bromobenzene in the presence of Pd(PPh₃)₄, reported in 1977, is probably the first example of Pd-catalyzed allylation of organic halides,⁹⁶ the allyl–alkenyl coupling is generally to be avoided in favor of the alkenyl–allyl coupling for a couple of reasons. Firstly, alkylmetals are generally prepared from the corresponding allyl halides. Their preparation with retention of regio- and stereochemistry is frequently quite challenging, generally more challenging than the preparation of the corresponding electrophiles. Secondly, allylmetals with a carbon–carbon double bond in the β,γ position tend to act as catalyst poisons more readily than benzylmetals. In this regard, allylmetals of low intrinsic nucleophilicity containing Sn and Si may be promising in the absence of other difficulties. This point largely remains to be experimentally established, however.

On the other hand, the Pd-catalyzed alkenyl–allyl coupling reactions of Zn, Al, and Zr alkenylmetals are generally favorable processes, even though unwanted allyl rearrangement accompanied by stereoisomerization can be a usually minor but potentially serious side reaction in cases where allyl groups are γ-mono- or β,γ-disubstituted. Allylic electrophiles are often so reactive toward Pd that allylic chlorides as well as a wide variety of oxygenated allyl derivatives, such as acetates, carbonates, phosphates, and even silyl ethers, are sufficiently reactive in this reaction. γ,γ-Disubstituted allyl derivatives can often be used with little or no sign of regio- and stereoisomerization. In marked contrast with the Tsuji–Trost allylation,⁹⁷ the Pd-catalyzed alkenyl–allyl coupling reactions proceed with clean stereoinversion at the allylic carbon center.⁹⁸

The number of natural products synthesized by the Pd-catalyzed alkenyl–allyl coupling is still relatively small. Nonetheless, strictly regio- and stereospecific syntheses of α-farnesene and its 6Z isomer,⁹⁹ (+)-hennoxazole A,¹⁰⁰ as well as a series of coenzyme Q's and menaquinones,¹⁰¹ persuasively point to its synthetic potential (Scheme 3). Both Pd and Ni complexes are highly satisfactory for catalyzing the alkenyl–benzyl and alkenyl–allyl coupling reactions.^{99,101–103}

2.5.3. Pd-Catalyzed Allenylation and Propargylation

The Pd-catalyzed reactions of various types of organometals containing aryl, alkenyl, alkynyl, allenyl, and alkyl groups with either propargyl or allenyl electrophiles give predominantly or exclusively the corresponding allenes rather than alkynes.^{1a} Generally, zinc appears to be the most satisfactory counteraction among several others including Mg, Cu, Ag, B, Al, and Sn.^{1a}

The Pd-catalyzed reaction of propargylmetals or allenylmetals is less predictable than the corresponding reaction of propargyl or allenyl electrophiles. Both 1,4-enynes and enallenes or arylallenes have been obtained, depending on the reactant structures and reaction conditions (Scheme 4).^{104,105}

2.6. Alkyl–Alkenyl and Alkenyl–Alkyl Coupling Reactions

Alkyl halides and related electrophiles are substantially less reactive toward Pd than unsaturated organic electrophiles including those containing aryl, alkenyl, alkynyl, acyl as well as allyl, benzyl, and propargyl groups. The lower reactivity of alkyl halides toward Pd has been explained in terms of the lack of a proximal π bond. A difference in reactivity of at least a 100-fold between alkenyl

and alkyl iodides has been observed (eq 2).¹⁰¹ Mainly for this reason, Pd-catalyzed alkylation of alkenyl derivatives has been achieved mostly via the alkyl–alkenyl coupling. However, alkyl halides are not inert towards Pd. For example, the use of highly nucleophilic Pd complexes containing bulky trialkylphosphines, such as PCyp₃ (Cyp = cyclopentyl) and PCy₃ (Cy = cyclohexyl), has permitted the alkenyl–alkyl coupling between alkenylzinc derivatives and alkyl iodides, bromides, and tosylates.⁵⁶ Also noteworthy is the reaction of alkenylzirconium derivatives with alkyl bromides in the presence of 2.5 mol % of Pd(acac)₂ and LiBr (2 equiv) in THF–NMP.¹⁰⁶

Despite recent promising developments such as those mentioned above, the Pd-catalyzed alkylation of alkenyl derivatives is still achieved mostly by the alkyl–alkenyl coupling protocol. In this regard, alkylzincs are generally superior to the other alkylmetals that have been examined to date, although alkylborons¹⁰⁷ and alkylmagnesiums¹⁰⁸ are satisfactory in many cases. In some reactions with alkenyl chlorides, Mg is even distinctly superior to Zn (eq 3).²⁹ Another noteworthy recent development is that alkylalanes generated in situ via Zr-catalyzed asymmetric carboalumination of alkenes can now be vinylated with vinyl bromide under the Zn–Pd double metal-catalyzed conditions in ca. 70% overall yields in one pot.¹⁰⁹ This reaction will be further discussed in Section 3.1. A similar hydrozirconation–cross-coupling tandem process is also promising.¹¹⁰

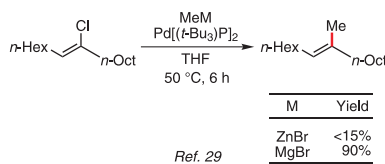
One should bear in mind that, in the Pd-catalyzed alkylation with alkylzincs or perhaps organozincs in general, the precise composition of alkylzincs, which significantly depends on the methods of their generation, affects the course of the subsequent cross-coupling process. One important determining factor is the alkyl/Zn/Li (or Mg) ratio. In a synthesis of (–)-discodermolide, it was shown to be desirable to add 3 equiv of *t*-BuLi to an alkyl iodide premixed with ZnCl₂ (Scheme 5).¹¹¹

One potentially attractive recent development is a Pd-catalyzed asymmetric hydroboration–transmetalation (B→Zn)–alkenylation process producing chiral alkenes of 52–83% ee's.¹¹² If both the enantiomeric purity and the modest yields of 35–41% can be improved, it would prove to be a useful asymmetric synthetic tool. Presumably, the chiral borane intermediates are not sufficiently reactive in the desired Pd-catalyzed alkenylation, although no mention was made to this effect in the paper. The corresponding Pd-catalyzed acylation led to similar yields and stereoselectivities. These results, taken together with a previously developed Pd- or Ni-catalyzed vinylation of chiral benzylic secondary alkylmetals containing Mg or Zn,^{1a} suggest that the development of a highly satisfactory and widely applicable Pd- or Ni-catalyzed asymmetric alkyl–alkenyl coupling might be imminent. A large number of natural products and related compounds have been synthesized by using the Pd-catalyzed alkenylation of alkylzinc derivatives (Table 3).^{49,86,101,109,111,113–135}

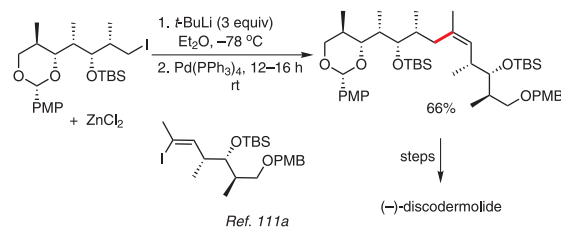
2.7. Acylation and Cyanation of Alkenyl Derivatives

2.7.1. Acylation of Alkenylmetals

The Pd-catalyzed reaction of a wide variety of organozincs with acyl chlorides¹³⁶ is one of the most generally applicable methods of acylation of organometals for the synthesis of ketones. Organozincs containing alkyl, aryl, alkenyl, and alkynyl groups have been successfully used. Particularly noteworthy are those cases where alkenyl- and alkynylzincs are utilized. α,β -Unsaturated ketones obtained as the products can, in principle, undergo competitive conjugate addition, as has been observed with organocoppers. However, this has not been a serious side reaction in the Pd-catalyzed acylation of alkenylzincs (eq 4).¹³⁶



eq 3



Scheme 5. The Pd-Catalyzed Alkyl–Alkenyl Coupling with an Alkylzinc in a Total Synthesis of (–)-Discodermolide.

Table 3. Alkenylation of Alkylzinc Derivatives in the Synthesis of Natural Products and Related Compounds

Year	Natural Product	Major Author	Ref.
1980	Dendrolasin	Negishi, E.	113
1980	Mokupalide	Negishi, E.	113
1980	(2 <i>E</i> ,6 <i>E</i>)-Farnesol	Negishi, E.	114
1987	(+)-Casbene	McMurry, J. E.	115
1989	(±)-Ageline A	Tokoroyama, T.	116
1989	Yellow scale pheromone	Millar, J. G.	117
1995	(–)-Discodermolide	Smith, A. B., III	111
1998	(+)-Amphidinolide J	Williams, D. R.	118
1999	Brevetoxin A	Nicolaou, K. C.	119
1999	(–)-Epothilone B	Schinzer, D.	120
1999	(+)-Pumiliotoxins A and B	Kibayashi, C.	121
2001	(<i>E</i>)- and (<i>Z</i>)- γ -Bisabolenes	Negishi, E.	49
2001	(–)-4a,5-Dihydrostreptazolin	Cossy, J.	122
2001	Mycolactones A and B	Kishi, Y.	123
2002	Coenzymes Q ₃ and Q ₁₀	Negishi, E.	101
2002	<i>trans</i> -Epothilone A	Altmann, K. H.	124
2002	(2 <i>E</i> ,6 <i>Z</i>), (2 <i>Z</i> ,6 <i>Z</i>), and (2 <i>Z</i> ,6 <i>E</i>)-Farnesols	Negishi, E.	101
2002	(2 <i>E</i> ,6 <i>Z</i> ,10 <i>E</i>)-Geranylgeraniol	Negishi, E.	101
2002	Menaquinone-3	Negishi, E.	101
2002	Oleandolide	Panek, J. S.	125
2002	Sphingofungin F	Ham, W.-H.	126
2002	Ionomycin	Lautens, M.	127
2003	Borrelinidin	Morken, J. P.	128
2003	Delactonmycin	Pilli, R. A.	129
2004	(–)-Callystatin A	Panek, J. S.	86
2004	Capensifuranone	Williams, D. R.	130
2004	(+)-Murisolin	Curran, D. P.	131
2004	Scyphostatin side chain	Negishi, E.	132
2004	Scyphostatin	Katoh, T.	133
2004	Siphonarienal	Negishi, E.	134
2004	Siphonarienolone	Negishi, E.	134
2004	Siphonarienone	Negishi, E.	134
2005	Ionomycin (a key intermediate of)	Negishi, E.	109
2005	Borrelinidin (a key intermediate of)	Negishi, E.	109
2005	Preen gland wax of graylag goose <i>Anser anser</i>	Negishi, E.	135

Although the Pd-catalyzed acylation of organozincs has been applied to the synthesis of several natural products, none involves a Pd-catalyzed alkenylation. A few interesting variants of the Pd-catalyzed acylation of organozincs have also been developed. In one of them, thiol esters are employed in place of acyl chlorides.¹³⁷ This reaction has been applied to the synthesis of at least one α,β -unsaturated enone, 1-(4-methoxyphenyl)-4-nonen-3-one, in 79% yield.^{137b} However, it is not readily apparent what advantage this reaction offers over the corresponding reaction with the acid chloride, from which the required thiol ester is prepared.

A few other more recent variations on the Pd-catalyzed acylation of organozincs include the Pd- or Ni-catalyzed reactions of organozincs with carboxylic anhydrides^{138,139a-c} and acyl fluorides.^{139d} In one procedure, carboxylic anhydrides are generated in situ from alkali metal carboxylates and ClCO_2Et .¹³⁸ Desymmetrization of symmetrical anhydrides under the influence of a chiral ligand appears to be promising. However, no examples are known in which alkenylzincs were used.

2.7.2. Cyanation of Alkenyl Electrophiles

The cyanation of alkyl halides with alkali metal cyanides and that of aryl halides with a stoichiometric amount of CuCN , i.e., the Rosenmund–Von Braun reaction, represent classic C–C bond-forming reactions. Their transition-metal-catalyzed counterpart was first reported by Takagi.^{140a} Under modified conditions, the reaction has also been applied to the cyanation of alkenyl electrophiles.^{141,142} Over the past decade or so, the use of other metal counterions and other reaction parameters has made the Pd-catalyzed cyanation more widely applicable. In particular, aryl bromides and even chlorides can now be satisfactorily cyanated with $\text{Zn}(\text{CN})_2$ in DMF or DMA in the presence of Pd catalysts containing PPh_3 , dppf , or other phosphines (eq 5).^{1a,143,144} However, despite extensive recent developmental work, little, if any, has been published on the cyanation of alkenyl electrophiles with $\text{Zn}(\text{CN})_2$.

2.8. α Alkenylation of Metal Enolates and α -Halo- α,β -unsaturated Carbonyl Compounds

The alkenylation, arylation, and alkynylation of α -halo- and β -halo- α,β -unsaturated carbonyl compounds are highly desirable synthetic operations.¹⁴⁵ The coupling with β -halo- α,β -unsaturated carbonyl compounds is a fundamentally very favorable process and has been termed *conjugate substitution*. Its Pd-catalyzed version, reported first in 1976,¹⁷ has since been extensively developed and applied to the synthesis of natural products and other organic compounds.^{1a} On the other hand, the corresponding reaction of α -halo- α,β -unsaturated carbonyl compounds has proved to be much more demanding.^{145b} Since the classical method of α substitution of carbonyl compounds by C–C-bond-forming reactions of enolates had until recently been practically limited to α substitution with alkyl groups, it was very desirable to overcome this critical limitation. Fortunately, all three classes of unsaturated carbon atom (alkenes, alkynes, and arenes) can be accommodated, in principle, by various protocols of Pd- or Ni-catalyzed α substitution of carbonyl compounds. One of the two most widely investigated protocols is the direct α substitution of metal enolates catalyzed by Pd or Ni complexes (Pd- or Ni-catalyzed *direct α substitution of metal enolates*).^{1a} This is clearly one of the most straightforward, efficient, and desirable approaches. In many demanding and delicate cases, however, this approach frequently suffers from difficulties associated with several aspects of the reaction most notably regioselectivity. To cope with difficulties pertaining to regiochemical control, an alternate approach involving Pd- or Ni-catalyzed α substitution of α,β -unsaturated carbonyl compounds

and related derivatives (Pd- or Ni-catalyzed *indirect α substitution via α substitution of α -halo- α,β -unsaturated carbonyl compounds*) has been developed.^{1a,145b} The relationship between these two methods is shown in **Scheme 6**.¹⁴⁶ Since α,β -unsaturated carbonyl compounds often serve as precursors to regiodefined enolates, their use as the starting carbonyl compounds in the latter approach is readily justified. Their α halogenation amounts to an additional step in comparison with the direct α substitution of regiodefined enolates derived from α,β -unsaturated enones. In many cases, however, the need for this extra step may be more than justified by (i) being able to strictly control the regiochemistry of the α substitution, and (ii) generally more favorable C–C-bond formation through the use of α -halo- α,β -unsaturated carbonyl compounds than by direct α substitution of enolates. Furthermore, in cases where α -substituted α,β -unsaturated carbonyl compounds are the desired final products, the latter protocol with α -halo- α,β -unsaturated carbonyl compounds should prove to be more advantageous than the α substitution of enolates. Although different, a related Pd-catalyzed α alkenylation of α -hetero-substituted β,γ -unsaturated carbonyl compounds is also noteworthy (**Scheme 7**).¹⁴⁷

Both types of α substitution reactions reported before 2000 have been systematically and comprehensively discussed.^{1a} Some of the more recent examples of the application to natural product synthesis^{74,92,148,149} of the Pd-catalyzed α substitution of α -halo- α,β -unsaturated carbonyl compounds with alkenyl- and alkynylzincs, are shown in **Scheme 8**.

3. Special Topics of the Pd-Catalyzed Alkenylation

3.1. Pd-Catalyzed Hydrometallation–Cross-Coupling and Carbometallation–Cross-Coupling Tandem Reactions

The hydrometallation–cross-coupling and carbometallation–cross-coupling tandem reactions, with or without the use of ZnBr_2 or ZnCl_2 as a cocatalyst,^{16,17,21–24} have played a major role in the Pd-catalyzed alkenylation involving Zn, Al, and Zr as well as B, Sn, and Cu. These “one-pot” procedures not only are step-economical, but also permit minimization of the use of cost-adding iodination or bromination and subsequent lithiation or other metallation reactions. In pursuit of highly satisfactory syntheses of alkenes via the Pd-catalyzed alkenylation, iterative procedures involving a minimum number of steps in each cycle, preferably one, have been recognized as being highly desirable in the syntheses of terpenoids, carotenoids, polypropionates, and other natural products containing oligomeric structural units. In this section, some of the noteworthy advances in this area, achieved mainly over the past decade, are presented with a focus on their applications to the synthesis of natural products.

3.1.1. Hydrozirconation–Cross-Coupling Tandem Reactions of 2-Alkynes

Whereas terminal alkynes can be hydrometallated highly regioselectively (typically >98%) with metal hydrides containing B, Al, and Zr, the corresponding reactions of internal alkynes are generally less regioselective.^{150,151} However, the hydrozirconation with HZrCp_2Cl , which contains not only bulky ligands but also a transition metal, can be more readily equilibrated under thermal conditions in the presence of an excess of HZrCp_2Cl than the corresponding reactions with boron and aluminum hydrides. Thus, the regioselectivity observed with 2-alkynes containing secondary alkyl groups can be improved to nearly 100% (**Scheme 9**).^{84,151,152} This procedure has been applied to the synthesis of some natural products, such as reveromycin B⁷⁸ and motuporin⁸⁴ (**Scheme 10**).

3.1.2. Iterative Tandem Carboalumination–Vinylolation for the Asymmetric Synthesis of Reduced Polypropionates

The Zr-catalyzed asymmetric carboalumination reaction (ZACA reaction) of terminal alkenes^{48,152} can be followed by (i) oxidation with O₂; (ii) iodination with I₂, PPh₃, and imidazole; and (iii) lithiation with *t*-BuLi, zincation with ZnBr₂ or ZnCl₂, and Pd-catalyzed vinylolation to produce another terminal alkene, which can be subjected to another round of this three-step cycle.¹⁵³ This catalytic three-step process has been successfully applied to efficient, catalytic, and asymmetric syntheses of reduced polypropionates and related compounds, such as siphonarinal,¹²⁸ siphonarionone,¹²⁸ siphonarionolone,¹²⁸ and the scyphostatin side chain.¹²⁷

The long-pending problem of how to carry out alkene hydroalumination, to generate alkylalanes, and directly achieve their Pd- or Ni-catalyzed cross-coupling has recently been overcome in the case of vinylolation.¹⁰⁹ This development has permitted iteration of the one-pot procedure for the unprecedentedly efficient and asymmetric construction of the reduced polypropionate segments of ionomycin and borrelidin (**Scheme 11**).¹⁰⁹

3.1.3. Iterative Carboalumination–Pd-Catalyzed Alkylation for the Synthesis of Terpenoids Containing 1,5-Diene Units

Although no one-pot carbometallation–cross-coupling tandem process is involved, an iterative two-step homologation procedure for the synthesis of terpenoids containing 1,5-diene units, such as mokupalide was developed as early as 1980.¹¹³

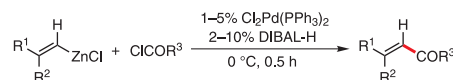
In many cases where there are three or more isoprene units in the target molecule, it would be more efficient to devise iterative procedures involving one-step incorporation of one isoprene unit.⁴⁷ This has been successfully applied to the synthesis of coenzymes Q_n (*n* = 3,10), menaquinone 3, the less commonly encountered (2*E*,6*Z*)- and (2*Z*,6*Z*)-farnesols, and even (2*E*,6*Z*,10*E*)-geranylgeraniol (**Scheme 12**).¹⁰¹ The formation of undesired stereoisomers was not detected in all of these syntheses, although successful synthetic designs must carefully avoid the potentially competitive formation of byproducts, such as cyclopropylcarbinyl derivatives, and pay extra care to the use of the potentially more capricious (*Z*)-1,4-diiodo-2-methyl-1-butene.¹⁰⁹

3.2. Pd-Catalyzed Double Alkenylation Using 1,1-Dihalo-1-alkenes and Related Compounds

As discussed throughout Sections 2 and 3.1, the regio- and stereoselective hydrometallation of internal alkynes and carbometallation of terminal alkynes provide convenient and selective routes to trisubstituted alkenes. Even so, there are many instances of trisubstituted alkenes, where new and alternate synthetic routes are desirable. Three related classes of 1,1-disubstituted 1-alkenes (**Figure 3**) have collectively provided some useful routes to trisubstituted alkenes. The discussion in this section will focus mainly on the selective and stepwise Pd-catalyzed double cross-coupling of 1,1-dihalo-1-alkenes and their use in natural product synthesis.

3.2.1. Pd-Catalyzed Double Cross-Coupling Reactions of 1,1-Dihalo-1-alkenes with Zn, Al, and Zr Organometals

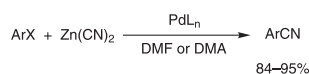
The palladium-catalyzed trans-selective monoarylation of 1,1-dichloro-1-alkenes with arylmagnesium derivatives was first reported in 1987.¹⁵⁴ Several examples of a second Pd-catalyzed arylation, also with arylmagnesium derivatives, were presented



R ¹	R ²	R ³	Yield	Stereoselectivity
<i>n</i> -Pent	H	Me	76%	>99% <i>E</i>
<i>n</i> -Hex	H	MeO	56%	>98% <i>E</i>
<i>n</i> -Hex	Me	Me	77%	>98% <i>E</i>

Ref. 136

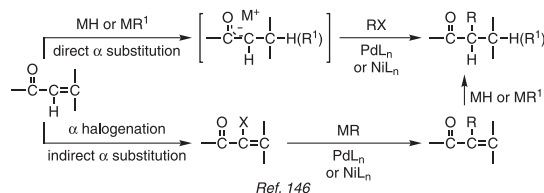
eq 4



Ar = aryl; X = I, Br, Cl
 PdL_n = Pd(PPh₃)₄, Pd(dppf)Cl₂, others

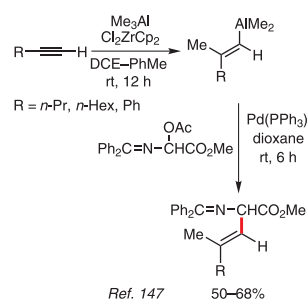
Ref. 143,144

eq 5



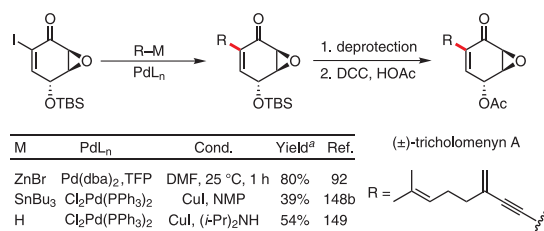
Ref. 146

Scheme 6. Pd- or Ni-Catalyzed Direct α Substitution vs. Indirect α Substitution.

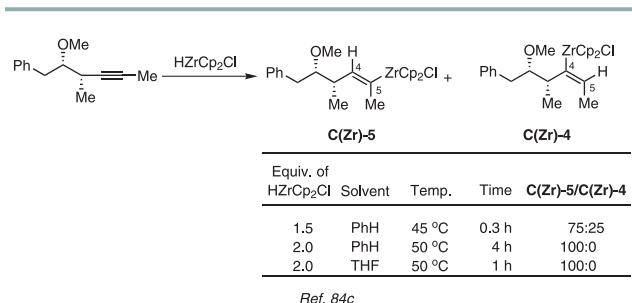


Ref. 147

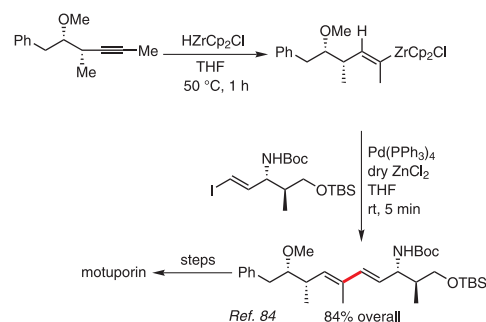
Scheme 7. Pd-Catalyzed α Alkenylation of α -Imino- α -acetoxyacetates.

^a Yield of the cross-coupling step.

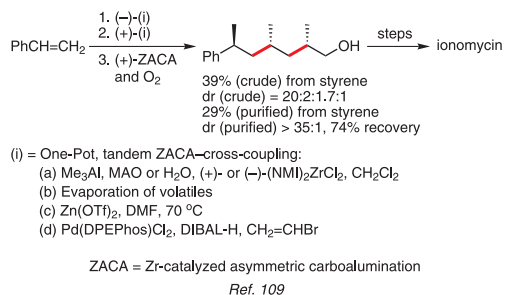
Scheme 8. Pd-Catalyzed α Alkenylation and α Alkynylation of α -Iodo- α,β -unsaturated Carbonyl Compounds in Natural Product Synthesis.



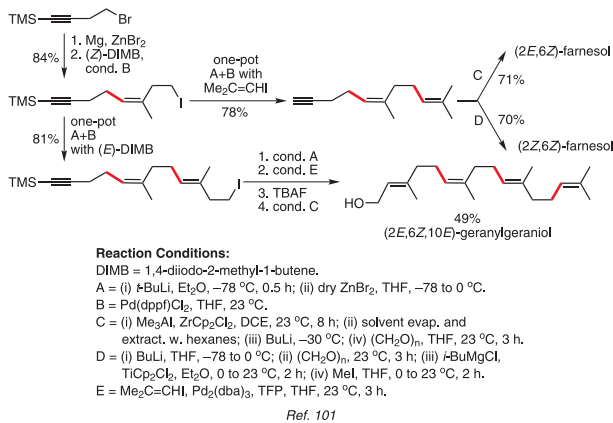
Scheme 9. Improvement of the Regioselectivity of the Hydrozirconation of 2-Alkynes.



Scheme 10. The Synthesis of Natural Products by the Hydrozirconation of 2-Alkynes Followed by Cross-Coupling.



Scheme 11. Iterative One-Pot Homologation of Reduced Polypropionates via ZACA-Pd-Catalyzed Vinylation.



Scheme 12. Iterative One-Pot Homologation of Terpenoids Containing 1,5-Diene Units with (*E*- and (*Z*)-1,4-Diiodo-2-methyl-1-butenes.

in the same paper. In the only example of *trans*-selective monoalkylation reported in the same paper, the use of *n*-BuMgBr did not give the desired product at all, but that of *n*-BuZnCl led to the desired monobutylated product, *trans*-2-chloro-1-phenyl-1-hexene, in 81% yield. The Pd-catalyzed second alkylation of this monobutylated intermediate with *n*-HexMgBr gave the desired trisubstituted alkene with full retention of configuration in 77% yield. Evidently, the first-stage alkylation was strongly aided by the fact that the starting compound was β,β -dichlorostyrene, since attempts to achieve a related *trans*-selective monoalkylation of 2-alkyl-substituted 1,1-dichloro- or 1,1-dibromo-1-alkenes under the same conditions failed.¹⁵⁴

Many subsequently published papers reported Pd-catalyzed *trans*-selective monosubstitution reactions of 1,1-dichloro- and 1,1-dibromo-1-alkenes with arylzincs,¹⁵⁵ alkenylzincs,^{77,156a} alkenylzirconiums,⁷⁷ alkenylborons,¹⁵⁷ aryl- and vinylstannanes,¹⁵⁸ and alkynes in the presence of CuI and a base.^{156b,159} However, the scope of the second substitution via Pd-catalyzed cross-coupling to produce trisubstituted alkenes had until recently been essentially limited to a few examples. In particular, there was only one example of methylation in the second step of the disubstitution of an apparently highly activated β,β -dibromostyrene derivative.¹⁵⁸

With the goal of developing Pd-catalyzed, stepwise double substitution procedures that are well-suited for the synthesis of various types of natural product, a series of systematic investigations have been conducted, which focused on the Pd-catalyzed *trans*-selective single-stage arylation, alkenylation, or alkynylation of 2-alkyl-substituted 1,1-dihalo-1-alkenes—followed by a second-stage alkylation, especially methylation and ethylation (**Scheme 13**).^{160–162} These investigations led to the following noteworthy findings:

- Both 1,1-dichloro- and 1,1-dibromo-1-alkenes, readily obtainable from the corresponding aldehydes, can be selectively monosubstituted ($\geq 98\%$ *trans*) in good yields with aryl-, alkenyl-, and alkynylzinc reagents by using Pd(DPEphos)Cl₂ as catalyst. Alkynylzincs are generally superior to terminal alkynes used in conjunction with a catalytic amount of CuI and (*i*-Pr)₂NH, especially in cases where 1,1-dichloro-1-alkenes are employed.
- In the second-step substitution, alkylation with alkylmetals, such as Me₂Zn, Et₂Zn, and higher homologues, can be achieved in excellent yields by using Pd[(*t*-Bu)₃P]₂ as catalyst. Under these conditions, little or no alkene stereoisomerization is observed.
- Perhaps, the most striking finding in this series of investigations is that the second-stage alkylation in the presence of Pd(DPEphos)Cl₂ or those Pd complexes containing more conventional phosphines, such as dppf, PPh₃, or TFP, is often accompanied by nearly complete stereoinversion of the initially dihalo-bearing double bond.¹⁶³ With DPEphos and dppf, $\geq 97\%$ stereoinversion has been observed in many cases.

1,1-Dihalo-1-alkenes containing a 2-alkenyl or 2-alkynyl group do not undergo stereoinversion at all, whereas the presence of an aryl group in the same position induces partial stereoisomerization. Chelation of Pd by a π bond in the γ,δ position must inhibit stereoinversion. Although the mechanism of this interesting stereoinversion is still unclear at this time, stereoinversion via a π - σ - π rearrangement—widely accepted as the mechanism for stereoinversion of allylmetals—must not be operative, as this mechanism must invariably proceed with double inversions, which were not observed. The mechanism shown in **Scheme 14**, on the other hand, appears to be not only compatible with the observed facts, but also very plausible.

Irrespective of mechanistic details, the synthesis of either *E,E* or *Z,E* conjugated dienes from the same starting compounds in a high-yielding and stereoselective manner should be of considerable synthetic utility, as suggested by a recent synthesis of (–)-callystatin A.⁸⁶

3.2.2. Synthesis of Unsymmetrically Substituted Conjugated Diynes via Pd-Catalyzed Alkenylation with 1,1-Dichloroethylene

Unsymmetrically substituted conjugated diynes have been prepared most commonly by the Cu-catalyzed alkynyl–alkynyl coupling called the Cadiot–Chodkiewicz reaction.¹⁶⁴ This synthesis requires two steps from the two terminal alkynes to be coupled, including the conversion of one or the other alkyne into the corresponding 1-haloalkyne. The main limitation of this method is that the reaction tends to produce rather frequently a mixture of the desired diyne and two unwanted symmetrically substituted diynes.¹⁶⁴ This difficulty has also been observed in the corresponding Pd-catalyzed alkynyl–alkynyl coupling, although some very favorable cases are known. A strictly “cross-selective” route to conjugated diynes via a Pd-catalyzed monoalkynylation of 1,2-dihaloethylenes^{165,166} has been devised as a superior alternative, as discussed in Section 3.3. Although highly selective and widely applicable, this reaction suffered from the high cost of the 1,2-dihaloethylenes starting materials. To overcome this drawback, an alternative method that starts with 1,1-dichloroethylenes was developed. It has long been known that the Pd-catalyzed monoalkynylation of inexpensive vinylidene chloride gives 2-chloro-1-en-3-yne in excellent yields provided that 5 equiv of vinylidene chloride is used.¹⁶⁷ This reaction has been applied in a highly satisfactory and economical synthesis of unsymmetrically substituted conjugated diynes (Scheme 15).¹⁶⁸

3.2.3. 1,1-Dimetallo-1-alkenes and 1-Hetero-substituted 1-Alkenylmetals in the Pd-Catalyzed Alkenylation

The hydrometallation and carbometallation of 1-metallo-1-alkenes are often highly regio- and stereoselective, producing 1,1-dimetallo-1-alkenes mostly via syn addition. In cases where the two metals in 1,1-dimetallo-1-alkenes are sufficiently different, monohalogenation and monosubstitution with other heteroatoms can give 1-heterosubstituted 1-alkenylmetals. These 1,1-disubstituted alkenes can, in principle, be converted into various trisubstituted alkenes via a Pd- or Ni-catalyzed cross-coupling. Even though reactions of this class of compounds have been used in the synthesis of temarotene (Scheme 16)¹⁶⁹ and discodermolide,¹⁷⁰ the current scope of highly satisfactory and synthetically useful applications appears to be still rather limited. This, however, is potentially a promising field for exploration and development.

3.3. Pd-Catalyzed Alkenylation Utilizing 1,2-Dihalo-1-alkenes and Related Compounds

1,2-Dihaloethylenes are, in principle, a group of attractive synthetic modules or synthons. Even if one considers only Cl, Br, and I, there are six each of (*E*)- and (*Z*)-1,2-dihaloethylenes. Of these, (*E*)-ClCH=CHCl, (*Z*)-ClCH=CHCl, (*E*)-BrCH=CHBr, and (*E*)-BrCH=CHI are commercially available. (*E*)-ClCH=CHI, which is already synthetically useful, might be commercialized in the near future. On the other hand, the synthetic value of ICH=CHI and BrCH=CHCl is not clear at this point. Some of the earlier contributions, mostly by the Linstrumelle–Alami group¹⁷¹ and that of Rossi,¹⁷² have been reviewed.^{1a} In these studies, (*E*)- or (*Z*)-ClCH=CHCl and *E/Z* mixtures of BrCH=CHBr were used. An

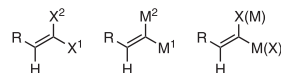
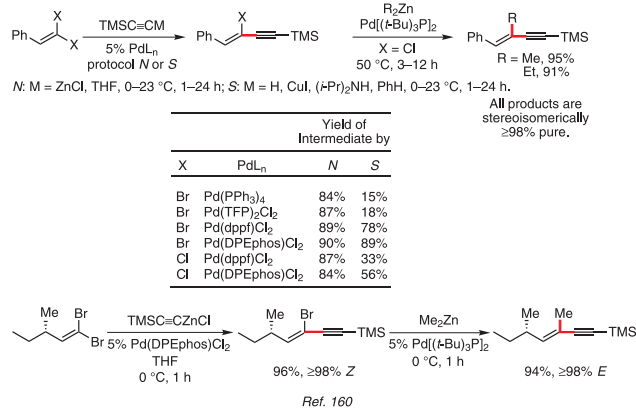
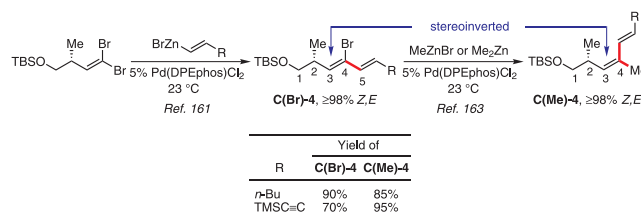


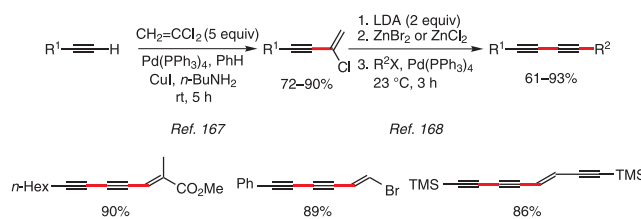
Figure 3. 1,1-Dihalo-1-alkenes and Related Compounds.



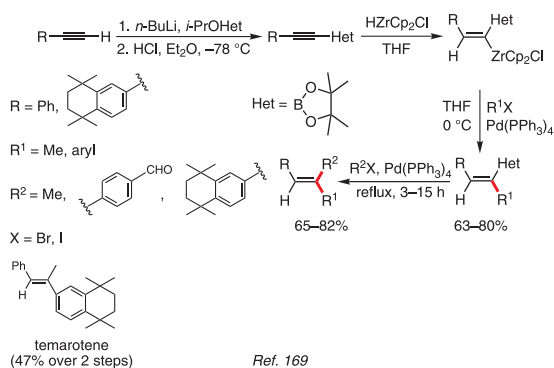
Scheme 13. Pd-Catalyzed Selective and Stepwise Disubstitution of 1,1-Dihalo-1-alkenes with Organozincs.



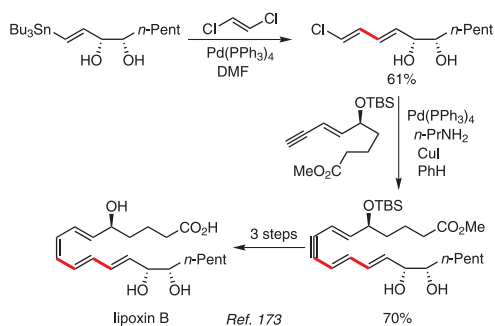
Scheme 14. Pd-Catalyzed *E*=*Z* Isomerization of 2-Pallado-1,3-dienes.



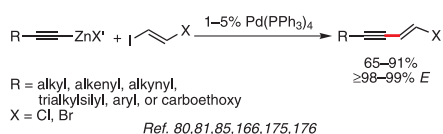
Scheme 15. The Pd-Catalyzed, Strictly “Pair-Selective”, Two-Step Synthesis of Unsymmetrically Substituted Conjugated Diynes.



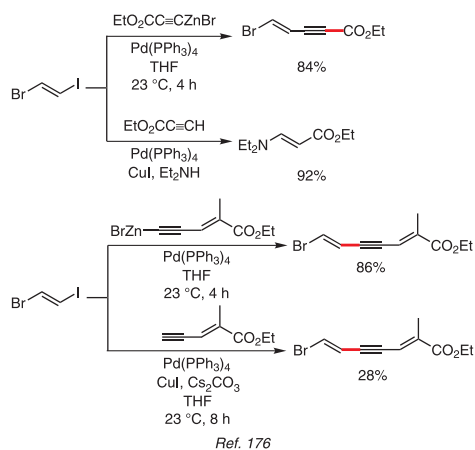
Scheme 16. The Pd-Catalyzed Two-Stage Cross-Coupling with 1-Bora-1-zircona-1-alkenes.



Scheme 17. The Synthesis of Lipoxin B via a Pd-Catalyzed Alkenylation and Alkynylation of (*E*)-ClCH=CHCl.



eq 6



Scheme 18. Comparison of the Negishi and Sonogashira Coupling Reactions in the Pd-Catalyzed Alkynylation of (*E*)-BrCH=CHI.

excess (≤ 5 equiv) of the 1,2-dihaloethylene was typically needed to attain high monosubstitution and/or trans-selectivity levels. Nonetheless, some of these reactions appear to be highly promising, as suggested by the synthesis of lipoxin B (**Scheme 17**).¹⁷³ Also attractive and promising are some cyclization reactions via Pd-catalyzed alkynyl-alkenyl coupling using (*Z*)-ClCH=CHCl.^{15,174} The discussion in this section will focus, however, on the use of (*E*)-ClCH=CHI, (*E*)-BrCH=CHI, and (*E*)-BrCH=CHC≡CSiMe₃, which is derived from (*E*)-BrCH=CHI.

3.3.1. Pd-Catalyzed Selective Monosubstitution of (*E*)-2-Chloro- and (*E*)-2-Bromo-1-iodoethenes

The presence of the second halogen atom in 1,2-dihalo-1-alkenes renders these compounds significantly more reactive than ordinary monohaloalkenes in their Pd-catalyzed monosubstitution reactions. Less well appreciated is that the second substitution of the monosubstitution products derived from 1,2-dihaloalkenes is also substantially more favorable than the corresponding reaction of the same monohaloalkenes in their free alkene forms. After all, the initial products of monosubstitution are monohaloalkene-Pd complexes ready for the second oxidative addition via a strictly intramolecular process. For these reasons, any of the 1,2-dihalo-1-alkenes containing Cl, Br, and/or I are sufficiently reactive in the Pd-catalyzed cross-coupling. Indeed, the main concern in their Pd-catalyzed monosubstitution is how to prevent an unwanted second substitution. This is precisely the reason why a large excess of ClCH=CHCl is commonly used to minimize unwanted disubstitution. Although not fully established, this difficulty may be expected to be further magnified in the cases of BrCH=CHBr and ICH=CHI. Little, if any, is known about BrCH=CHCl. In ClCH=CHI, two carbon-halogen bonds are maximally differentiated, and monosubstitution of the iodine is expected to be more favorable. On the other hand, the second substitution of the chloroalkene products with a different organometal than the one used for the first substitution is generally less favorable than the corresponding reaction of bromoalkenes. In this respect, BrCH=CHI is a more desirable reagent than ClCH=CHI. It would be advantageous to consider both BrCH=CHI and ClCH=CHI and then compare the overall results for optimization. In cases where the cost of these 1,2-dihaloethylenes is a significant factor, ClCH=CHCl may also be tested and compared. In contrast to the Pd-catalyzed cross-coupling of ordinary monohaloalkenes, the corresponding monosubstitution of 1,2-dihaloethylenes has proved to be generally much more capricious and unpredictable. Nevertheless, the Pd-catalyzed monoalkynylation of (*E*)-ClCH=CHI and (*E*)-BrCH=CHI has been developed into a dependable and widely applicable reaction (**eq 6**).^{80,81,85,166,175,176} In this regard, some striking differences between the use of alkynylzincs and terminal alkynes containing electron-withdrawing groups should be noted (**Scheme 18**).¹⁷⁶

As expected, the Pd-catalyzed alkenylation of (*E*)-ClCH=CHI was favorable,^{60,79} but the corresponding reaction of (*E*)-BrCH=CHI required extensive optimization. After screening many catalysts and reaction parameters, a set of parameters consisting of InCl₃ (≤ 0.34 equiv), 1% Pd(DPEphos)Cl₂, 2% DIBAL-H, 2% TFP, and THF was found to be almost uniquely satisfactory (yields of the monoalkenylated products ranged from 77 to 91%).⁶⁰ This has also been applied to the related arylation; however, the corresponding alkylation has not been satisfactory.

The 1-chloro- and 1-bromoalkenes, obtained as described in the preceding two paragraphs, rarely represent the final natural products. However, pitamide A is one such rare example, which has been prepared by using this approach.⁷⁹

3.3.2. Pd-Catalyzed Second-Stage Substitution Reactions of Alkenyl Chlorides and Bromides, and the One-Pot Tandem Disubstitution of 1,2-Dihaloethylenes

Even though 1-chloro-1-en-3-yne and 1-chloro-1,3-dienes, obtained as described in Section 3.3.1, are considerably more reactive than 1-chloro-1-monoenes in the Pd-catalyzed cross-coupling due to the presence of conjugated π bonds, their Pd-catalyzed cross-coupling reactions are significantly more sluggish than the corresponding reactions of their bromo analogs. Nevertheless, a highly satisfactory (71–97% yields) set of conditions has recently been found for their alkylation and arylation.¹⁷⁷ It consists of the use of alkyl- or arylmagnesium halides, ZnCl_2 (0.6 equiv), 5% Pd(dppf) Cl_2 , and THF at reflux temperature. This development has significantly elevated the synthetic value of (*E*)- ClCH=CHI and (*E*)- ClCH=CHCl vis-à-vis (*E*)- BrCH=CHI .

The Pd-catalyzed disubstitution of (*E*)- ClCH=CHI and (*E*)- BrCH=CHI can be achieved without isolation of the monosubstitution products, as exemplified by the Pd-catalyzed one-pot dialkynylation.¹⁷⁶ Construction of the pentaenediylne framework of xerulin was achieved by a Pd-catalyzed two-step alkynylation–alkenylation.⁸⁰ A similar Pd-catalyzed alkynylation–alkenylation of (*E*)- BrCH=CHI has been applied to the synthesis of *cis*- and *trans*-bupleurynols (**Scheme 19**).⁸⁵

A useful variation of the Pd-catalyzed alkynylation–alkenylation of (*E*)- BrCH=CHI is to use its C–I bond as an electrophile but convert the C–Br bond into a nucleophilic C–Zn bond, as in the preparation of ethyl 2-methyl-2,4-heptadien-6-ynoate, a key intermediate in the synthesis of 6,7-dehydrostipiamide.⁸⁷

3.3.3. Iterative Carbon–Carbon-Bond Formation by the Pd-Catalyzed Cross-Coupling of 1,2-Dihaloethylenes and 1-Halo-1-buten-3-yne

1,2-Dihaloethylenes and 1-halo-1-buten-3-yne discussed above can be used as two- and four-carbon synthons, respectively, for the iterative construction of carbon skeletons containing repeating units derived from them. In the synthesis of xerulin,⁸⁰ an iterative process was utilized to synthesize a bromodiendiyne as a key intermediate. It should also be noted that this procedure can, in principle, be iterated as many times as desired. Although this process has not yet been applied to the synthesis of conjugated triynes or higher oligoyne, it has been employed for the synthesis of various conjugated diynes.^{165,166} It is a satisfactory and strictly “pair-selective” method, but a potentially more economical diyne synthesis, shown in Scheme 15, could prove to be more economical in most cases.

One highly attractive application of (*E*)-1-bromo-4-trimethylsilyl-1-buten-3-yne is to use it as a four-carbon synthon for the iterative construction of conjugated oligoene including oligoene macrolides, carotenoids, and retinoids. A highly efficient, selective, and general method for the synthesis of conjugated (*all-E*)-oligoenes of type $(\text{CH=CH})_n$ via an iterative tandem hydrozirconation–palladium-catalyzed cross-coupling has recently been developed (**Scheme 20**).¹⁷⁸ It promises to be applicable to the efficient synthesis of various oligoene macrolides.¹⁷⁹

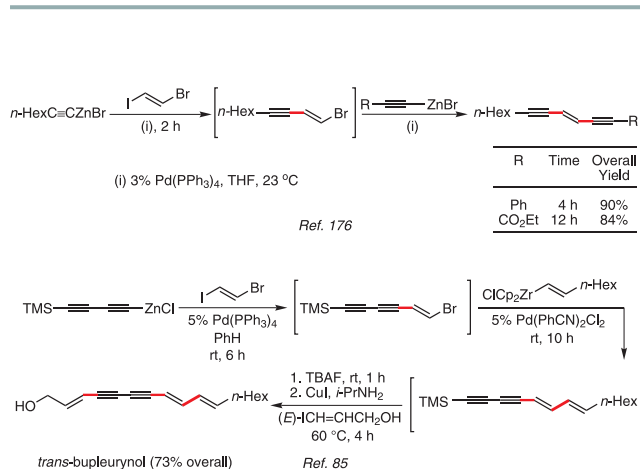
A related iterative carboalumination–cross-coupling process has also been developed and applied to the synthesis of both symmetrical and unsymmetrical carotenoids as well as retinoids.⁸¹ It is not only highly efficient but also ≥ 98 –99% stereoselective, even after incorporation of several stereodefined trisubstituted alkene units along with similar numbers of disubstituted alkene units.

3.3.4. 1,2-Dimetalloethylenes, 1-Metallo-2-haloethylenes, and Other Related Alkene Synthons

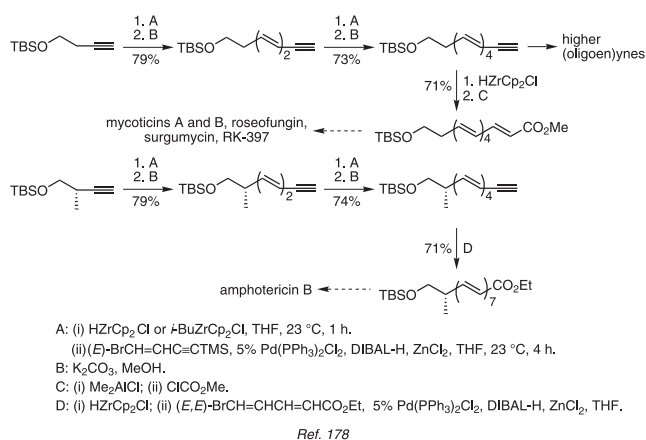
A number of classes of 1,2-dimetalloethylenes and 1,2-dimetallo-1-alkenes are conceivable, and some of those that contain Zn, B, Si, and Sn were briefly discussed in Section 2.2.1.^{1a} In Scheme 1, (*E*)- $\text{Bu}_3\text{SnCH=CHZnCl}$ is shown to be far superior to (*E*)- $\text{Bu}_3\text{SnCH=CHSnBu}_3$ in the Pd-catalyzed reaction with methyl (*E*)-3-bromo-2-methylacrylate.³⁰ A related (*all-E*)-1,3,5-hexatriene derivative was recently used to synthesize xerulinic acid (**Scheme 21**).⁸⁸

4. Conclusions

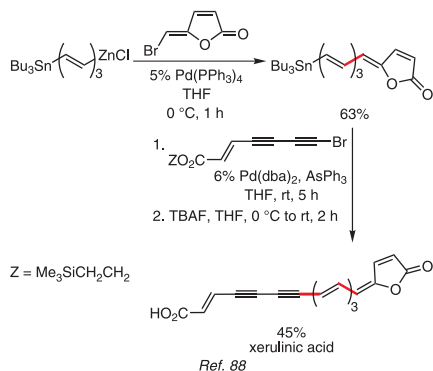
- Since the discovery of the Pd-catalyzed alkenylation by the Negishi coupling in the mid-1970s,^{16–18,21–24} it has been extensively developed into a widely applicable, highly selective, and generally satisfactory method for the synthesis of alkenes by attaching a C–C single bond onto a C=C moiety.
- Generally speaking, zinc offers a very desirable combination of (i) high reactivity under the Pd-catalyzed conditions and (ii) a surprisingly favorable chemoselectivity profile. Furthermore, zinc salts, such as ZnCl_2 and ZnBr_2 , can be used as promoters in the Pd-catalyzed cross-coupling reactions of other organometals including those containing Li, Mg, B, Al, Sn, Cu, and Zr primarily through transmetalation to Zn (Scheme 1). This has effectively expanded the scope of the Pd-catalyzed organozinc cross-coupling. In some cases of alkenylation with alkenylmetals containing Al and Zr, however, InCl_3 and InBr_3 can be more favorable promoters than Zn salts.⁶⁰ It is also worth noting that organomagnesiums, which are generally inferior to the corresponding organozincs, may prove to be superior to the latter, as suggested by recent results obtained with certain alkenyl chlorides.²⁹ It is not inconceivable that the hard and soft acids and bases principle is operative in the Pd-catalyzed cross-coupling as well.
- Until recently, the great majority of the Negishi coupling examples had been carried out in the presence of Pd catalysts containing PPh_3 , TFP, dppf, and dppp. More recent studies have indicated that those containing DPEphos, trialkylphosphines (e.g., $\text{P}(t\text{-Bu})_3$, PCy_3 , PCyp_3), and 2-dialkylphosphinobiphenyls, as well as some non-phosphine ligands, are not only useful in many demanding cases, but also complementary among themselves (Figure 1 and Schemes 13 and 14). It is important to note that, although these structurally more varied and/or complex ligands will add to the cost of carrying out the Pd-catalyzed cross-coupling, higher costs of ligands and catalysts can be offset by more favorable results, in particular by higher turnover numbers (TONs). In this context, it is encouraging to learn from recent studies that the TONs in the Pd-catalyzed cross-couplings, including the Negishi coupling, can generally and readily reach the 10^3 – 10^5 levels and even the $>10^6$ levels in some cases.⁶¹
- Of the sixteen cross-coupling combinations for the Pd-catalyzed alkenylation discussed throughout this article, only four classes of reaction, namely allyl–alkenyl, propargyl–alkenyl, enoxy–alkenyl, and alkenyl–alkyl coupling reactions remain underdeveloped. Fortunately, allyl–alkenyl, propargyl–alkenyl, and alkenyl–alkyl coupling reactions may be substituted with the corresponding alkenyl–allyl, alkenyl–propargyl, and alkyl–alkenyl coupling reactions to attain the same synthetic goals in most cases. α Alkenylation of carbonyl compounds can also be achieved via the Pd-catalyzed reaction of alkenylzincs with α -haloones (Section 2.8). Thus, the



Scheme 19. The Pd-Catalyzed Dialkynylation and Alkenylation of (*E*)-BrCH=CHI.



Scheme 20. The Synthesis of Conjugated Oligoenes via an Iterative Hydrozirconation–Cross-Coupling Tandem Process.



Scheme 21. The Synthesis of Xerulinic Acid via an Alkenyl–Alkenyl Coupling with (*all-E*)-6-Stanna-1,3,5-hexatrienylzinc Chloride.

Pd-catalyzed alkenylation can, in principle, be employed for the synthesis of all conceivable types of alkenes. The Pd-catalyzed alkenylation by the Negishi coupling is not only generally favorable in twelve out of sixteen cross-coupling combinations for the synthesis of alkenes, but also either the most satisfactory or one of the most satisfactory cross-coupling protocols known today along with the Pd-catalyzed alkenylation via alkenylborons (Suzuki coupling).^{1,5,6} Some of the other currently known protocols involving Mg,^{9,10} In,¹¹ Si,^{1,12} and Cu¹³ may also be further developed into widely used ones. Especially noteworthy are the alkenyl–alkenyl (Sections 2.3 and 3) alkynyl–alkenyl (Sections 2.4, 3.2, and 3.3), and alkyl–alkenyl (Sections 2.6, 3.1, and 3.2) couplings that currently appear to be most generally and satisfactorily achieved by the Negishi protocol.

- One of the advantages of the Pd-catalyzed alkenylation by the Negishi coupling is that Al, Zr, and Zn collectively offer various selective hydrometallation and carbometallation reactions, the products of which can be directly used for cross-coupling with minimal synthetic manipulations (Section 3.1).
- The previously underdeveloped and capricious stepwise disubstitution of 1,1-dihalo-1-alkenes has now been developed into a selective, predictable, and satisfactory synthetic method (Section 3.2). The use of organozincs in conjunction with Pd(DPEphos)Cl₂ and Pd(dppf)Cl₂ in the first substitution step and Pd[(*t*-Bu)₃P]₂ and related alkylphosphine-containing complexes in the second substitution step has been the key to recent successes in many cases. In the second substitution step of 2-halo-1,3-dienes, the use of Pd(DPEphos)Cl₂ and other conventional catalysts containing dppf, PPh₃, and so on has led to potentially useful and near-complete stereoinversion of the carbon–carbon double bond.¹⁶³
- The Pd-catalyzed alkenylation discussed above has been significantly supplemented by the introduction of 1,2-dihaloethylenes and 1-halo-1-buten-3-yne as two- and four-carbon synthons (Section 3.3). The combined use of 1-halo-1-buten-3-yne and hydrometallation or carbometallation permits efficient and selective iterative syntheses of oligoenes including oligoene macrolides and carotenoids (e.g., Scheme 20).

5. Acknowledgments

The corresponding author (EN) wishes to dedicate this article to his lifelong mentor, the late Professor Herbert C. Brown, who passed away on December 19, 2004. His guidance and assistance over almost four decades (1966–2004) have played numerous positive and crucial roles in EN's career. Indeed, Professor Brown's suggestion to develop alkyne-hydroboration-based routes to prostanoids in the late 1960s turned EN's attention first to Cu–B, then to Ni–B, and eventually to Pd–Al, Zr, and Zn through Ni–Al, Zr, and Zn combinations during the 1972–1978 period at Syracuse University. Over 60 graduate students and postdoctoral associates have participated in this endeavor, and we are deeply indebted to their dedicated efforts. Although it is not practical to mention all of their names here, many of them are shown in pertinent references cited herein. EN is especially grateful to seminal contributions by the first four contributors, i.e., S. Baba, A. O. King, N. Okukado, and D. E. van Horn. This project at Purdue has been mainly supported by the National Science Foundation, the National Institutes of Health, and Purdue University including the H. C. Brown Distinguished Professorship Fund. Earlier support by the Research Corporation, the ACS Petroleum Research Fund, and Syracuse University is also gratefully acknowledged.

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Ei-ichi Negishi, H. C. Brown Distinguished Professor of Chemistry, Purdue University, grew up in Japan and received his Bachelor's degree from the University of Tokyo (1958). He then joined the chemical company Teijin. In 1960, he came to the University of Pennsylvania on a Fulbright Scholarship and obtained his Ph.D. degree in 1963. He then returned to Teijin, and, in 1966, joined Professor H. C. Brown's group at Purdue as a postdoctoral associate. He was appointed Assistant to Professor Brown in 1968. It was during the following few years that he began to see the need for catalytic ways of promoting organoborane reactions. In 1972, he was appointed Assistant Professor in the Department of Chemistry at Syracuse University, where he began his lifelong investigations of transition-metal-catalyzed organometallic reactions for organic synthesis. Between 1976 and 1978, he published about 10 papers describing the Pd- or Ni-catalyzed cross-coupling reactions of various organometals including those of Mg, Zn, B, Al, Sn, and Zr. Today, those cross-coupling reactions that employ organometals containing Zn, Al, and Zr are widely known as the Negishi coupling. Negishi was promoted to Associate Professor at Syracuse University in 1976, and invited back to Purdue University as Full Professor in 1979. In 1999, he was appointed the inaugural H. C. Brown Distinguished Professor of Chemistry. He has received a number of awards, including the 1987 Guggenheim Fellowship, the 1996 A. R. Day Award, a 1997 Chemical Society of Japan Award, the 1998 ACS Organometallic Chemistry Award, a Humboldt Senior Researcher Award, Germany (1998–2001), and the 2000 RSC Sir E. Frankland