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Transition Metal-Catalyzed Organometallic Reactions that Have Revolutionized Organic Synthesis

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The Pd- or Ni-catalyzed cross-coupling reactions of organometals containing Zn, Al, Zr, and B as well as related reactions of Mg and several other metals collectively represent the most widely applicable organic skeleton construction method discovered and developed over the past several decades, allowing the synthetic chemists to synthesize practically all types of organic compounds. Some of the seminal and critically important discoveries and early developments in the 1970s as well as their current scope (Tables 2 and 3) are briefly discussed. Some of the notable discoveries and developments include (1) identification of superior properties of Pd relative to Ni, (2) the broad scope of Pd- or Ni-catalyzed cross-coupling with respect to metal counter cations including Zn, Al, Zr, B, and Mg, (3) the hydrometallation–Pd-catalyzed cross-coupling tandem processes for selective syntheses of alkenes, dienes, oligoenes, and oligoenynes, (4) double metal catalysis involving Pd or Ni and added metal compounds containing Zn, In, Li, and others, and (5) realization of high turnover numbers ($\geq 10^3$–10^5) through the use of chelating phosphines, such as DPEphos and dppf. In these reactions, the metal counter cations in organometals and Pd or Ni are to work successively via transmetallation.The Zr-catalyzed alkyne carboalumination and the Zr-catalyzed asymmetric carboalumination of alkenes (ZACA reaction) have provided efficient and selective routes to methyl-branched (*E*)-trisubstituted alkenylalanes and 2-substituted chiral alkylalanes, respectively. These reactions provide two additional examples of prototypical transition metal-catalyzed organometallic reactions. Significantly, they can be readily combined with the Pd- or Ni-catalyzed cross-coupling for the synthesis of trisubstituted alkenes embracing a wide variety of natural products, such as terpenoids, carotenoids, and others, as well as various chiral organics including deoxypolypropionates and saturated terpenoids. The Zr-catalyzed alkyne carboalumination has been applied to the synthesis of well over 100 complex natural products (Table 4), while the ZACA reaction has been transformed from a mere scientific novelty to a full-fledged asymmetric synthetic method that is catalytic in both transition metal (Zr) and chiral auxiliaries through a series of breakthroughs (Schemes 12–17).

1. Introduction and Historical Background

1.1 Why Metals? Why Transition Metals? Organic compounds consist mostly of C, H, O, N, and a few to several other heteroatoms including P, S, and some halogens. Their synthesis, however, does not have to be limited to these ten or so elements. Although this author is no historian of chemistry, the use of Na by Wurtz[1a] and Fittig and Tollens[1b] as well as that of Pd for catatylic reduction by Kolbe[2a] and Saytzeff[2b] were reported well over a century ago. Even if one somewhat arbitrarily excludes all groups 15–18 elements in addition to C and H as non-metallic elements and all radioactive elements for safety and other reasons, there still are about 60 metallic elements including 25 groups 1–3 and 12–14 non-transition metals, 23 d-block transition metals excluding Tc and 13 lanthanides excluding Pm. Some of them including Be, Cd, Hg, Tl, Sn, and Pb appear to be categorically associated with toxicity-related problems, and their use in organic synthesis, even if necessary, will have to be made with ample precaution.

Simply stated, metals (M), as defined above from the viewpoint of organic synthesis, can induce polarization of $M^{\delta+}$–$C^{\delta-}$ bonds to provide carbanionic species or carbon nucleophiles. Less well appreciated but equally or perhaps even more important is their ability to readily and conveniently provide Lewis acidic sites for inducing a wide variety of synthetically useful reactions. Furthermore, it has been increasingly well recognized that the d-block transition metals represent a couple of dozen of elements that collectively exhibit some ultimately desirable chemical reactivities. In addition to providing (1) $M^{\delta+}$–$C^{\delta-}$ bonded nucleophiles and (2) metal-centered Lewis acids or electrophiles mentioned above, d-block transition metals can provide simultaneously one or more empty and filled non-bonding orbitals. And yet, many of their complexes can exist as stable and long-lived species that can be stored at room temperature for months and years as exemplified by $Cl_2Pd(PPh_3)_2$. With these frontier orbitals, i.e., HOMOs and LUMOs, readily available and accessible, d-block transition metals can widely interact with π-bonds and even with various

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C–H, C–C, and other σ bonds in manners similar to those of carbenes, which may be conveniently termed "carbene-like" reactivity. The majority of them appear to proceed by concerted processes of low activation energies leading to facile and selective chemical transformations. In addition to the seemingly inconsistent combination of ready availability, practical stability, high reactivity, and high selectivity, d-block transition metals display one more incredible property. Namely, many of their reactions are readily reversible under given sets of reaction conditions. Carbenes, usually generated as short-lived unstable species, may readily add to alkenes to give cyclopropanes, but its reverse process is very rare at best. There are many classes of compounds, such as sulfur-containing compounds, that can be readily oxidized and/or reduced but perhaps not both under one given set of reaction conditions. This ready reversibility under one set of reaction conditions is indeed one crucial requirement for any redox-type catalysis, and this indeed represents one of the fundamental properties of d-block transition metals that set them apart from virtually all of the other elements.

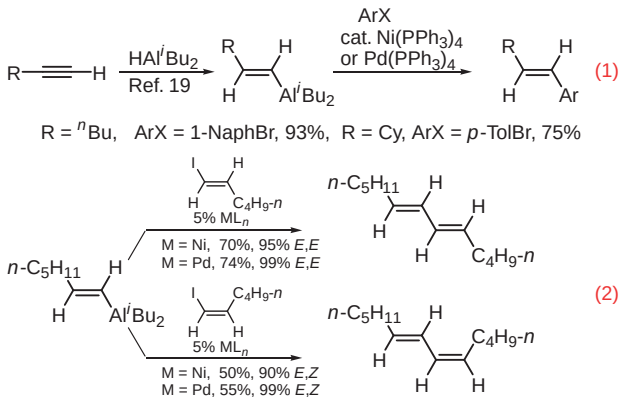
Although application of non-transition metals, such as Na, and transition metals, such as Pd, primarily as electron-donating reducing agents initiated the use of metals in organic synthesis, the first major revolutionary development in metal-mediated organic synthesis may well be the Barbier-initiated organomagnesium chemistry that reached maturity through the development of the Grignard reagents and the Grignard reaction,[3] which has been significantly reinforced by inclusion of organoalkali metal chemistry.[4] It is not unreasonable to include also the enolate-based chemistry of alkali metal and Mg enolates as important variants of the Grignard and organoalkali metal chemistry. In versatility, no other synthetic methods discovered and developed before World War II could even begin to compete with the Grignard and related organoalkali metal chemistry including enolates and related variants. Therefore, it is indeed gratifying to note that the first Nobel Prize in Chemistry recognizing organometallic chemistry was jointly awarded in 1912 to V. Grignard for "the discovery of the Grignard reagent" and to P. Sabatier for "his method of hydrogenating organic compounds" with transition metals.

1.2 Why Transition Metal-Catalyzed Organometallic Reactions? As versatile as the Grignard reagents and organoalkali metals were, their synthetic scope was still severely limited. For one thing, they are generally not very capable of interacting with organic halides and related electrophiles containing aryl, alkenyl, alkynyl, and other related unsaturated groups. As discussed in the preceding section, transition metals can readily interact with such organic compounds. Irrespective of the distinction between transition metals and non-transition metals, consideration of binary combinations of 60 or so synthetically available metals can lead to "conceptual" expansion of the periodic table. If one assumes each of the binary combinations of 60 metals displays its unique synthetic capabilities, it would be tantamount to having 3600 elemental options from the synthetic viewpoint. This notion can, of course, be further expanded by considering combinations of three or more metals. From a practical viewpoint, it would be ideal to use all metals in catalytic quantities. If not, the number of metals used stoichiometrically should be limited to one. *The Merck Index* (13th Ed.)[5] lists 446 "organic name reactions," of which about 100 have been discovered and/or developed since 1945. Well over 60 of them use metals, about half of which use transition metals. However, less than 20 appear to involve their catalytic use. The Wacker oxidation[6] of alkenes to aldehydes and ketones involves an ingeniously devised double transition metal-catalylic cycles using Pd and Cu, while the Ziegler–Natta polymerization[7] is a Ti- or Zr-catalyzed alkene polymerization which may or may not be catalytic in Al depending on mechanistic details.

Although not well-developed and unlisted in *the Merck Index*, Kharasch and others reported their pioneering investigations of transition metal-catalyzed Grignard reactions with Cu, Fe, and Co.[8] Most of the early results were rather disappointing, but later investigations by Kochi and Tamura led to the development of satisfactory procedures for Cu- and Fe-catalyzed alkylation with Grignard reagents.[9] In these pioneering studies, however, neither Ni nor Pd was apparently used. An epoch-making discovery was concurrently made in 1972 by the Tamao–Sumitani–Kumada group[10] in Japan and the Corriu–Masse group[11] in France, when they reported the Ni–phosphine complex-catalyzed Grignard cross-coupling. Although the latter group did not follow up the initial discovery, the former group has systematically developed their discovery into what is now known as the Tamao–Kumada coupling.[10b] The discovery of the Ni-catalyzed Grignard reagents led to that of the Pd-catalyzed Grignard cross-coupling reported first by Yamamura, Moritani, and Murahashi[12] and then by Fauvarque and Jutand[13] and by Sekiya and Ishikawa[14] during the 1975–1976 period. An isolated publication of the Pd-catalyzed reaction of alkynylsodium[15] should also be noted. These groups of workers published just one or two papers each during these and following few years.

Over the past 30–35 years, the Ni- or Pd-catalyzed Grignard cross-coupling has steadily and firmly established its role as a useful and indispensable synthetic tool. Nevertheless, the current widespread use of the Pd- or Ni-catalyzed cross-coupling has required the discoveries and developments of those protocols involving metals of intermediate electronegativities represented by Zn, Al, and Zr widely known as the Negishi coupling[16] as well as more electronegative B widely known as the Suzuki coupling.[17]

1.3 Discovery of the Pd- or Ni-Catalyzed Cross-Coupling Reactions of Organometals Containing Zn, Al, Zr, and B. This author's interest in the transition metal-catalyzed cross-coupling originated in his desire to make good use of alkenylboranes readily accessible via hydroboration of alkynes. Urged by his postdoctoral mentor, the late Professor H. C. Brown, he attempted to develop alkenylboron-based protocols for the synthesis of prostaglandins without much success in the late 1960s. This study later led to the development of what appeared to be the first widely applicable and fully stereocontrolled borane-based syntheses of (*E*,*E*)- and (*E*,*Z*)-1,3-dienes,[18] which were shown to be applicable to the syntheses of bombykol[18b] and a pheromone of a grapevine moth, *Lobesia botrana*.[18c] As a fledgling Assistant Professor at Syracuse University seeking new avenues for his research, he sensed both the need and the vast potential in the transition metal-catalyzed

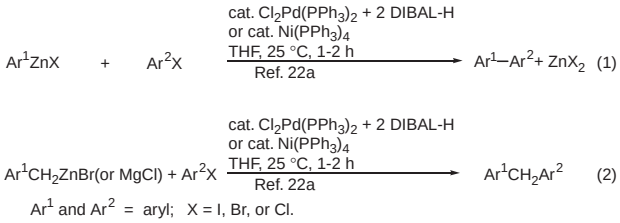


Scheme 1.

organometallic reactions, as discussed earlier, and proposed to develop the Cu-catalyzed cross-coupling of alkenylboron compounds. Amidst a series of failures, the Ni-catalyzed Grignard cross-coupling of Tamao et al.[10a] was noticed, and a quixotic notion of catalyzing the desired alkenylboron cross-coupling with Ni–phosphine complexes crossed his mind. Although all attempts failed with either alkenylboranes or alkenylborates, they led to the discovery in 1976 of the Ni-catalyzed cross-coupling of alkenylalanes readily accessible via hydroalumination of alkynes[19] (First equation in Scheme 1).

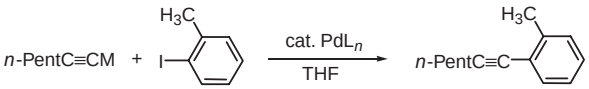
In the course of developing highly stereoselective alkenyl–alkenyl coupling, however, a significant limitation associated with Ni-catalysts was observed. Specifically, the stereoselectivities for the syntheses of (*E*,*E*)- and (*E*,*Z*)-1,3-dienes were 95 and 90%, respectively, which were distinctly lower than those observed in the organoboron migratory insertion reactions mentioned earlier. This was when structurally related Pd and Pt complexes were tested. At that time, a survey of the literature by the author's group indicated that nothing was known about the use of Pd and Pt in catalytic cross-coupling, even though the papers by Murahashi et al.[12] and by Cassar[15] mentioned earlier appeared before submission of a couple of papers in 1976 by the author's group. Whereas Pt–PPh_3 complexes were not effective, Pd–PPh_3 complexes induced highly stereoselective alkenyl–alkenyl coupling,[20] as shown in Scheme 1. The results shown in Scheme 1 indicated for the first time (i) Pd- or Ni-catalyzed cross-coupling of organoaluminums, (ii) some distinctly superior property of Pd relative to Ni, i.e., essentially full retention of alkene geometry, and (iii) one-pot hydrometalation–cross-coupling tandem processes.

When alkenylzirconocene chlorides, also readily generated in situ from alkynes via hydrozirconation, smoothly underwent the desired Pd- or Ni-catalyzed cross-coupling,[21] the author began sensing that his initially desperate and quixotic notion might actually prove to be generally applicable. In the meantime, very favorable Pd- or Ni-catalyzed cross-coupling reactions of organozincs containing aryl, benzyl, and alkynyl groups were also discovered in 1977[22] (Scheme 2). In the alkynylation, the use of Ni catalysts led to known competitive cyclotrimerization of alkynes to give arenes, but this side reaction was not at all competitive in the Pd-catalyzed alkynylation,[22b,22c] revealing another significant feature favoring Pd over Ni.



Scheme 2.

Table 1. Reactions of 1-Heptynylmetals with *o*-Tolyl Iodide in the Presence of $Cl_2Pd(PPh_3)_2$–DIBAL-H[23]



M	Temp/°C	Time/h	Product yield/%	Starting material/%
Li	25	1	trace	88
Li	25	24	3	80
MgBr	25	24	49	33
ZnCl	25	1	91	8
HgCl	25	1	trace	92
HgCl	reflux	6	trace	88
BBu_3Li	25	3	10	76
BBu_3Li	reflux	1	92	5
Al(Bu-*i*)$_2$	25	3	49	46
$AlBu_3Li$	25	3	4	80
$AlBu_3Li$	reflux	1	38	10
$SiMe_3$	reflux	1	trace	94
$SnBu_3$	25	6	83	6
$ZrCp_2Cl$	25	1	0	91
$ZrCp_2Cl$	reflux	3	0	80

These findings prompted the author's group to systematically screen various metals in the Pd-catalyzed alkynyl–aryl coupling. Both alkynylmetals and aryl halides are readily and widely available. This study indicated that Zn, B, and Sn were the three most favorable metals, which were followed by Mg and Al, but that some other metals including Li, Hg, Si, and Zr essentially failed to give the desired products under the conditions used[23] (Table 1). Later, it was found that alkynyllithiums can readily displace PPh_3, thereby serving as catalyst poisons.[24] Although not fully clarified, alkynylmercuries appeared to interfere with Pd catalysis through participation in some undesirable redox processes. Since Me_3Si and other silyl groups have since been shown to serve as convenient protecting groups in the Pd-catalyzed alkynylation, the complete inertness of alkynylsilanes is a blessing in disguise, but the failure observed with alkynylzirconium reagents remained as an unclarified puzzle, especially in the light of the favorable results observed with alkenylzirconocene chlorides.[25]

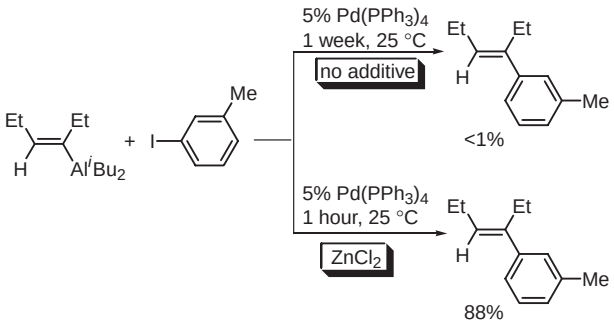
This study revealed some useful findings that have contributed to laying the foundation of the Pd-catalyzed cross-coupling, of which the following two are especially noteworthy. Firstly, the three most widely used metal counter cations, Zn, B, and Sn, were found to be the three most favorable metals. Although the use of allyltin derivatives by Kosugi et al.[26] was reported a year earlier, the author's report on the use of organoborons marked the discovery of the Pd-catalyzed

organoboron cross-coupling, predating the first report by the Suzuki group in 1979.[27] Secondly, alkynylzincs displayed by far the highest reactivity under the catalytic conditions employed. It is very gratifying to note today that the Pd-catalyzed cross-coupling reactions of organometals containing Zn and B known as the Negishi coupling and the Suzuki coupling, respectively, represent the cornerstones of the very widely used Pd- or Ni-catalyzed cross-coupling. Many have asked the author by saying, "Why did you not pursue your initial goal of developing transition metal-catalyzed organoboron cross-coupling?" For one thing, the author thought the Pd- or Ni-catalyzed cross-coupling of organometals containing Zn, Al, and Zr as well as Mg was collectively superior to that with B. He tends to think it is true in the majority of cases even today. It is also true at the same time that, until he totally omitted any plans involving the use of B in 1976, no external fund had been granted him with a single exception of a small but immensely precious Research Corporation grant in his fourth year. Whether he was treated fairly or not may be debatable. In retrospect, however, it was one of the biggest blessings in disguise given to him. Without this hardship, he may not have discovered and/or developed many of those reactions discussed above. He also did come back to B by discovering the Pd-catalyzed α-allylation of enoxyborates of ketones.[28]

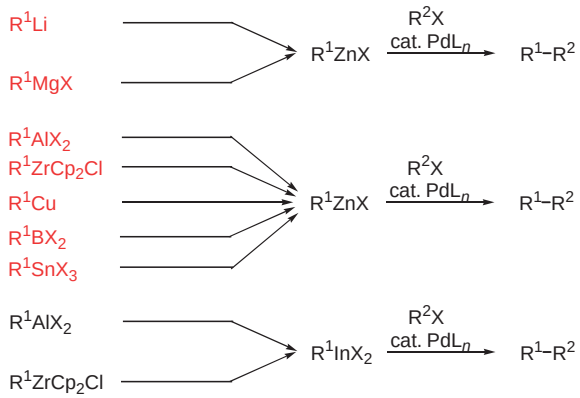
The discovery of the generally high reactivity of organozincs under Pd- or Ni-catalyzed conditions led the author to another widely applicable notion of double metal catalysis that can operate through transmetalation, although other mechanisms are also conceivable. Through the use of $ZnCl_2$, $ZnBr_2$,[29] and more recently introduced $Zn(OTf)_2$[30] as co-catalysts, the synthetic scopes of the Pd- or Ni-catalyzed cross-coupling of organometals containing Al, B, Cu, Sn, Zr, and so on have been very significantly expanded[16] (Schemes 3 and 4). Moreover, the concept of double metal catalysis has been extended through inclusion of other co-catalysts containing metals, such as Li and other alkali metals,[31] Mg,[32] Cu,[33] and In.[34]

Nearly ten foundation-laying publications by the author's group published during the 1976–1978 period,[19–23,29] were further supplemented with a couple of dozen seminal papers on the Pd- or Ni-catalyzed alkylation,[35] allylation,[28,36] benzylation,[22a,37] and acylation[38] reported during the following decade. In the meantime, many other groups, most notably those led by Stille et al. (since 1978)[39] and Suzuki et al. (since 1979),[17b,27] have made very substantial contributions leading to yet another round of substantial expansions over the past decade or so, the discussion of which is beyond the scope of this article.

This author firmly believes that, since the discoveries and development of the Grignard and related organoalkali metal chemistry in the early 20th century, no other synthetic method has brought about a broader and more profound impact on the organic synthesis as a whole than the Pd- or Ni-catalyzed cross-coupling with organometals containing Zn, B, Al, Zr, Mg, and several other metals. It may not be a gross overstatement to say that the Pd- or Ni-catalyzed cross-coupling is applicable to the synthesis of practically all types of organic compounds in many cases of which either no alternative direct routes exist or no better and satisfactory procedures are available. Clearly, further seminal and developmental investigations are needed, but the Pd- or Ni-catalyzed cross-coupling methodology is here to stay for use by all synthetic chemists.



Scheme 3.

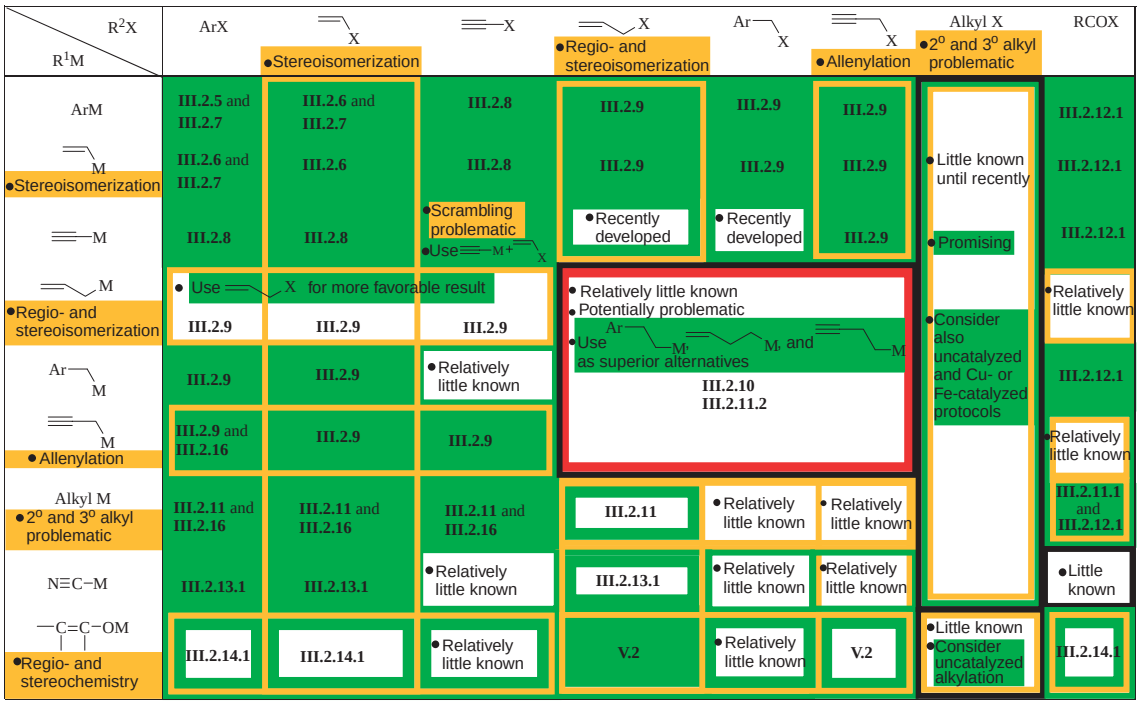


Scheme 4.

2. The Current Scope of the Pd- or Ni-Catalyzed Cross-Coupling and Its Application to the Natural Product Syntheses

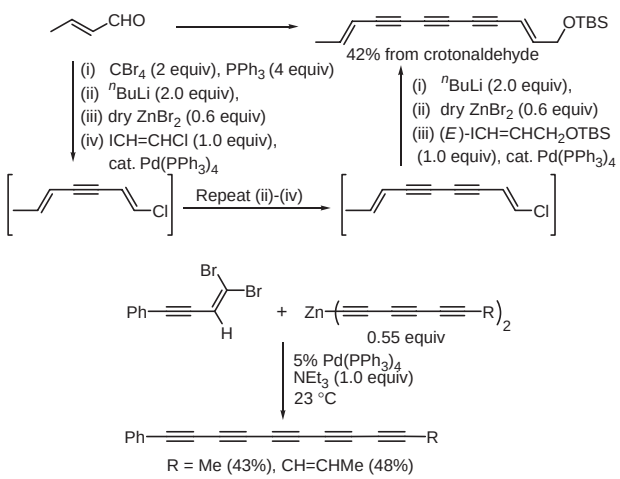
Most of the results on the Pd-catalyzed cross-coupling as of several years ago were systematically reviewed in Part III of *the Handbook of Organopalladium Chemistry for Organic Synthesis* edited by this author.[40] The data available as of several years ago permitted the preparation of Table 2. For detailed information, the readers are referred to pertinent chapters indicated in the table. Of the 72 types of cross-coupling represented by the same number of boxes, covering practically all conceivable types of organic compounds, well over 50 of them are at least partially green, indicating that the corresponding types of cross-coupling either work very well (indicated by fully green boxes) or are promising, even though more work is needed for more reliable scope delineation. Until recently, the use of alkyl electrophiles had been considered to be difficult because of the generally sluggish oxidative addition of alkyl halides with those phosphines which were commonly used for cross-coupling, such as PPh_3. Over the past decade or so, the use of bulky alkyl-containing phosphines,[41] such as ^{t}Bu$_3$P, *N*-heterocyclic carbenes,[42] and others[43] has changed the scope of those cases where alkyl halides are used. What do not appear to have been as yet well delineated are their merits and demerits relative to (i) classical uncatalyzed alkylation protocols involving organometals containing Li and Mg and (ii) their Cu- or Fe-catalyzed counterparts.[9,44] This topic, however, is not discussed further in this paper.

Table 2. Scope and Limitations of the Pd-Catalyzed Cross-Coupling with Organometals Containing Zn, B, Al, Zr, Mg, etc.



Note: Numbers indicated are the pertinent chapter numbers in *Handbook of Organopalladium Chemistry for Organic Synthesis*, ed. by E. Negishi, Wiley-Interscience, New York, **2002**, Vol. 2, p. 3279.

Potentially more problematic and challenging are those nine types of cross-coupling involving allyl, benzyl, and/or propargyl groups, where "pair"-selectivity and regioselectivity as well as stereoselectivity, if applicable, need to be well controlled.[45] Fortunately, highly satisfactory alternate routes to the same desired compounds have been systematically developed by the author's group through the use of homoallyl-, homopropargyl-, and homobenzylmetals.[35,46] Whereas the ingeniously devised Biellmann allyl–allyl coupling[47] requires several steps for homologation of isoprenoids by one isoprene unit, the Pd-catalyzed homoallyl–alkenyl coupling permits not only a one-step homologation with a pair of *E* and *Z* five-carbon modular synthons prepared in two steps from homopropargyl alcohol but also essentially complete (≥98%) regio- and stereoselectivities.[46] Another long-pending problem was how to achieve highly "pair"-selective alkynyl–alkynyl coupling. Neither the classical Cadiot-Chodkiewicz reaction[48] nor any of the Heck, Sonogashira, and Negishi Pd-catalyzed alkynyl–alkynyl coupling reactions[49] is predictably and satisfactorily "pair"-selective. This problem has been overcome by resorting to the fully "pair"-selective and comparably efficient Pd-catalyzed alkynyl–alkenyl coupling using (*E*)-ICH=CHCl or (*E*)-ICH=CHBr prepared in one step from HC≡CH and ICl or IBr,[50] respectively. Once either of these synthons is prepared, a highly efficient and selective synthesis of conjugated triynes and higher oligoynes can also be prepared in one or less step per one ethyne unit[51] (Scheme 5).

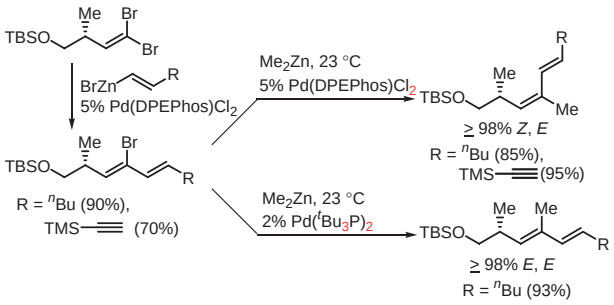


Scheme 5.

As indicated above, the development of the Pd- or Ni-catalyzed cross-coupling is by no means complete. Some seemingly mysterious puzzles and difficulties have been encountered even in the recent past and some still exist even today. For example, the Pd-catalyzed alkynyl–benzyl coupling reaction had been difficult and unknown, until Sarandeses et al.[52] reported satisfactory results obtained with alkynylindiums. Prompted by this report, the author's group reinvestigated systematically both alkynyl–benzyl[53] and alkynyl–allyl[54] coupling reactions and found that alkynylmetals containing Zn, In, and B used in conjunction with $Pd(dppf)Cl_2$ and $Pd(DPEphos)Cl_2$ can lead to excellent results. Another recent surprise in the area of Pd- or Ni-catalyzed cross-coupling is that certain alkenyl halides can undergo nearly complete stereoinversion during the Pd-catalyzed cross-coupling,[55] mandating modification of the long-standing paradigm stating that alkenyl electrophiles should undergo cross-coupling with retention of stereochemis-

try (Scheme 6). Both promotion and prevention of this hitherto unknown phenomenon are of synthetic and basic chemical significance and are currently under investigation.

Finally, the Pd-catalyzed cross-coupling in the past, especially in academia, has been performed typically with 1–5 mol % of a Pd catalyst. For economical and other reasons, it is desirable to reduce the amounts of generally expensive Pd or even Ni catalysts, preferably to the $\leq$0.1–0.01 mol %, at which level a catalyst costing \$10000/mol would effectively cost mere \$1–10/mol. A recent survey of the Pd-catalyzed aryl–aryl, alkenyl–aryl, aryl–alkenyl, alkenyl–alkenyl, and alkynyl–alkenyl coupling reactions with organozincs and or-



Scheme 6.

Table 3-1. Application of the Negishi Coupling to the Synthesis of Natural Products and Other Compounds of Medicinal and Agrochemical Interest: Aryl–Aryl Coupling (Negishi Protocol)

Year	Name of natural product	Major author	Year	Name of natural product	Major author
1979	Steganone (Ni catalyst)	R. A. Raphael[57]	1996	Korupensamine A & B	T. R. Hoye[62]
1992	Biphenomycin B	U. Schmidt[58]	2000	Losartan	W. Cabri and
1994	Xenalepin	K. Koch[59]	2000	Tasosartan	R. Di Fabio[63]
1995	Egonol	A. Ohta[60]	2001	(−)-Cytisine	J.-C. Plaquevent[64]
1995	(±)-Machicendiol	A. Ohta[60]	2001	Eupomatenoid-15	T. Bach[65]
1995	Magnolol	N. A. Lebel[61]	2002	Diazonamide A	K. S. Feldman[66]
1995	(−)-Monoterpenyl magnolol	N. A. Lebel[61]	2003	PDE472 (an inhibitor of phosphodiesterase Type 4D)	P. W. Manley and M. Acemoglu[67]

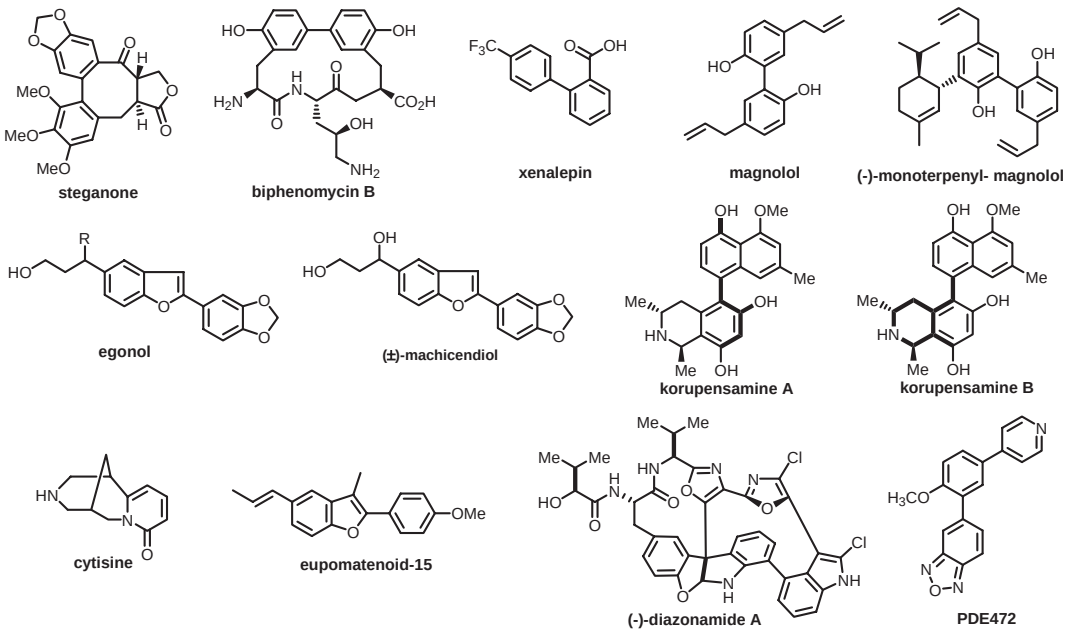


Table 3-2. Application of the Negishi Coupling to the Synthesis of Natural Products and Other Compounds of Medicinal and Agrochemical Interest: Aryl–Alkenyl and Alkenyl–Aryl Coupling (Negishi Protocol)

Year	Name of natural product	Major author	Year	Name of natural product	Major author
1990	(*Z*)-Tamoxifen	R. McCague[68]	2001	(−)-Diazonamide A	P. G. Harran[72]
1990	Vineomycinone B2 methyl ester	M. A. Tius[69,70]	2003	UB-165(nicotinic acetycholine receptor)	T. Gallagher[73]
1996	ICIA5504	R. Rossi[71]			

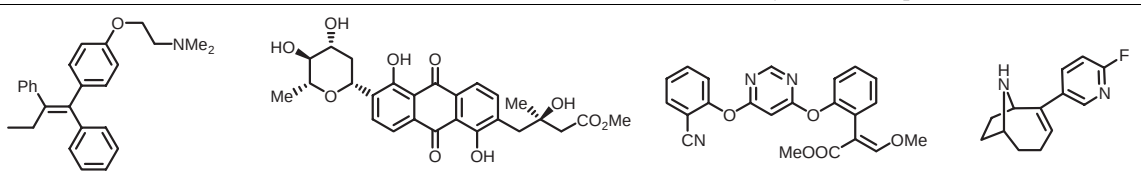


Table 3-3. Application of the Negishi Coupling to the Synthesis of Natural Products and Other Compounds of Medicinal and Agrochemical Interest: Alkenyl–Alkenyl Coupling (Negishi Protocol)

Year	Name of natural product	Major author	Year	Name of natural product	Major author
1987	Piperovatine	L. Crombie[74]	2000	Pitiamide A	P. Wipf[87]
1991	Methyl dimorphecolate	J. Duffault[75]	2000	Xerulin	E. Negishi[88]
1991	Vitamin A	E. Negishi[76]	2001	β-Carotene	E. Negishi[88]
1995	Papulacandin D	A. G. M. Barrett[77,78]	2001	γ-Carotene	E. Negishi[89]
1996	Strobilurin A	R. Rossi[71]	2001	(−)-Diazonamide A	P. G. Harran[72]
1996	Discodermolide	S. L. Schreiber[79]	2001	Eunicenone A	E. J. Corey[90]
1996	Nakienone B	E. Negishi[80]	2001	FR901464	E. N. Jacobson[91]
1996	Zaragozic acid C	I. Paterson[81]		(antitumor antibiotics)	
1997	Gadain	R. Rossi[82]	2002	Motuporin	J. S. Panek[92]
1997	Savinin	R. Rossi[82]	2004	*cis*-Bupleurynol	M. G. Organ[93]
1997	Nakienone A	E. Negishi[83]	2004	*trans*-Bupleurynol	M. G. Organ[93]
1998	(±)-Carbacyclin	E. Negishi[84]	2004	(−)-Callystatin A	J. S. Panek[94]
1999	Lissoclinolide	E. Negishi[85]	2004	6,7-Dehydrostipiamide	E. Negishi[95]
1999	Reveromycin B	E. A. Theodorakis[86]	2004	Xerulinic acid	R. Bruckner[96]

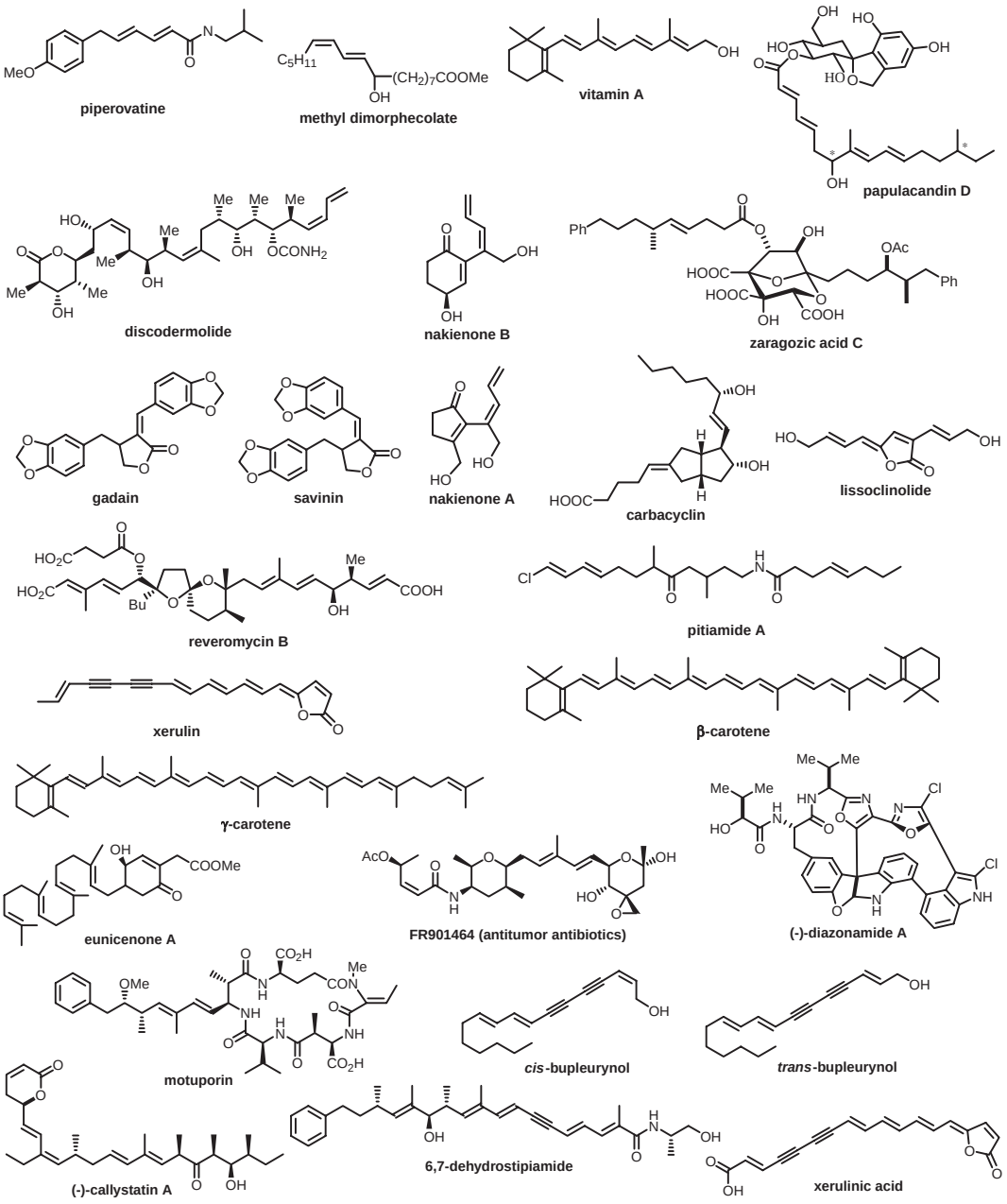


Table 3-4. Application of the Negishi Coupling to the Synthesis of Natural Products and Other Compounds of Medicinal and Agrochemical Interest: Alkynylation (Negishi Protocol)

Year	Name of natural product	Major author	Year	Name of natural product	Major author
1982	*Cortinellus berkeleyanus*	P. Vermeer[97]	2001	(−)-Salicylihalamide A	A. Fürstner[102]
1988	Marasin	J. Boersma[98]	2001	(−)-Salicylihalamide B	A. Fürstner[102]
1997	Freelingyne	E. Negishi[99]	2004	Ant venom	M. G. Organ[103]
2000	Xerulin	E. Negishi[88]	2004	*cis*-Bupleurynol	M. G. Organ[93]
2000	(±)-Harveynone	E. Negishi[100]	2004	*trans*-Bupleurynol	M. G. Organ[93]
2000	(−)-Tricholomenyn A	E. Negishi[100]	2004	Duocarmycin SA	K. Hiroya[104]
2001	(+)-Adociacetylene B	B. W. Gung[101]	2004	6,7-Dehydrostipiamide	E. Negishi[95]
2001	(−)-Adociacetylene B	B. W. Gung[101]			

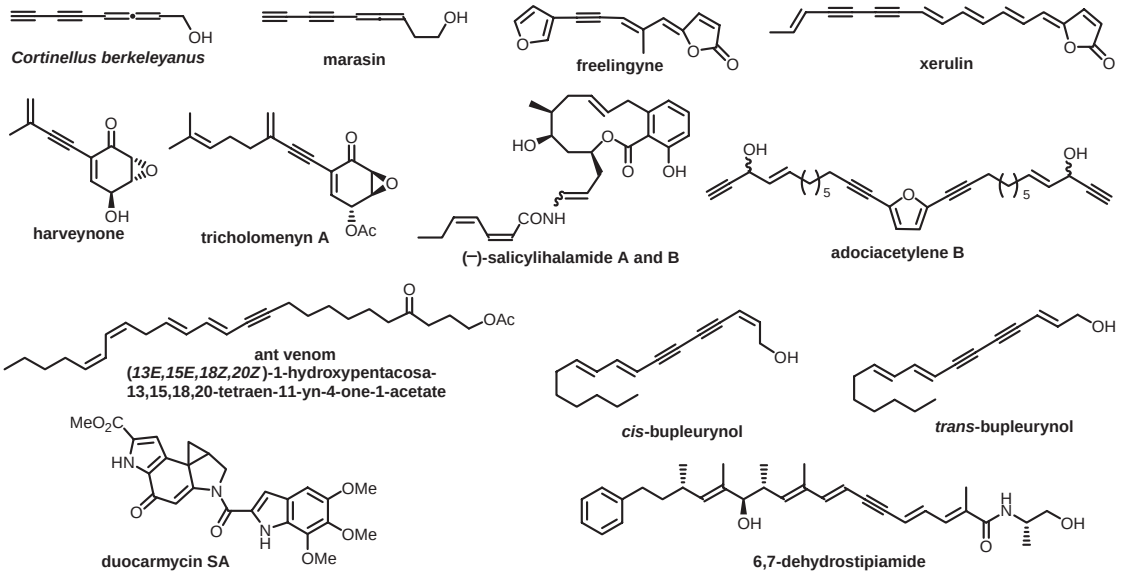


Table 3-5. Application of the Negishi Coupling to the Synthesis of Natural Products and Other Compounds of Medicinal and Agrochemical Interest: Allylation, Benzylation, and Propargylation (Negishi Protocol)

Year	Name of natural product	Major author	Year	Name of natural product	Major author
1981	α-Farnesene	E. Negishi[105]	1998	Coenzyme Q_6	B. H. Lipshutz[108]
1981	(*Z*)-α-Farnesene	E. Negishi[105]	1998	Coenzyme Q_7	B. H. Lipshutz[108]
1982	*Cortinellus berkeleyanus*	P. Vermeer[97]	1998	Coenzyme Q_{10}	B. H. Lipshutz[108]
1995	(3*Z*,6*Z*)-Dodeca-3,6-dien-1-ol	A. C. Oehlschlager[106]	1998	Menaquinone-3	B. H. Lipshutz[108]
1996	Hennoxazole A	P. Wipf[107]	2002	Coenzyme Q_3 and Q_{10}	E. Negishi[109]
1998	Coenzyme Q_3	B. H. Lipshutz[108]	2002	Menaquinone-3	E. Negishi[109]
1998	Coenzyme Q_5	B. H. Lipshutz[108]	2004	Furano-epothilone D	D. Schinzer[110]

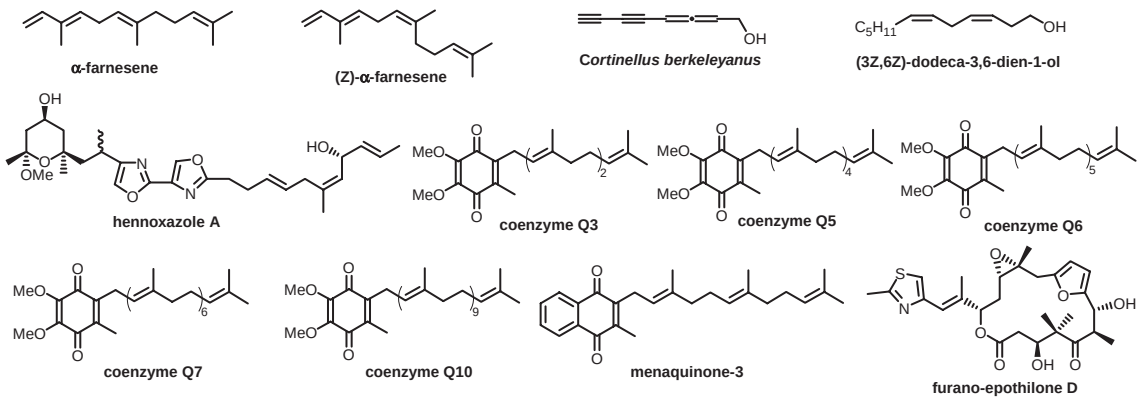
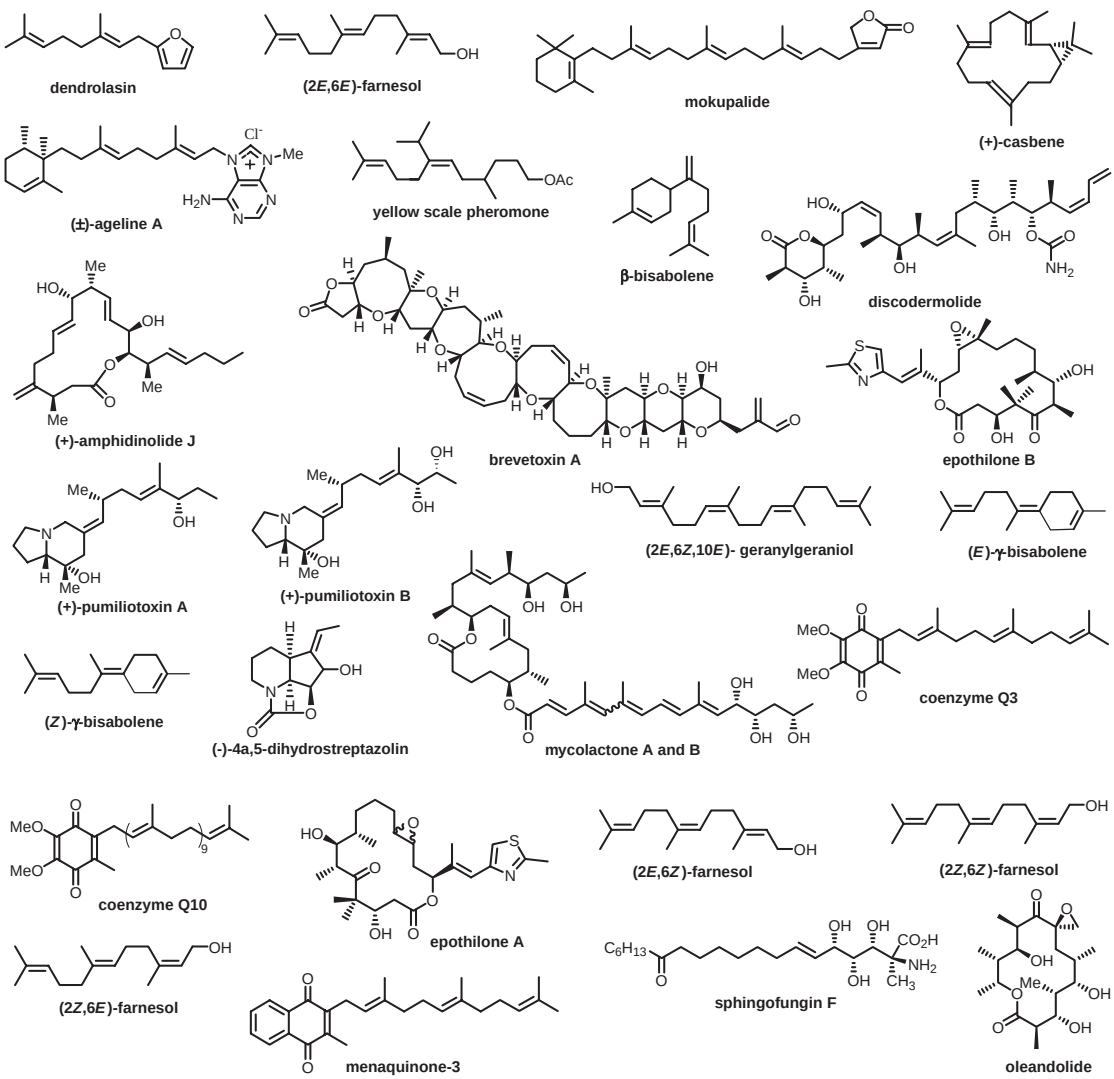


Table 3-6. Application of the Negishi Coupling to the Synthesis of Natural Products and Other Compounds of Medicinal and Agrochemical Interest: Alkylation, Homoallylation, Homopropargylation, and Homobenzylation (Negishi Protocol)

Year	Name of natural product	Major author	Year	Name of natural product	Major author
1980	Dendrolasin	E. Negishi[111]	2002	(2*E*,6*Z*)-Farnesol	E. Negishi[109]
1980	(2*E*,6*E*)-Farnesol	E. Negishi[112]	2002	(2*Z*,6*Z*)-Farnesol	E. Negishi[109]
1980	Mokupalide	E. Negishi[111]	2002	(2*Z*,6*E*)-Farnesol	E. Negishi[109]
1987	(+)-Casbene	J. E. McMurry[113]	2002	Menaquinone-3	E. Negishi[109]
1989	(±)-Ageline A	T. Tokoroyama[114]	2002	Oleandolide	J. S. Panek[131]
1989	Yellow scale pheromone	J. G. Millar[115]	2002	Sphingofungin F	W.-H. Ham[132]
1994	β-Bisabolene	R. Rossi[116]	2003	Borrelidin	J. P. Morken[133]
1995	(+)-Discodermolide	A. B. Smith, III[117]	2003	Delactonmycin	R. A. Pilli[134]
1998	(+)-Amphidinolide J	D. R. Willams[118]	2004	(−)-Callystatin A	J. S. Panek[94]
1999	Brevetoxin A	K. C. Nicolaou[119–123]	2004	Capensifuranone	D. R. Williams[135]
1999	(−)-Epothilone B	D. Schinzer[124]	2004	(+)-Murisolin	D. P. Curran[136]
1999	(+)-Pumiliotoxin A and B	C. Kibayashi[125]	2004	Scyphostatin	E. Negishi[137]
2000	(2*E*,6*Z*,10*E*)-Geranylgeraniol	E. Negishi[109,126]	2004	Scyphostatin	R. J. K. Taylor[138]
2001	(*E*)- and (*Z*)-γ-Bisabolene	E. Negishi[127]	2004	Scyphostatin	T. Katoh[139]
2001	(−)-4*a*,5-Dihydrostreptazolin	J. Cossy[128]	2004	Siphonarienal	E. Negishi[140]
2001	Mycolactones A and B	Y. Kishi[129]	2004	Siphonarienolone	E. Negishi[140]
2002	Coenzyme Q_3	E. Negishi[109]	2004	Siphonarienone	E. Negishi[140]
2002	Coenzyme Q_{10}	E. Negishi[109]	2005	Ionomycin (intermediate)	E. Negishi[141]
2002	(−)-Epothilone A	K. H. Altmann[130]	2005	Borrelidin (intermediate)	E. Negishi[141]



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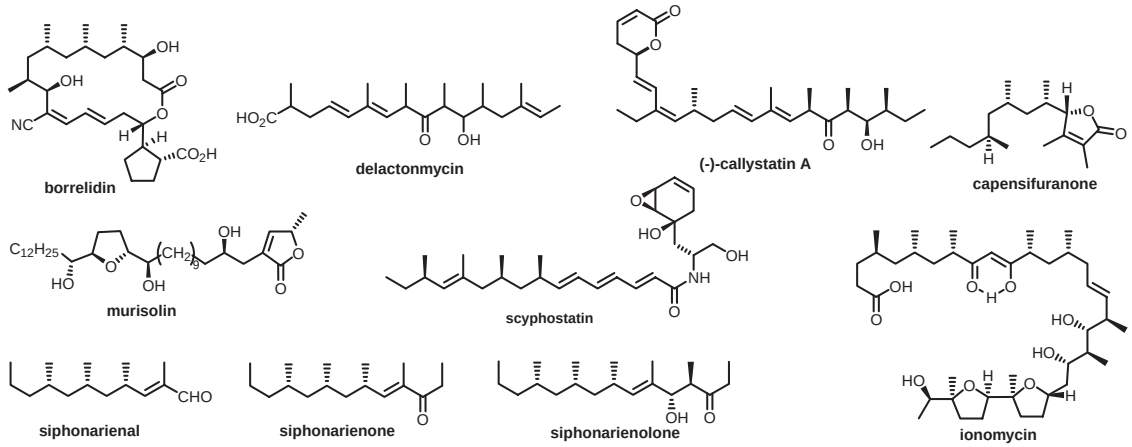
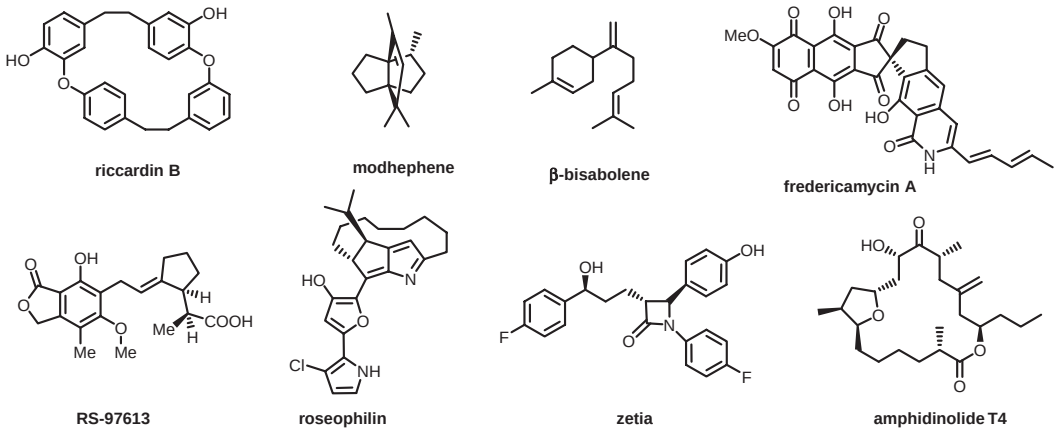


Table 3-7. Application of the Negishi Coupling to the Synthesis of Natural Products and Other Compounds of Medicinal and Agrochemical Interest: Acylation (Negishi Protocol)

Year	Name of natural product	Major author	Year	Name of natural product	Major author
1985	Riccardin B	M. Iyoda[142]	1998	Roseophilin	A. Fürstner[146]
1990	(±)-Modhephene	D. P. Curran[143]	1998	Zetia (a cholesterol absorption inhibitor)	S. B. Rosenblum[147]
1994	β-Bisabolene	R. Rossi[116]			
1996	Fredericamycin A	P. A. Evans[144]	2002	Amphidinolide T4	A. Fürstner[148]
1996	RS-97613	D. B. Smith[145]			

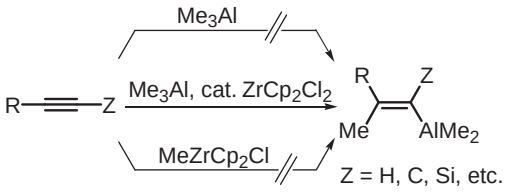


ganic iodides revealed that all of the reactions tested yielded turnover numbers (TON) exceeding 10^5 along with good product yields in cases where chelating ligands, such as dppf and DPEphos, were used.[56] This author is inclined to propose the use of product yield–TON profiles for more reliable and useful comparisons of various protocols rather than mere product yields observed at high catalyst loading levels, e.g., 5 mol %.

The synthetic scope and utility of the Pd- or Ni-catalyzed cross-coupling may be most vividly appreciated by noting numerous examples of its application to natural product syntheses. In Table 3[57–148] consisting of 7 subtables, only some representative examples of those that involve the use of Negishi coupling are listed in the chronological order.

3. Discovery and Development of the Zr-Catalyzed Alkyne Carboalumination and Its Application to the Natural Product Syntheses. Dynamic Polarization as a Means of Activation of One Lewis Acid by Another

The alkyne hydrometalation–Pd-catalyzed cross-coupling tandem process discussed in Sect. 1 has provided a very attractive, efficient, and selective route to disubstituted alkenes. In view of a large number of naturally occurring organic compounds of important biological activities containing trisubstituted alkenes, especially those with branching Me groups, it became highly desirable to have the corresponding carbometalation, especially methylmetation, of alkynes. At the time this author became interested in such reactions in the mid-1970's, he was familiar with Normant's carbocupration of alkynes reported several years earlier.[149,150] Unfortunately, the reaction was not well suited for the single most important case of methylcupration, which required running the reaction typically at around $-20\,^{\circ}C$ for several days to a week. Whereas hydroboration is a very facile process, attempts to induce methylboration of alkynes in the author's group were not successful. In view of the short C–B bond length (1.57 Å for Me_3B)[151] and the small empty 2p orbital of B, the steric hindrance factor may be a major hurdle to be overcome. Noting the substantially longer C–Al bond length (1.97 and 2.14 Å for the terminal



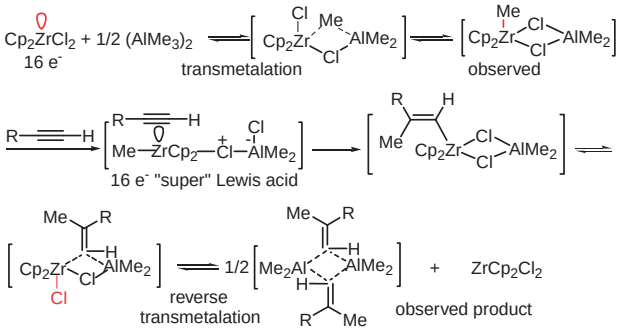
Scheme 7.

and bridging Me–Al bonds of Me_3Al, respectively),[151] the reaction of phenylacetylene with Me_3Al, was investigated. Little or no reaction was observed at room temperature. At elevated temperatures (≥70–80 °C), terminal alumination of phenylacetylene was observed. This author's vague familiarity with the Ziegler–Natta polymerization of alkenes with alkylaluminums and Ti salts[7] prompted him to consider the use of a homogeneous mixture of Me_3Al and $TiCp_2Cl_2$ in CH_2Cl_2. The very first reaction of PhC≡CPh with this bimetallic reagent in a 2:1:1 molar ratio of Me_3Al, $TiCp_2Cl_2$, and PhC≡CPh run at room temperature produced, after hydrolysis, the desired (*Z*)-α-methylstilbene in 84% yield in ≥98% stereoselectivity.[152] Iodinolysis gave the corresponding iodide in 75% yield.[152] A later investigation[153] fully identified the carbometalation product as the corresponding alkenyltitanocene chloride. Thus, this reaction is only stoichiometric in Ti. Much more disappointing was that the synthetic scope of the reaction turned out to be very limited. The reaction of alkyl-substituted alkynes was complicated with competitive allene formation, and terminal alkynes were susceptible to terminal metalation.[152]

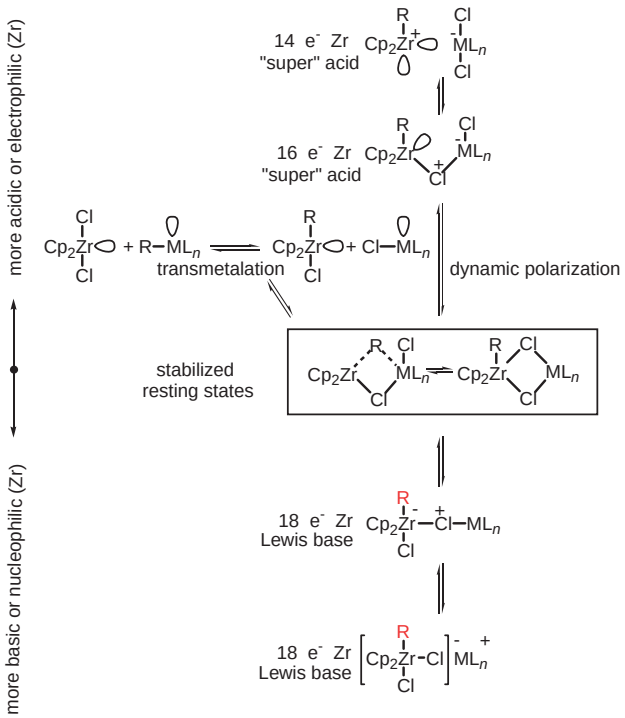
All of the above-mentioned difficulties were overcome at one sweep merely by substituting $TiCp_2Cl_2$ with $ZrCp_2Cl_2$.[154] As suggested by Scheme 7, the Me_3Al–$ZrCp_2Cl_2$ reagent reacts well with a wide variety of terminal, internal, and terminally metalated alkynes in a regio- and stereoselective manner. With terminal alkynes, the regioselectivity of about 95% has been observed with $ZrCp_2Cl_2$. A recent study by Lipshutz[155] shows that it can be further improved to ≥98–99% by using bulky indene-containing ligands. Alternatively, the use of controlled quantities, e.g., 0.9–0.95 equivalents, of reagents in subsequent reactions can often lead to ≥98% regioisomerically pure products, leaving behind less reactive internally metalated species unreacted. The stereoselectivity observed with non-metalated alkynes is very nearly 100%. From a more basic chemical viewpoint, the reaction proved to be catalytic in $ZrCp_2Cl_2$. Particularly noteworthy is that both Zr and Al are needed, since either omission of $ZrCp_2Cl_2$ or the use of preformed $MeZrCp_2Cl$ free of Al leads to no reaction.

Extensive mechanistic studies[156] have led to a mechanism in which a "super"-Lewis acidic dipolar bimetallic complex best represented by $MeZrCp_2$–$^+$Cl–$^-$$AlMe_2Cl$ must serve as the crucial reactive species. The required Me–Cl exchange via transmetalation is clearly observable by NMR spectroscopy. Although an alternative Al-centered process cannot be completely ruled out, the C–Zr bond addition, or carbozirconation, mechanism appears to be most plausible. This mechanism requires a reversible double transmetalation process shown in Scheme 8, and the needed driving force must be provided by energetically favorable and observable formation of the doubly alkenyl-bridged alkenylalane dimer as a stable product.

It was realized and explicitly discussed as early as 1981[157]



Scheme 8.



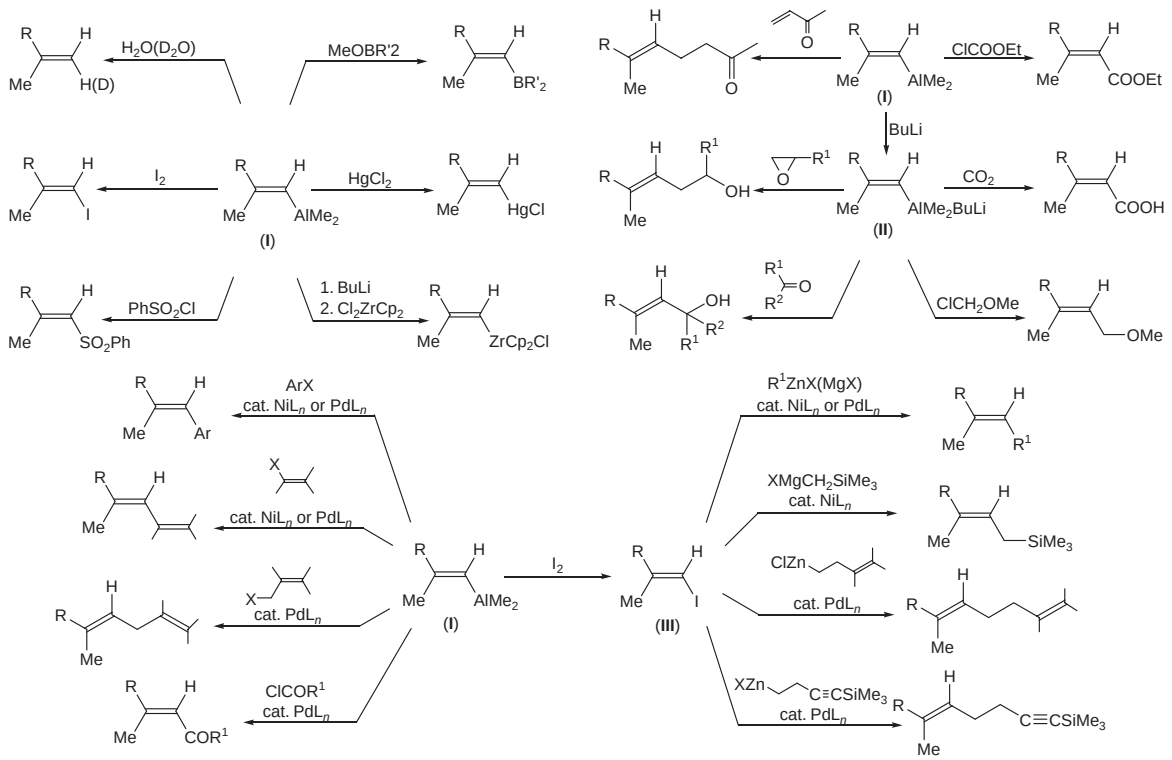
Scheme 9.

that interaction between two Lewis acidic metal compounds species can lead to not only transmetalation but also dynamic and static (or permanent) polarization. The significance of transmetalation has been amply demonstrated throughout this article including this section. What should be firmly noted here is that interaction between two Lewis acidic species can lead to the formation of a variety of bimetallic species of various degrees of acidity (or electrophilicity) and basicity (or nucleophilicity) through polarization, as illustrated by using $16e^-$ $ZrCp_2Cl_2$ as one Lewis acid. Relative Lewis acidity and basicity of $ZrCp_2$-containing species are schematically indicated by their positions on a vertical scale (Scheme 9). These modes of bimetallic activation between the Lewis acidic species, same or different, have been recently termed as "the two-is-better-than-one" principle.[158] As discussed earlier, the Pd- or Ni-catalyzed cross-coupling must involve transmetalation permitting sequential utilization of two metals. In the Zr-catalyzed carboalumination, generation of a "super"-Lewis acidic $16e^-$ zirconocene derivative must require dynamic polarization involving simultaneous participation of both Zr and Al at the

crucial stage, which must, however, be preceded and followed by reversible transmetalation (Scheme 9). Within the past ten years, the author has come to realize that his concept shares a basic principle with G. Olah's concept of "super" acid generation dealing mostly with Brønsted acids.[159] These concepts of activation of an acid by another acid are so fundamental that their basic scientific and practical chemical values should prove to be vast and profound. Yamamoto and Futatsugi have fully generalized the concept and has been consciously and masterfully exploiting the principle to advance organic synthetic methodology.[160]

A series of detailed structural and mechanistic investigations have revealed that the Zr-catalyzed ethyl- and higher alkylalumination can be complicated by cyclic carbometalation processes induced via highly intriguing bimetallic β-agostic interaction.[161] The absence of β-H in the Me group protects the Zr-catalyzed methylalumination from all of these complications stemming from cyclic carbometalation. The Zr-catalyzed allyl- and benzylalumination reactions[162] also appear to be favorable, perhaps for the same reason, but more work is needed for their full development as useful synthetic reactions. Intense efforts are also being made to develop synthetically more dependable and useful Zr-catalyzed ethyl- and higher alkylalumination.

In marked contrast with the limitations mentioned above, the Zr-catalyzed alkyne methylalumination has proved to be dependably and predictably applicable to a vast range of alkynes. Its synthetic utility may be readily appreciated by inspecting various transformations that alkenylalanes obtainable via Zr-catalyzed alkyne methylalumination can undergo (Scheme 10)[163] and their applications to the synthesis of well over 100 complex natural products (Table 4[164–297]). Although most of the carbonyl groups are incompatible with the reaction, alcohols and amines as well as halogens can be tolerated. In fact, one of the best forms of their protection is not to use any of the widely used protecting groups. Instead, it is advisable to use one extra equivalent of Me_3Al that can serve as a convenient and superior protecting group.



Scheme 10.

Table 4. Application of the Zr-Catalyzed Carboalumination of Alkynes to the Stereoselective Syntheses of Natural Products

Year	Name of natural product	Major author	Year	Name of natural product	Major author
1978	Geraniol, ethyl geranate	E. Negishi[164]	1983	Retinals	W. H. Okamura[171]
1980	Monocyclofarnesol	E. Negishi[165]		Verrucarin J (**2**)	W. R. Roush[172]
	Mokupalide (**1**)	E. Negishi[166]		Udoteatrial	J. K. Whitesell[173]
	Dendrolasin		1984	Verrucarin J (**2**)	W. R. Roush[174]
	Farnesol	E. Negishi[167]		Brassinolide (**3**)	K. Mori[175]
	Brassinolide	J. B. Siddall[168]		Castasterone, dolicholide	
1981	*a*-Farnesene	E. Negishi[169]		Dolichosterone	
1982	Verrucarins A&J	W. R. Roush[170]		Verrucarin B[1]	W. R. Roush[176]

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Year	Name of natural product	Major author	Year	Name of natural product	Major author
1985	Zoapatanol	R. C. Cookson[177]		Concanamycin A	I. Paterson[220]
	Mycarose, *epi*-axenose	W. R. Roush[178]		(−)-PI-091 (**14**)	N. Iwasawa[221]
	Aurodox, efrotomycin	K. C. Nicolaou[179]		(+)-Curacin A (**11**)	J. D. White[222]
1986	Sesquiterpenes	H. J. Reich[180]		(3*Z*)-*a*-Farnesene	E. Negishi[223]
	Lophotoxin (**4**)	M. A. Tius[181]		FK-506 (**7**)	R. E. Ireland[224]
1987	Methyl kolavenate (**5**)	T. Tokoroyama[182]		Freelingyne (**15**)	E. Negishi[225]
	Milbemycin β_3 (**6**)	P. J. Kocienski[183]	1998	1233A	Y. Langlois[226]
1988	Brassinolide (**3**)	K. Mori[184]		(+)-Curacin A (**11**)	G. Pattenden[227]
	(+)-Sterpurene	W. H. Okamura[185]		Concanolide A	K. Toshima[228]
1989	FK-506 (**7**)	A. B. Smith, III[186]		Concanoamycin A	K. Toshima[229]
	Lophotoxin (**4**)	I. Paterson[187]		(−)-Pateamine A (**12**)	D. Romo[230]
	(*Z*)- and (*E*)-3,4-Dimethyl-hex-3-ene-1,6-diols	P. Deslongchamps[188]		Aurisides (**16**)	K. Yamada[231]
				(+)-Calyculin A	A. B. Smith, III[232]
	Ageline A	T. Tokoroyama[189]		(−)-Calyculin B	
	Lacrimin A (**8**)	P. Kocienski[190]		Okinonellin B (**17**)	D. Romo[233]
	Milbemycin β_1	S. V. Ley[191]		Menaquinone-3, CoQ_5	B. H. Lipshutz[234]
1990	Lacrimin A (**8**)	P. Kocienski[192]		Steroids	P. Deslongchamps[235]
	Avermectin B_{1a} (**9**)	S. V. Ley[193]	1999	Elenic acid	R. C. Hoye[236]
	FK-506 (**7**)	R. E. Ireland[194]		(−)-Bafilomycin A (**18**)	W. R. Roush[237]
1991	Avermectin B_{1a} (**9**)	S. V. Ley[195]		1233A	S. V. Ley[238]
	Vitamin A	E. Negishi[196]		Amphidinolide B (**19**)	T. K. Chakraborty[239]
	Phytol	S. Takano[197]		Epolactaene	S. Kobayashi[240]
1992	Aboa of theonellamide F	Y. Hamada and T. Shioiri[198]		CoQ_6, CoQ_7, CoQ_8	B. H. Lipshutz[241]
				(+)-Calyculin A	A. B. Smith, III[242]
	Gorgiacerone	L. A. Paquette[199]		(−)-Calyculin B	
	Pseudopterolide		2000	Pateamine (**12**)	G. Pattenden[243]
	Tobagolide			Amphidinolide B	G. Pattenden[244]
	Inhibitor of 2,3-oxidosqualene-lanosterol cyclase	A. C. Oehlschlager[200]		Phomactin D (**13**)	R. L. Halcomb[245]
				CoQ_{10} (**20**)	E. Negishi[246]
				Scyphostatin (**21**)	T. R. Hoye[247]
	Milbemycin K	S. Takano[201]		(*S*)-Methanophenazine	U. Beifuss[248]
	C(1)–C(14) tetraene unit of calyculin A	A. G. Barrett[202]		(*R*)-Methanophenazine	
				Aplyronines (**22**)	J. A. Marshall[249]
1993	1233A	P. M. Wovkulich and M. R. Uskokovic[203]		Methanophenazine	U. Beifuss[250]
			2001	Phomactin core	V. H. Rawal[251]
	Forskolin	P. Welzel[204]		Bafilomycin A_1 (**18**)	S. Hanessian[252]
	Milbemycin E	E. J. Thomas[205]		Concanamycin F (**23**)	K. Toshima[253]
	Callosobruchusic acid	A. Carpita[206]		Formamicin	W. R. Roush[254]
	A.B.C.[6.6.6] tricycles	P. Deslongchamps[207]		(+)-Ratjadone (**24**)	U. Bhatt[255]
1994	Suspensolide (**10**)	A. C. Oehlschlager[208]		(+)-Calyculin A	A. G. M. Barrett[256]
	Anastrephin			(10*R*,11*S*)-(+)-Juvenile hormones	K. Mori[257]
	Epianastrephin				
	Inhibitors of 2,3-oxidosqualene-lanosterol cyclase	A. C. Oehlschlager[209]		Bisdeoxylophotoxin	G. Pattenden[258]
				Ratjadone (**24**)	M. Kalesse[259]
				(−)-Fumagillol	J. Eustache[260]
	Manoalide	P. Kocienski[210]		β-Carotene,	E. Negishi[261]
1995	Curacin A (**11**)	W. H. Gerwick[211]		γ-Carotene (**25**), vitamin A	
	Curacin A (**11**)	J. D. White[212]	2002	(−)-Bafilomycin A_1 (**18**)	W. R. Roush[262]
	Vitamin A	A. R. de Lera[213]		Bafilomycin V_1	J. A. Marshall[263]
	Pateamine A (**12**)	D. Romo[214]		Rhizoxin D (**26**)	J. D. White[264]
1996	Pateamine (**12**)	G. Pattenden[215]		Meneaquinone-3	E. Negishi[265]
	Hygrolidin	S. Hashimoto[216]		CoQ_3, CoQ_{10}	
	Phomactin D (**13**)	Y. Yamada[217]		Vicenistatin	K. Kakinuma[266]
	CoQ_3, CoQ_4, CoQ_5	B. H. Lipshutz[218]		CoQ_{10}	B. H. Lipshutz[267]
	Vitamin K_1, vitamin K_2			Callipeltosides, aurisides	H. F. Olivo[268]
1997	(−)-7-Deacetoxyalcyonin acetate	L. E. Overman[219]		(−)-Sanglifehrin A	L. A. Paquette[269]
				β-Carotene,	A. R. De Lera[270]

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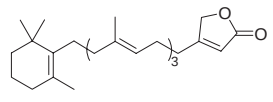
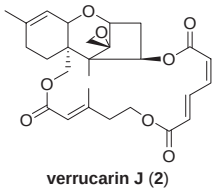
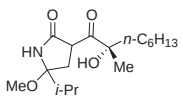
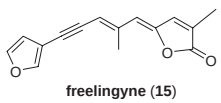
Continued.

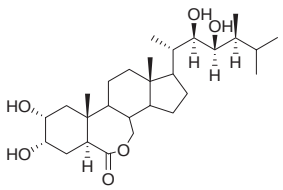
Year	Name of natural product	Major author	Year	Name of natural product	Major author
	(3*R*,3′*R*)-Zeaxanthin			(+)-Raspailol A, (+)-raspailol B	
	Serotonin antagonist LY426965	S. E. Denmark[271]	2004	Bafilomycin A_1 (**18**)	R. Lett[285]
				(+)-Phomopsidin	M. Nakada[286]
	(+)-Curacin A	G. Pattenden[272]		Guanacastepene A	O. Kwon[287]
2003	Manoalide	P. Kocienski[273]		MetAP-2 inhibitors	J. Eustache[288]
	Carbazomadurin A	H. Knolker[274]		(−)-SNF4435 C	K. A. Parker[289]
	Bafilomycin A_1 (**18**)	J. Prunet[275]		(+)-SND4435 D	
	Leptofuranin D	J. A. Marshall[276]	2005	Bisdeoxylophotoxin	G. Pattenden[290]
	Phomactin A	R. P. Hsung[277]		d-*trans*-Tocotrienoloic acid	S. M. Hecht[291]
	(9*Z*)- and (11*Z*)-8-Methylretinals	A. R. de Lera[278]		Placidenes	D. Trauner[292]
				Norzoanthamine	T. Irifune[293]
	Rhizoxin D (**26**)	J. W. Leahy[279]	2006	Bipinnatin J	D. Trauner[294]
	Ent-haterumalide NA	B. B. Snider[280]		Mycolactone A&B	E. Negishi[295]
	Ergosterine derivatives	U. Groth[281]		Epolactaene	E. Negishi[296]
	(±)-Phomactin A	G. Pattenden[282]		*N*-Acetylcysteamine	A. Kirschning[297]
	(±)-Phomactin A	G. Pattenden[283]		Thioester of seco-proansamitocin	
	(+)-Rottnestol	M. A. Rizzacasa[284]			

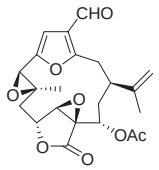


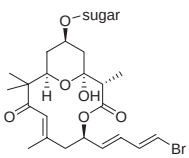


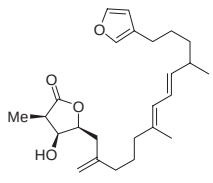


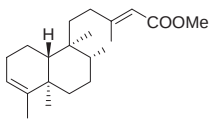


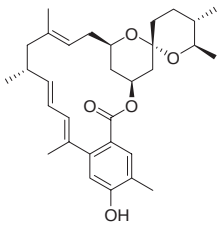


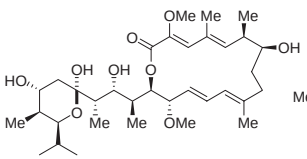


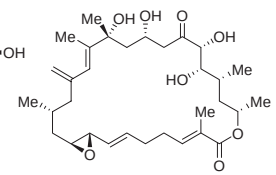


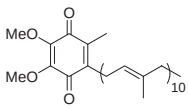


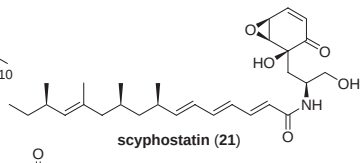


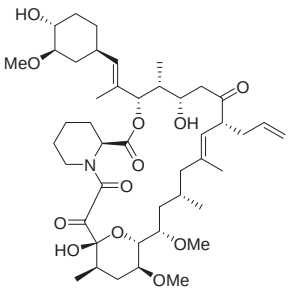


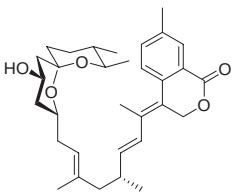


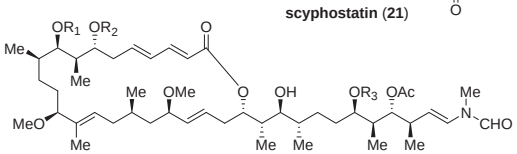


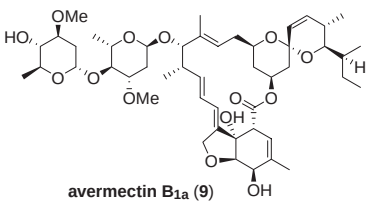


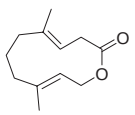


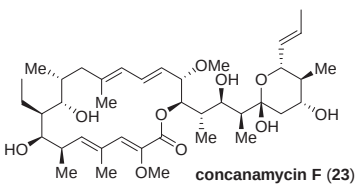












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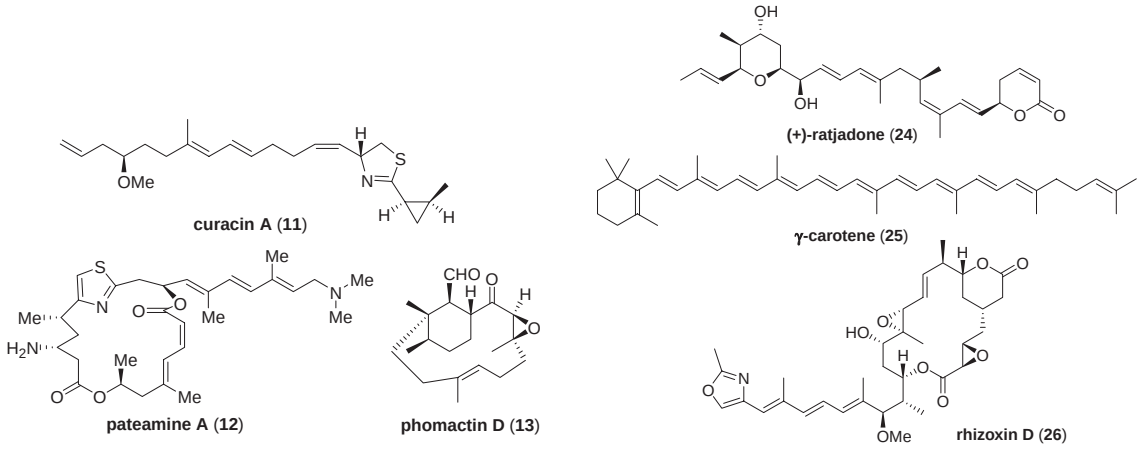
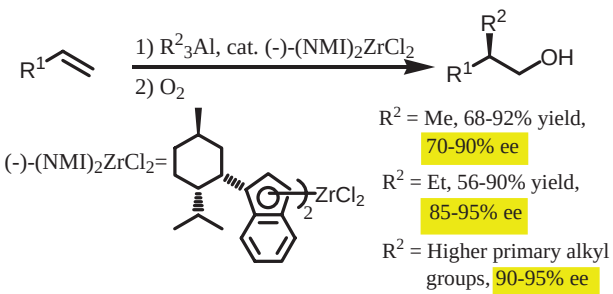


Table 5. Comparison of the ZACA Reaction with the Ziegler–Natta–Kaminsky Polymerization

Feature	ZACA reaction	Ziegler–Natta–Kaminsky Polymerization
Degree of polymerization (DP)	1	$\gg 1 \rightarrow$ ensemble of polymers of various DP
Alkyl group to be added	Me and RCH_2CH_2 but not $R^1R^2CHCH_2$	$R^1R^2CHCH_2$ except in the very first step
Stereochemistry	Both absolute and relative stereochemistry crtitically important	Tacticity (relative stereochemistry) is critically important but not absolute chemistry



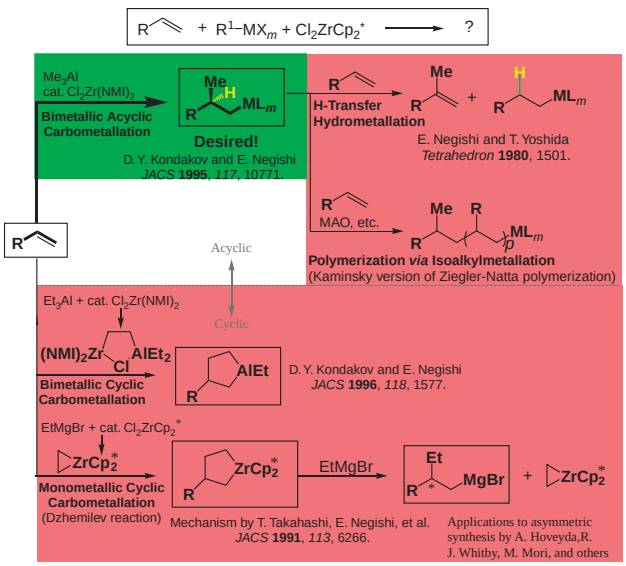
Scheme 11.

4. Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA Reaction). A Prototypical Asymmetric C–C Bond Formation Reaction that Is Catalytic in Both Transition Metal and Chiral Auxiliary

4.1 Discovery of the ZACA Reaction. The discovery of the Zr-catalyzed alkyne carboalumination discussed in the preceding section suggested to the author that the corresponding reaction of alkenes should also be feasible. Although some unsuccessful attempts were made with the achiral Me_3Al–$ZrCp_2Cl_2$ reagent system shortly after the discovery of its alkyne carboalumination, successful discovery of the ZACA reaction was delayed by seventeen long years, and two seminal papers reporting its discovery were finally published in 1995[298] and 1996[299] (Scheme 11). Of a dozen or so chiral indene-containing Zr-catalysts tested, dichlorobis(1-neomenthylindenyl)-zirconium, $(NMI)_2ZrCl_2$, of Erker et al.[300] gave the most favorable results both in product yield and enantioselectivity. Addition of methylaluminoxane (MAO),[301] isobutylaluminoxane (IBAO),[302] or just water[301] has been shown to be effective in accelerating otherwise sluggish reactions. In the meantime, the homogeneous modification of the Ziegler–Natta alkene polymerization represented by the Kaminsky protocol was developed.[303] This reaction must share some common fundamental features with the author's single-stage ZACA reaction, even though the two reactions also display some fundamentally different features, as briefly indicated in Table 5. Another extensive development with zirconocene derivatives made concurrently but independently was the predominantly stoichiometric cyclic carbozirconation discovered and developed by a large number of workers including the author's group.[304] Some catalytic processes involving cyclic carbozirconation[304b,304c] investigated by various workers including Dzhemilev et al.[305] and Takahashi et al.[306] were ingeniously applied to the development of some catalytic asymmetric processes by Hoveyda et al.[307] and later by Whitby et al.[308] and Mori et al.[309] Despite the common use of chiral zirconocene derivatives, this cyclic carbozirconation-based asymmetric C–C bond-formation reactions and the ZACA reaction display almost totally different reaction profiles and synthetic scopes (Table 6). In fact, both this cyclic process and the Kaminsky-type alkene polymerization represent some reactions to be avoided for observing favorable results in the ZACA reaction. As it turned out, however, the most troublesome side reaction to be avoided was the product-depleting H-transfer hydrometalation of isoalkylalanes[310] formed as the desired products.[298] Indeed, this had been the dominant reaction until bulky indene-based ligands were used.

Table 6. Comparison of the ZACA Reaction with the Zr-Catalyzed Carbometalation Proceeding via Cyclic Carbozirconation

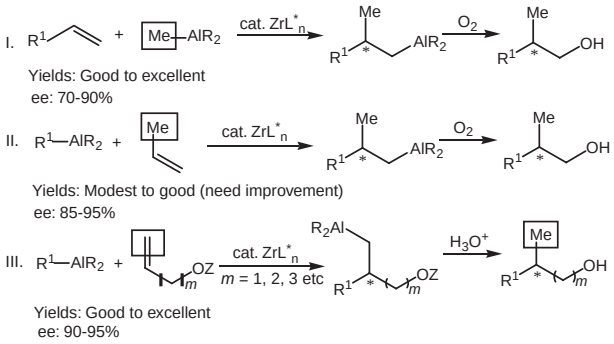
Feature	ZACA Reaction	Zr-catalyzed carbometalation via cyclic carbozirconation
Alkyl groups	Me and RCH_2CH_2 but not $R^1R^2CHCH_2$	Me cannot be used (no β-H) Et works well but ^{n}Pr and higher RCH_2CH_2 are low-yielding (<40–50%).
Heteroatoms	O, N, S, and halogens can be accomodated but not necessary	Allylic O, N, S, etc. appear to be critically needed for high asymmetric induction.
Counter cation	Al (Zn?)	Mg, Zn, and Al. Li cannot sustain Zr catalysis.
Mechanism	Acyclic and bimetallic	Cyclic



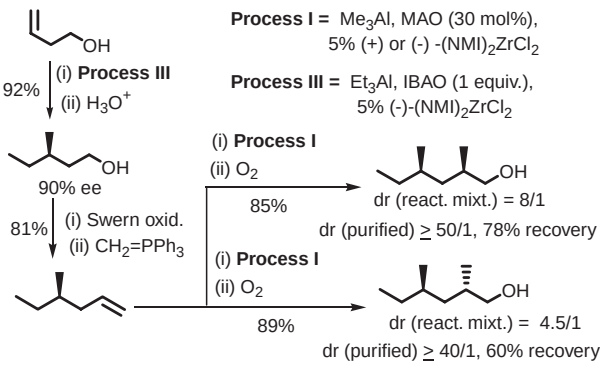
Scheme 12.

Although presentation of a detailed account is neither practical nor intended here, the summary shown in Scheme 12, which is based on literally hundreds of papers published since the 1970's should prove to be informative. In this scheme, various competing processes discussed above are shown in proper perspective, and the scheme indicates how essential it is to avoid (i) H-transfer hydrometalation, (ii) alkene polymerization, and (iii) the entire cyclic carbozirconation manifold. In reality, essentially no difficulty was encountered in avoiding alkene polymerization, presumably because of (a) the use of $\leq$1 molar ratio of an alkene to alkylalanes (typically 1/1–1/3) and (b) the absence of rate-accelerating aluminoxanes in early investigations. Although the current scope of the ZACA reaction is practically limited to the use of alkylalanes containing Me, Et, and primary alkyls represented by RCH_2CH_2, it should be noted that, in contrast with the Zr-catalyzed alkyne carboalumination, Et and higher primary alkyls of the RCH_2CH_2 type do react satisfactorily, exhibiting significantly higher enantioselectivity of $\geq$85–90% than methylalumination.[299] Isoalkyl groups, i.e., $R^1R^2CHCH_2$, cannot be used due to competitive β-H transfer hydrometalation. In contrast, the olefin polymerization must undergo a series of isoalkylmetalation except in the initiation step. Much more dangerous and delicate was the undesired competition coming form cyclic carbozirconation.[299] With alkylmetals containing Li or Mg, it does appear to be virtually impossible or very difficult at best to avoid the cyclic carbozirconation manifold. Less basic and more acidic organoalanes therefore are critically needed. Although there may be some other satisfactory metals, choice appears to be limited. Organoborons have not thus far yielded favorable results. In many respects, Zn lies between Mg and Al, and it does appear promising. However, more work is needed for full clarification and/or development. Even with Al, bimetallic (Zr–Al) cyclic carbometalation can be competitive, and they must be consciously suppressed for observing clean and useful ZACA reaction.[299] To this end, promotion of the desired ZACA reaction through the use of proper solvents, such as CH_2Cl_2 is critically important.

4.2 Development and Application of the ZACA Reaction. Despite some room for improvement, especially (i) improvement of the enatioselectivity of methylalumination and (ii) realization of higher turnover numbers through elevation of the current level of 20–100 to $\geq 10^3$–10^4, the ZACA reaction promises to provide a widely applicable, efficient, and selective asymmetric method for the synthesis of a variety of chiral organic compounds. Its earlier application to the synthesis of reduced terpenoids including vitamins E and K and phytol provided highly efficient routes to theses targets,[302,311] but some difficulties were encountered in the product purification. In view of a large number of naturally occurring and biologically important deoxypolypropionates, intense efforts for the development of efficient and selective methods for their synthesis have been made in the author's group. Through several conceptual and methodological breakthroughs, a highly efficient and satisfactory method has been developed, and further developmental work is still ongoing. Most of the currently known and widely used methods for the constructions of deoxypolypropionates are stoichiometric, requiring typically three steps for each homologation by one propylene unit.[312] Only a few other transition metal-catalyzed methods are known, of which one that involves catalytic asymmetric conjugate addition by Feringa et al. [313] is noteworthy. Even so, however, one homologation cycle appears to require typically three steps. Several breakthroughs achieved in the author's group briefly outlined below should prove to be useful in other methodological de-



Scheme 13.



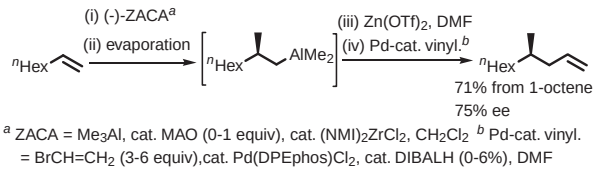
Scheme 14.

velopments as well.

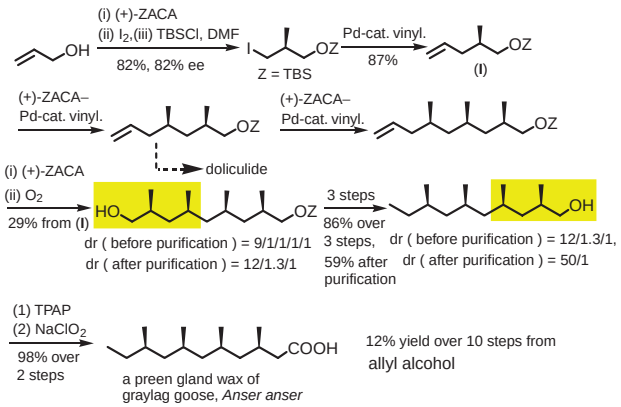
4.2.1 Three Complementary Protocols for the Preparation of 2-Methyl-1-alkanols: As indicated in Scheme 13, addition of the Me–Al bond via ZACA reaction leads to 70–90% ee, typically 70–80%.[312] The same products can be obtained in 85–95% ee by adding Et and higher alkyl groups and Al to propene and by using $(NMI)_2ZrCl_2$ of the opposite chirality. Both isomers of $(NMI)_2ZrCl_2$ are obtainable from the appropriate isomers of menthol with comparable ease. Moreover, addition of alkyl–Al bonds to free allyl[314] and homoallyl alcohols[312] as well as longer ω-alken-1-ols by ZACA reaction is generally high-yielding and highly enantioselective, typically around 90% ee. These three protocols can often be used interchangeably.

4.2.2 Enantioselective Amplification through Kinetic Resolution: Although often overlooked even today, a combination of two chiral compounds or fragments of average enantiomeric purity of 90% (or 80% ee) will produce products containing two chiral centers of overall enantiomeric purity of almost 99% (or 98% ee).[312] At this point, all that is needed to obtain stereoisomerically pure products is to remove two diastereomers, which is fundamentally more facile than enatiomeric separation (Scheme 14).

4.2.3 Dependably General Chromatographic Separation of 2,4-Dimethyl-1-hydroxybutyl Derivatives: On the basis of the generalization stated above, diastereomeric separation of various 2,4-dimethyl-1-hydroxybutyl derivatives was attempted by chromatography. In all cases that have been carried out to date, one round of ordinary chromatographic separation using silica gel and hexane–EtOAc has been sufficient to purify the desired major stereoisomers to ≥97–98% pure materials.[30,312,314–316] As needed, this operation may be repeated. The author has thus far failed to locate any prior claim to this effect in print. Regardless of its chronology, it should prove to be widely useful also in related cases. Accumulation of such pieces of information should be made, and an accumulated body of information should be made widely known and readily accessible to the practicing synthetic chemists.



Scheme 15.



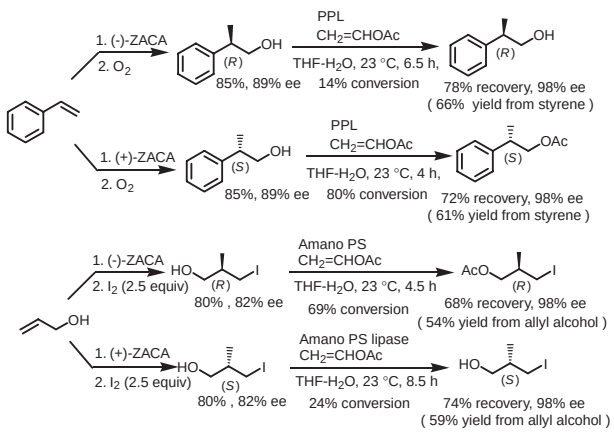
Scheme 16.

4.2.4 One-Pot ZACA–Pd-Catalyzed Vinylation Tandem Process for One-Step Iterative Homologation by a Propylene Unit: Initially, the author's group used a three-step iterative homologation cycle for incorporation of one propylene unit,[312,315,316] which consisted of (a) ZACA-oxidation, (b) iodination, and (c) metalation–Pd-catalyzed vinylation. Since the initial ZACA reaction product is an alkylalane, its direct use in the Pd-catalyzed vinylation was explored by skipping oxidation, iodination, and back-metalation via lithiation with two equivalents of ^{t}BuLi. Although $Zn(OTf)_2$ rather than $ZnBr_2$ or ZnI_2 was required, one-pot homologation cycle proceeding in nearly 70% overall yields was thus developed (Scheme 15).[30,314] In several cases, this one-pot homologation process was repeated four times without any stereoisomeric purification.[30,314] If one makes a reasonable assumption of an average enantioselectivity of 90% (or 80% ee) at each of the four asymmetric centers, the overall enantiomeric purity may reliably be estimated to be 99.985% (or 99.97% ee). Starting from allyl alcohol, one can readily synthesize terminally differentiated tetramethyl-1,9-nonanediol derivatives that can be fully purified by two chromatographic operations, namely one 2,4-dimethyl-1-hydroxybutyl unit at a time, and a few required synthetic manipulations, as exemplified in Scheme 16.[314]

4.2.5 ZACA–Lipase-Catalyzed Acetylation Synergy: Having developed an unprecedentedly efficient method for the synthesis of deoxypolypropionates, it was acutely realized that, only if ZACA products containing just one asymmetric

carbon center can be readily and predictably purified, the ZACA-based asymmetric synthetic method would become much more widely applicable. The author only recently became fully aware of the following strengths and weaknesses of the previously known lipase-catalyzed (*S*)-selective acetylation: (1) Enantiomerically pure (*R*)-2-methyl-1-alkanols can be reliably obtained from their racemic mixtures although the maximally attainable yield (or recovery) of (*R*)-alcohols of $\geq$98% ee is limited to 50% or more specifically $\leq$25% if $E = 10$, $\leq$35% if $E = 20$, and $\leq$45% if $E = 100$, where E (enantiomeric ratio or selectivity factor) $= \ln[(1 - C)(1 - ee)]/\ln[(1 - C)(1 + ee)]$ and C and ee are the extent of conversion and the enantiomeric excess of the unreacted alcohol, respectively.[317] As such, it is not an attractive method, especially if the starting 2-methyl-1-alkanols are very expensive. (2) Much more strikingly and importantly, the lipase-catalyzed acetylation method is practically incapable of providing the $\geq$99% pure acetates of (*S*)-2-methyl-1-alkanols from their racemic mixtures in one cycle, since it can be reliably predicted that the maximally attainable yields of $\geq$99% pure acetates should be $\leq$1–2% ($E \leq 100$).[317] Iterative purification processes, in which the target purity must be gradually elevated, will be required. This theoretical prediction also points to a significant advantage in being able to start with enantiomerically enriched (*S*)-2-methyl-1-alkanols. Some maximally attainable yields of $\geq$99% pure acetates of (*S*)-2-methyl-1-alkanols can be predicted as follows: $\leq$80% if the initial ee_o is 70% and E is 50; $\leq$85% if ee_o is 80% and E is 30; $\leq$95% if ee_o is 90% and E is 20.[317] It is clear that neither ZACA reaction alone nor lipase-catalyzed acetylation alone is capable of providing a satisfactory method for the synthesis of either *R* or *S* isomer of 2-methyl-1-alkanols of $\geq$99% isomeric purity but that a combination of the two would be, provided that (a) the ZACA reaction is sufficiently enantioselective, preferably $\geq$80–90% ee but minimally $\geq$70% ee and (b) the E values are sufficiently high, preferably $\geq$20–30. The ZACA–lipase-catalyzed acetylation tandem process has indeed been successfully applied to the purification of either *R* or *S* isomers of 2-methyl-1-alkanols, as represented by the results shown in Scheme 17.[314,318]

The number of chiral natural products synthesized through the use of ZACA reaction is still limited to fifteen or so including some fragmentary intermediates, as summarized in Table 7. Except for pitiamide A synthesized by Wipf et al.,[319] all of them have been synthesized in the author's group. This situation must be changed soon. To this end, commercialization of chiral ligands, Zr catalysts, and some versatile chiral synthons as well as further methodological advances are highly desirable.



Scheme 17.

5. Concluding Remarks

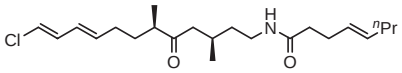
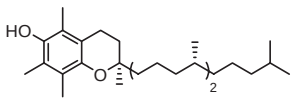
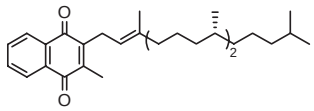
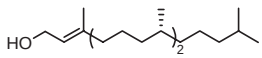
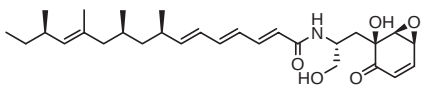
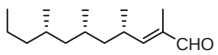
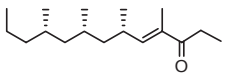
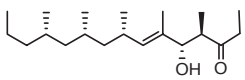
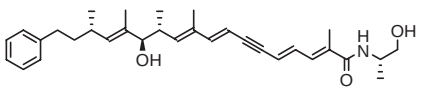
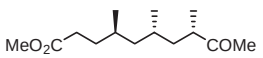
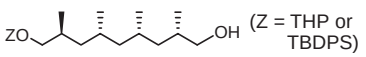
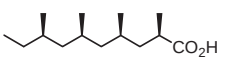
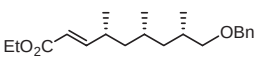
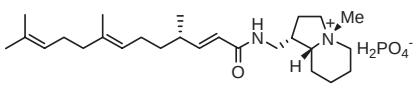
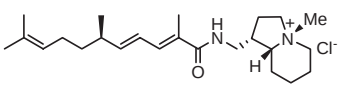
A couple of dozen d-block transition metals offer a number of attractive synthetic opportunities and distinguish themselves primarily because (1) they can simultaneously provide one or more valence-shell empty orbitals and filled nonbonding orbitals, often as readily accessible and/or stable species and (2) their chemical processes are often readily reversible even in cases where redox processes are involved. The former permits their participation in synergistic bonding schemes thereby imparting them "carbene-like" reactivities, while the latter permits their participation in catalytic processes.

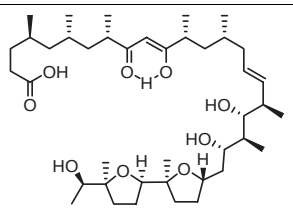
Binary combinations of elements offer vast synthetic opportunities that are not previously available or have been difficult to realize. Particularly attractive are the binary combinations of two metallic elements offering ubiquitous and reversible transmetalation as well as dynamic and permanent polarization leading to highly active electrophiles and nucleophiles (the two-is-better-than-one principle). Ideally and ultimately, it might be desirable to use all metals catalytically. Realistically, however, versatility, general applicability, specificity, selectivity, and other reaction characteristics must be simultaneously optimized in an overall sense. Consideration of these fundamentally important factors often points to transition metal-catalyzed organometallic reactions as a realistically attractive class of reactions that can ably satisfy various seemingly contradictory requirements mentioned above.

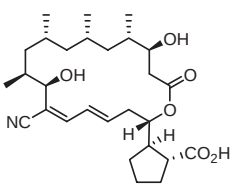
Systematic and long-ranging investigations based on these fundamental, if very simplistic, concepts and principles have led the author's group to the discoveries and/or development of (i) Pd- or Ni-catalyzed cross-coupling reactions of organometals containing Zn, B, Al, Zr, and others, (ii) Zr-catalyzed single-stage carboalumination of alkynes, and (iii) Zr-catalyzed asymmetric carboalumination of alkenes (ZACA reaction) among others. Together with some other protocols discovered and/or developed by other workers, most notably those of Tamao and Suzuki, the Pd- or Ni-catalyzed cross-coupling very likely represents the most widely applicable and yet highly selective synthetic method discovered and developed over the past several decades. Single-stage selective carbometalation including both alkyne and alkene carboalumination reactions catalyzed by Zr represents a novel synthetic pattern that was virtually nonexistent before 1970. In view of its fundamental significance, it appears destined to continue substantially expanding the horizon of the synthetic methodology in general. Gratifyingly, the synthetic community has very favorably embraced the Zr-catalyzed alkyne carboalumination. It is hoped that the newly discovered and developed ZACA reaction will also be similarly welcomed by the synthetic community.

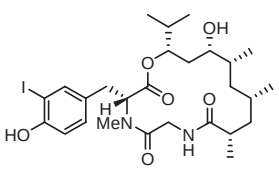
The author sincerely acknowledges most enjoyable collaborations with his co-workers and their immense contributions

Table 7. Natural Products Synthesized via ZACA Reaction

Natural product (Year)	Structure
Pitiamide A (2000)[319]	
Vitamin E (2001 and 2002)[302,311]	
Vitamin K (2001)[311,318]	
Phytol (2001)[311]	
Scyphostatin (side chain) (2004)[315]	
Siphonarienal (2004)[316]	
Siphonarienone (2004)[316]	
Siphonarienolone (2004)[316]	
6,7-Dehydrostipiamide (2004)[320]	
Ionomycin (**A**) (C1–C10 fragment) (2005)[30]	
Borrelidin (**B**) (C3–C11 fragment) (2005)[30]	
Preen gland wax of the graylag groose, *Anser anser* (2006)[314]	
Doliculide (**C**) (C1–C9 fragment) (2006)[314]	
(+)-Stellattamide A (side chain) (2007)[318]	
(+)-Stellattamide B (side chain) (2007)[318]	


ionomycin (**A**)


borrelidin (**B**)


doliculide (**C**)

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