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Magical Power of Transition Metals: Past, Present, and Future (Nobel Lecture)**

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carbometalation · cross-coupling · Negishi coupling · palladium

Biography

I was born on July 14, 1935 in Changchun, China, as a Japanese citizen. My family moved to Harbin when I was one and then to Seoul, Korea, two years before the end of World War II. I was admitted to an elementary school in Harbin at age six, a year earlier than normal, and I then went to Seoul as an eight-year old third grader. Shortly after the end of World War II in 1945, my family returned to Japan and moved into a house in Tokyo which my parents had purchased several years earlier and had miraculously survived many intensive bombings. A much more serious problem for my parents was how to feed a rapidly growing family of seven, with five children ranging from twelve to one. Their solution to this food-shortage problem was to move to an underdeveloped patch of land of a little less than one acre about 50 km southwest of the center of Tokyo. Although my father's attempt to become a farmer there was not very successful, this naturally wooded area called "Rinkan" in Yamato city, Kanagawa prefecture, became what I consider even now my "first hometown", where I spent my junior high school (seventh–ninth grades), high school (tenth–twelfth grades), and college years (1953–1958; five years as I needed to repeat my junior year due to gastrointestinal illness).

Despite all these difficulties, I recall my early school years through to the ninth grade mostly with positive and enjoyable memories. Although I virtually never studied outside the classroom through to the ninth grade, I was quite alert and enjoyed most of the classes, with the exception of calligraphy and Japanese language. But, I enjoyed the after-school hours before darkness even more. Those short after-school hours in the nearly six-month-long Harbin winters were spent skating in the playground covered with ice. I hardly recall my indoor activities before darkness through to my ninth grade. Several classmates and I in our junior high school jointly collected naturally growing grasses for rabbits, and took care of chickens—which virtually every family in our area were raising for food and minor supplementary income—but we never forgot to set aside some time for playing ball games and so on. For some reason, I found a world atlas on our very modest bookshelf to be to my liking and almost daily looked at it in the evening, especially during my Harbin days. Even with this manner of approach, I luckily established myself as one of the top students throughout my elementary and junior high school years.

My first setback, if only a temporary one, hit me when I applied for an "elite" high school in our prefecture called Shonan High School. Despite my superior scholastic standing, I was declared ineligible, because I was a year younger than my classmates. Luckily, several of my teachers at Yamato Junior High School, including my classroom teacher, S. Koyama, and music class teacher, T. Suzuki, who was the father of my future wife, Sumire, successfully persuaded Shonan High School officials to accept me. At Shonan, where only the top few of my 200-plus classmates at Yamato Junior High School attended, my lifestyle described above was no longer satisfactory. Nor was I sufficiently ambitious about my higher education. I soon noticed that the entire school was obsessed with a single notion of intensely training and successfully sending as many students as possible to several of the most highly rated universities, represented by the University of Tokyo, several other former Imperial Universities such as Kyoto, Osaka, and Nagaya, as well as Tokyo Institute of Technology.

Throughout my first year at Shonan, I was still mostly limiting my studying to that in the classrooms, which led me to earn the 123rd place in scholastic standing among a little more than 400 classmates. After a brief moment of disappointment, I then realized that, whereas there were a little more than 100 students who were ahead of myself, there were also nearly 300 others behind me. Back in those days, about 30–40 students, including one-time repeaters, were successfully entering the University of Tokyo each year from Shonan. It then suddenly occurred to me that, if I studied as hard as I could, even I might have a legitimate chance of entering the University of Tokyo, which until then appeared far beyond my reach.

For the first time in my life, I instantly became a self-motivated and highly disciplined model student devoting most of my available time to intensive studying. I would wake up a couple of hours earlier than the rest and spend those extra hours in preparation for the classes each day. No more solitary explorations of my favorite Shonan seaside area, especially Enoshima Island, after classes. Each evening, I would study until after 11 pm, when I heard mother's gentle

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reminder saying: "Is it not about time to stop studying and go to bed?" In retrospect, I feel very fortunate that neither of my parents ever told me to study more or harder in my life. For one thing, they themselves were very busy just for our survival, even though I did sense their silent but strong mental support for my higher education.

At the end of the first semester in my 11th grade, my scholastic ranking rose to 9th among a little more than 400 students. I then reached the top position at the end of the 11th grade and maintained that position through the 12th grade. Toward the end of the 11th grade and through most of the 12th grade, a series of several mock college entrance examinations were given, and I managed to earn the highest overall scores three out of five times. Naturally, my confidence grew sharply. At the same time, however, I began to feel an intense psychological pressure against never failing in the upcoming real entrance examinations as the top student at Shonan. Indeed, this mental pressure was most intense on those days of the two-day entrance examinations at the University of Tokyo, and both my mental and physical conditions were at their worst, not far short of being outright sick. I really thought my performance on those two days was at its worst, and I felt more than halfway certain that I had failed. Fortunately, I did pass, perhaps barely, and became one of the youngest college entrants at age 17 in the stiflingly rigid Japanese system. Fortunately, there was no age-based opposition this time.

In retrospect, I now consider the oft-criticized rigorous college entrance examination system in Japan to be a highly valuable and effective training of teenagers in preparation for their research and other professional careers, especially in science and engineering areas. Even today, 55–60 years later, I frequently resort to my mathematical and scientific background, which I quite firmly built in my high school days in preparation for the college entrance examinations.

Having accomplished my high school goal, my eccentric and erratic lifestyle took another 180-degree turn. Even though my major in college was nonbiological science engineering, our curriculum for the first two years at the Komaba campus, designated as General Education, was full of nonscientific classes including a second foreign language, German for myself, law, economy, psychology, and so on, along with a limited number of mathematical and natural science classes. With some exceptions, neither students who had just survived very demanding college entrance examination, nor professors, who probably were mostly interested in and preoccupied with pursing their own professional interests, appeared to be sufficiently interested in learning or teaching the subject matter. For example, there were two different classes of German in my curriculum. Most of the students in these classes were taking German lessons for the first time in their lives. One class dealt strictly with German grammar. In the other class, we were asked to deal from the very beginning with German novels and poems. I recall our trying to read and interpret Goethe's poems, while consulting with a German–Japanese dictionary for almost every word with little grammatical knowledge. This was clearly a very poor way of learning any foreign language. Coupled with a serious lack of effort on my part, my knowledge and ability in German are even today very limited and poor. Nearly the same can be said about most of the other subjects as well.

In the meantime, I quickly diverted my time, interest, and efforts to some off-campus activities, such as 1) listening to Western classical music, especially that composed by Mozart, Beethoven, Brahms, Chopin, Dvorak, Grieg, Tchaikovsky, and so on, 2) singing and conducting in a small choir group, mostly performed at the small house of my music teacher at Yamato Junior High School, Tsuguo Suzuki, who later became my father-in-law (Figure 1). Kenji Suzuki, Tsuguo's eldest son and one of my classmates at Shonan High School and also at the University of Tokyo, was the other leader of the small choir group. To my disappointment, Sumire, the older of two daughters of Tsuguo Suzuki and my future wife, would stay away from our choir activities, even though she was undoubtedly forced to listen to the sounds we generated in the small house. For one thing, she was younger by three years than most of the choir group members (two years younger than myself), and she probably felt she did not belong to our choir group. Even so, Sumire and I started dating during my freshman year, and we rapidly got closer with time.

As I spent much of my available time in these extracurricular activities, I all but forgot my self-motivated study-

Figure 1. Early family photos. Top: The Suzuki family (ca. 1950). Back row: Tsugo Suzuki (father), Sumire, Misao (mother), Kenji; front row: Akemi, Yutaka, Yuzuru. Bottom: The Negishi family (1958): Back row: Sumire, Masako, Fusae (mother), Shizuko, Chieko, Noriko; front row: Akiko, Ei-ichi.

ing. Even today, I occasionally regret my lack of continued efforts which I acquired during the latter half of Shonan High School. Clearly, I was primarily responsible for this academically nonproductive two-year period at Komaba campus of the University of Tokyo, but I also believe that there was considerable room for improvement in many areas of curriculum development.

Despite my failure to make due efforts, I was surprised and much relieved when I learned that my scholastic ranking at the end of the first year was just in the top third of about 450 nonbiological science and engineering majors. This permitted me to choose one of the most highly coveted departments, at that time, namely, applied chemistry specializing in Industrial Chemistry for my Junior and Senior years. In and around 1955, ten years after the end of World War II, the Japanese economy was rapidly growing, in part because of the unfortunate Korean War near Japan. In particular, the newly rising non-natural polymer industry was booming and attracting young scientists and engineers, such as myself to join this booming field.

Despite all these promising aspects, I experienced probably the hardest and least productive time in my life. First of all, it required almost two hours one way or four hours both ways to commute between my home in Yamato and the Hongo campus of the University of Tokyo. Our class schedule in my junior year was packed with a series of lecture and laboratory classes packed with superficial discussions and experiments on various industrial chemical processes from 8 am to about 5 pm every day. Only in a relatively small number of classes did we learn some fundamentally important chemistry. Unfortunately, however, most of these classes were, in my opinion, rather poorly taught. In a class on quantum chemistry, for example, a widely known textbook (Japanese version) entitled "Valence" by Coulson was chosen, but virtually no penetrating and nourishing discussions were presented in class. In fact, I needed to wait for four more years until I took a class on this same subject with the same textbook (original English version) at the University of Pennsylvania, before I was finally permitted to acquire all the important quantum chemical background at an adequate and useful level.

Between physically demanding commuting requiring almost four hours of standing in jam-packed commuter trains and highly time-demanding but seemingly non-nourishing lectures and laboratory classes, I began suffering from gastrointestinal problems by July of 1955. The problems got worse during the latter half of that summer break, and I was finally hospitalized for a few weeks, which prevented me from taking all of the mid-year tests. Eventually, I was forced to repeat my junior year.

In retrospect, this major setback proved to be a blessing in disguise. For one thing, I had plenty of my own time to think, plan, and do some new things for myself according to my own wishes. I read almost indiscriminatingly a wide range of books ranging from the Bible, although I was not a Christian, to "how to ..." publications. Through all these reading and thinking activities, I reached my own notion that "happiness" must be the ultimate goal for each of us and that the following are the four essential components of it: 1) good health, 2) happy surroundings including one's own family and beyond, 3) selection and pursuit of a worthy professional career, and 4) one or more enjoyable and lasting hobbies.

With my renewed life goals, I restarted my junior year in April, 1956. This time, I decided to rent a small room across from the Hongo campus, but I would go home almost every weekend from Friday evening to Sunday evening. Another new item I added to my plans was learning conversational English, which I considered to be critically important for my career development. Throughout my junior and senior years, however, I remained critical about a combination of mostly superficial descriptions of various chemical processes and a small number of fundamentally important subjects that were, in my opinion, rather poorly discussed in classrooms. Clearly, I was also responsible for my inability to make better use of these classes. My music-related activities were maintained and exercised over the weekends, and I began steadily dating Sumire, with a growing notion of our eventually getting married.

During the latter half of my junior year, I applied for a lucrative scholarship from one of the leading synthetic polymer companies, Teijin, Ltd., and successfully obtained it with the agreement of my joining Teijin upon graduation with a BS degree. This virtually eliminated my concerns over various financial matters, including the costs of dating Sumire. I regret very much that amid all of these activities, my efforts in my Senior Research project based mostly on experimental work were kept to a minimum.

On the day of graduation with the degree of Bachelor of Engineering in March 1958 (Figure 2), Sumire and I announced our engagement to our parents in a small restaurant near Akamon ("Red Gate") of the Hongo campus.

At Teijin, I was assigned to be a research chemist at Iwakuni Research Laboratories, the main research facility then of Teijin, which was located near Hiroshima in the Inland Sea area. One of my superiors there asked me to systematically explore chemical reactions of polymers to come up with modified polymers with superior properties. It soon was apparent to me that my synthetic organic chemical background was woefully weak. I immediately told myself, "I

Figure 2. Classmates at the University of Tokyo (1958).

should rebuild almost from scratch my synthetic organic chemical background," something I already had been vaguely hoping to do independently of this episode. The most obvious thing to do was to return to the University of Tokyo as a graduate student to pursue a master's degree. The main difficulty was how to raise the tuition fees, as virtually no graduate teaching assistantship was available back then in Japan. I then recall the welcome speech by the President of Teijin, Mr. S. Ohya, in which he was strongly urging all new members of the company to study and master some foreign languages, especially English, German, and French. He also told us about the Fulbright-Smith-Mund All-Expense Scholarship that permitted highly qualified recipients to study in the USA for up to three years, and he further indicated that, if anyone at Teijin wins this scholarship, Teijin would grant a leave of absence with some additional financial support. As indicated earlier, I had been studying on my own conversational English for about three years. So, I decided to pursue the recommended course of events. In fact, Teijin Iwakuni Research Laboratories soon hired a native English-speaking foreign tutor, and I started taking an English conversation class, which proved to be a most useful experience for me to acquire a solid foundation for my conversational English. Once again, my self-motivated diligent study habits came back, and I quickly became quite proficient in practical English.

The two-stage Fulbright Examination on written and conversational English was by far the most competitive examination up to that point in my life, but I was luckily chosen as one of only the two who passed out of a little more than 150 applicants. Looking back, I consider my winning a Fulbright-Smith-Mund All-Expense Scholarship to go to the USA in 1960 and study toward my PhD degree in Synthetic Organic Chemistry to be the single most important turning point in my professional career.

The Fulbright Commission asked me to list three universities from which to select the final one through negotiations by the Fulbright Commission with the listed universities. With almost zero knowledge about American universities, I consulted the *Journal of Polymer Science*, which I was most frequently reading, and noted the names of three editorial board members who were at Princeton University (A. V. Tobolsky), University of Pennsylvania (C. C. Price), and Brooklyn Polytechnic Institute (C. G. Overberger). The Fulbright Commission chose the University of Pennsylvania for me.

After 8 weeks of English orientation classes at the University of Hawaii in August and September 1960, I came to the University of Pennsylvania in Philadelphia, where I spent three years for my PhD degree, which I obtained in December, 1963 under the guidance of Professor A. R. Day.

Before 1960 Japan had produced just one Nobel Laureate, H. Yukawa, who won a Nobel Prize in Physics in 1949 only four years after the end of World War II. Although I vaguely knew of him, he was a physicist in Kyoto, which is some 500 km away from Tokyo. So, he was like a figure in a fairy tale to me. On the other hand, a series of a dozen or more Nobel Laureates in sciences as well as those who had not won but were clearly destined to win Nobel Prizes visited Penn to give lectures during my stay there. On some other occasions, several of us at Penn would get together and drive to other universities within several hours of driving to attend lectures by Nobel Laureates. In this way, I attended easily more than a dozen lectures by Nobel Laureates including G. T. Seaborg, H. Staudinger, L. C. Pauling, M. Calvin, M. F. Perutz, J. C. Kendrew, K. Ziegler, R. B. Woodward, D. H. R. Barton, and H. C. Brown. I even personally talked to them. They were no longer some figures in fairy tales.

Through these opportunities, the Nobel Prize became something of reality to me. I must confess that, in my usually quixotic way, I even began thinking that, if I kept trying in the right direction and on the right track, I might even have a remote chance of winning one some day.

As a first-year graduate student at Pennsylvania, I was a reasonable PhD student in class. However, I am much more proud of the fact that I earned 8 consecutive grades of excellence in the Organic Cumulative Examinations, a feat essentially unheard of back then. This indeed gave me a tremendous amount of confidence in myself and in my potential research capability.

In the laboratories, however, I was, at least initially, rather clumsy and failed in a fair number of experiments. I then began questioning about many aspects of organic synthesis, as known then. "Why are so many organic synthetic reactions esoteric?" "Why are so many of them including acetoacetic ester and malonic ester syntheses roundabout and yet of limited synthetic scope?" It was around those days that the following dreamy, if childish notion occurred to me: If we could come up with widely applicable straightforward LEGO-like methods for hooking up two different organic groups, R^1 and R^2, together to produce $R^1–R^2$, the entire task of organic synthesis would be vastly simplified and generalized. In fact, the Grignard cross-coupling reaction shown in Eq. (1) had long been known, even though it might have been a relatively unimportant reaction with a very narrow synthetic scope within the vast scope of Grignard's Nobel Prize winning work known about a century ago.

$$R^1{-}MgX + X{-}R^2 \longrightarrow R^1{-}R^2 + MgX_2 \qquad (1)$$

$$X = Cl,\ Br\ \text{and/or}\ I$$

In the Grignard cross-coupling reaction shown in [Eq. (1)], Mg and halogens are used to promote the desired formation of $R^1–R^2$ both kinetically and thermodynamically. Through such simple but unmistakable considerations, I soon became obsessed with the notion of exploring organometallic chemistry for solving a wide range of problems in organic syntheses, which eventually led me to join H. C. Brown's group as a Postdoctoral Associate for two years (1966–1968) and then as his Assistant with the rank of Instructor for four more years (1968–1972). During the latter four-year period, I was given a considerable level of freedom to pursue my own ideas and plans. Indeed, it was during this four-year period that I became interested in possible uses of d-block transition metals as catalysts for promoting main-group-metal-containing organometallic reactions, such as those shown in [Eq. (1)].

Figure 3. Negishi with his former associates and with Professors S. Murahashi and M. Anastasia at his side.

In addition to some pioneering work by M. S. Kharasch, which led to the copper-catalyzed alkylation of Grignard reagents by J. Kochi in 1971 and its nickel-catalyzed version by K. Tamao and M. Kumada as well as by R. Corriu in 1972, some other initially stoichiometric reactions of organometals containing 1) Cu by H. Gilman, which was extensively further developed by E. J. Corey, 2) Pd, mostly π-allylpalladiums by J. Tsuji and by B. M. Trost, as well as arylpalladiums by R. F. Heck, and 3) Ni, mostly π-allylnickels by E. J. Corey, M. F. Semmelhack, and L. S. Hegedus became widely known from the late 1960s.

Figure 4. Nobel celebration at Purdue. Top: Negishi cutting the ribbon in the chemistry building. Bottom: News conference with Purdue President F. Córdova.

Figure 5. Sumire and Ei-ichi Negishi, December 2010.

Despite all these mostly stoichiometric reactions of organotransition metals, containing Cu, Ni, Pd, and some others, widely applicable methods for C−C bond formation that were highly catalytic (TON $\geq 10^3$–10^4) in transition metals were virtually unknown at the time I started my independent career as Assistant Professor at Syracuse University in July, 1972. I therefore chose with much enthusiasm: "Discovery and Development of New Organic Synthetic Reactions Catalyzed by Transition Metals" as the central topic of my life-long research projects, and one important aspect of it is the subject of my Nobel Lecture summarized below.

Nobel Lecture

Not long ago, the primary goal of the synthesis of complex natural products and related compounds of biological and medicinal interest was to be able to synthesize them, preferably before anyone else. While this still remains a very important goal, a number of today's top-notch synthetic chemists must feel and even think that, given ample resources and time, they are capable of synthesizing virtually any natural product and many analogues thereof. Accepting this notion, what would then be the major goals of organic synthesis in the 21st century? One thing appears to be unmistakably certain. Namely, we will always need, perhaps increasingly so with time, the uniquely creative field of synthetic organic and organometallic chemistry to prepare both new and existing organic compounds for the benefit and well-being of mankind. It then seems reasonably clear that, in addition to the question of what compounds to synthesize, that of how best to synthesize them will become increasingly more important. As some may have said, the primary goal would then shift from aiming to be the first to synthesize a given compound to seeking its ultimately satisfactory or "the last" synthesis.

If one carefully went over various aspects of organic synthetic methodology, one would soon note how primitive and limited it had been until rather recently or perhaps even today. For the sake of argument, we may propose here that the ultimate goal of organic synthesis would be to be able to synthesize any desired and fundamentally synthesizable organic compounds a) in high **y**ields, b) **e**fficiently (in as few steps as possible, for example), c) **s**electively, preferably all in ≥ 98–99 % selectivity, d) **e**conomically, and e) **s**afely, abbreviated hereafter as the **y(es)**[2] manner.

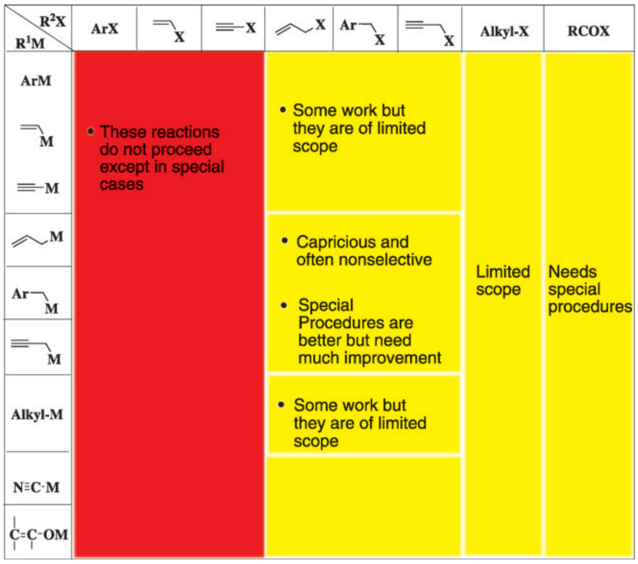
Half a century ago, however, only a limited number of cases of cross-coupling reactions using Grignard reagents and related organoalkali metals containing Li, Na, K, and so on were known. Their reactions with sterically less hindered primary and some secondary alkyl electrophiles (R^2X) are generally satisfactory (Scheme 1). Even so, the overall scope of their cross-coupling reactions was severely limited. One of their most serious limitations was their inability to undergo satisfactory C–C bond formation with unsaturated R^2X compounds containing unsaturated carbon groups, such as aryl, alkenyl, and alkynyl groups, with some exceptions[1] (Table 1).

$$R^1\text{–}M + R^2\text{–}X \xrightarrow{\text{with or without catalyst}} R^1\text{–}R^2 + M\text{–}X$$

R^1, R^2: carbon groups, M: metal or metal-containing groups,
X: halogens or other leaving groups

Scheme 1.

Table 1: Scope and limitations of uncatalyzed cross-coupling with Grignard reagents and organoalkali metals.



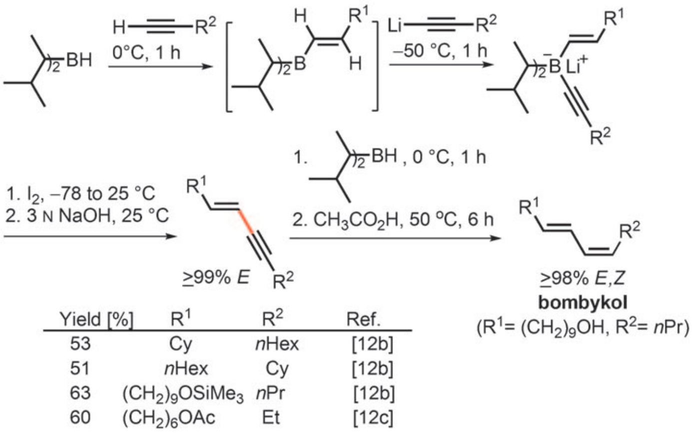
R²X / R¹M	ArX	═X	≡–X	allyl–X	Ar–CH₂–X	≡–CH₂–X	Alkyl-X	RCOX
ArM	• These reactions do not proceed except in special cases			• Some work but they are of limited scope			Limited scope	Needs special procedures
═M								
≡–M								
allyl–M				• Capricious and often nonselective • Special Procedures are better but need much improvement				
Ar–CH₂–M								
≡–CH₂–M								
Alkyl-M				• Some work but they are of limited scope				
N≡C-M								
C=C-OM								

Evolution of the Pd-Catalyzed Cross-Coupling

The cross-coupling methodology has evolved mainly over the past four decades into one of the most widely applicable methods for C–C bond formation. This is centered around the Pd-catalyzed cross-coupling with organometals containing Al, Zn, Zr (Negishi coupling),[2,3] B (Suzuki coupling),[2,4] and Sn (Stille coupling),[2,5] as well as those containing several other metals including Cu,[6] In,[7] Mg,[8] Mn,[9] and Si[10] (Hiyama coupling). Although of considerably more limited scope, both the seminal nature of the Ni-catalyzed Grignard cross-coupling of Tamao and Kumada[11a,b] as well as of Corriu,[11c] and its sustained practical synthetic values must not be overlooked in cases where its overall synthetic merits are comparable with or even superior to those Pd-catalyzed reactions mentioned above.

The evolution within the author's group actually began with the development of some selective C–C bond-forming reactions of alkenylboranes which led, most probably, to the earliest highly selective (≥ 98 %) syntheses of unsymmetrically substituted conjugated (*E,E*)- and (*E,Z*)-dienes,[12] following the pioneering studies of alkyne hydroboration by Brown[13] and subsequent C–C bond formation by Zweifel[14] (Scheme 2).

Despite these successes, however, the author's group began concurrently to explore the possibility of promoting the C–C bond formation with alkenylboranes and alkenylborates by using some transition metals. After a series of total failures with some obvious choices—namely a couple of cuprous halides, which were later shown to be rather impure—our attention then turned to a seminal publication by Tamao reporting a Ni-catalyzed Grignard cross-coupling (Tamao–Kumada–Corriu coupling).[11] Our quixotic plans for substituting Grignard reagents with alkenylboranes and alkenylborates were uniformly unsuccessful.[15] In retrospect, it must have been primarily due to the fact that all of our experiments



Yield [%]	R¹	R²	Ref.
53	Cy	*n*Hex	[12b]
51	*n*Hex	Cy	[12b]
63	(CH₂)₉OSiMe₃	*n*Pr	[12b]
60	(CH₂)₆OAc	Et	[12c]

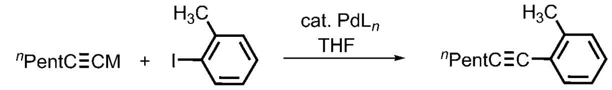
Scheme 2.

were run at 25 °C in THF. As soon as we replaced alkenylboron reagents with alkenylalanes, however, smooth Ni-catalyzed cross-coupling reactions of (*E*)-1-alkenyldiisobutylalanes with several aryl bromides and iodides took place to provide the cross-coupling products of $\geq 99\,\%$ *E* geometry.[15a] The corresponding Pd-catalyzed reactions were also observed, but no apparent advantage by the use of $[Pd(PPh_3)_4]$ in place of $[Ni(PPh_3)_4]$ was noticed. One of our main goals was to be able to synthesize stereo- and regiodefined conjugated dienes. Indeed, both the Ni- and Pd-catalyzed cross-coupling of alkenylalanes with alkenyl iodides proceeded as desired.[15b] In these reactions, however, the Pd-catalyzed reactions were distinctly superior to the corresponding Ni-catalyzed reactions, in that the Pd-catalyzed reactions retained the original alkenyl geometry to the extent of $\geq 97\,\%$, mostly $> 99\,\%$, whereas the corresponding Ni-catalyzed reactions showed the formation of undesirable stereoisomers up to 10 %.[15b]

Our literature survey revealed that there was one paper by Murahashi[8a] reporting four cases of Pd-catalyzed Grignard cross-coupling in 1975. We later learned that two other contemporaneous papers by Ishikawa[8c] and Fauvarque[8d] published in 1976 also reported examples of the Pd-catalyzed variants of the Ni-catalyzed Grignard cross-coupling. With our two papers published in 1976,[15] we thus reported, for the first time, Ni- and Pd-catalyzed cross-coupling reactions of non-Grignard reagents, namely organoalanes. Significantly, some unmistakable advantages associated with the use of Pd over Ni was also recognized for the first time.[15b]

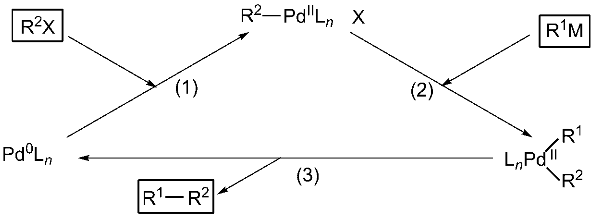
Sensing that the major player in the Pd-catalyzed cross-coupling might be Pd rather than the stoichiometric quantity of a metal countercation (M) and that the main role of M in R^1M (Scheme 1) might be to effectively feed R^1 to Pd, ten or so metals were screened by using readily preparable 1-heptynylmetals. As summarized in Table 2,[3a,16] we not only confirmed our earlier finding that Zn was highly effective,[8e] but also found that B and Sn were nearly as effective as Zn, even though their reactions were much slower. We then learned that examples of Pd-catalyzed cross-coupling with allyltins by Kosugi[5b] had been reported a year earlier in 1977, but the reaction of the borate marked the discovery of the Pd-catalyzed organoboron cross-coupling. As is well known, extensive investigations of the Pd-catalyzed cross-coupling reactions of organometals containing B by Suzuki[4c,d] and Sn by Stille[5c,d] began in 1979.

Table 2: Reactions of 1-heptynylmetals with *o*-tolyl iodide in the presence of $[Cl_2Pd(PPh_3)_2]$ and iBu_2AlH.



M	*T* [°C]	*t* [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**
$AliBu_2$	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

On the basis of a "three-step" mechanism consisting of 1) oxidative addition of R^2X to $Pd(^0)L_n$ species, where L_n represents an ensemble of ligands, 2) transmetalation between $R^2Pd^{II}L_nX$ and R^1M, and 3) reductive elimination of $R^1R^2Pd^{II}L_n$ to give R^1R^2 (Scheme 3) widely accepted as a reasonable working hypothesis,[3–5,8,11] we reasoned that, as long as all three microsteps are kinetically accessible, the overall process shown in Scheme 1 would be thermodynamically favored in most cases by the formation of MX. In view of the widely observed approximate relative order of reactivity of common organic halides toward Pd(0) complexes (Scheme 3), a wide range of Pd-catalyzed cross-coupling reactions of aryl, alkenyl, alkynyl, benzyl, allyl, propargyl, and acyl halides and related electrophiles (R^2X) as well as R^1M containing these carbon groups were further explored. In view of the distinctly lower reactivity of alkyl halides, including homobenzylic, homoallylic, and homopropargylic electrophiles, the use of alkylmetals as R^1M was considered.



1) oxidative addition, 2) transmetalation, 3) reductive elimination

R^1, R^2 = C groups; X = I, Br, Cl, OTf, etc.; M = metal countercation

Approximate relative order of reactivity of organic halides in oxidative addition to Pd:

Allyl, Propargyl > Benzyl, Acyl > Alkenyl, Alkynyl > Aryl >> simple Alkyl

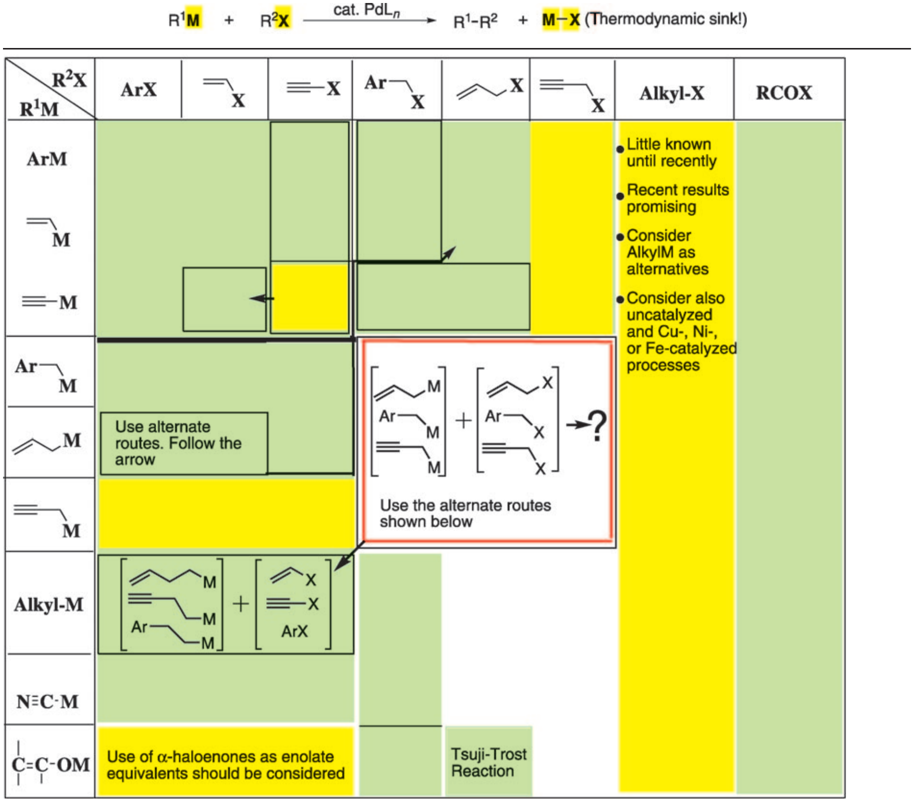
Scheme 3.

A couple of dozen papers published by us during the first several years in the 1980s on Pd-catalyzed 1) alkylation with alkylmetals,[17] 2) cross-coupling between aryl, alkenyl, or alkynyl groups and benzyl, allyl, or propargyl groups,[18] 3) the use of heterosubstituted aryl, alkenyl, and other R^1M and R^2M,[17d,19] as well as acyl halides,[20] and 4) allylation of metal enolates containing B and Zn that are not extra-activated by the second carbonyl group[21] amply supported the optimistic notion that the Pd-catalyzed cross-coupling might be very widely applicable with respect to R^1 and R^2 being cross-coupled.

Current Profile of the Pd-Catalyzed Cross-Coupling

Today, the overall scope of the Pd-catalyzed cross-coupling may be shown as summarized in Table 3. Although any scientific progress is evolutionary, comparison of Table 3 with Table 1 does give us an impression that the progress made in this area has been rather revolutionary. Regardlessly, it would represent one of the most widely applicable methods for C–C bond formation, which has begun to rival the conventional Grignard and organoalkali metal based methods as a whole for C–C bond formation. Much more importantly, these two, one modern and the other conventional, methods are mostly complementary rather than competitive with each other. As is clear from Table 3, a little more than half of the 72 classes of cross-coupling listed in Table 3 generally proceed not only in high yields but also in high selectivity (≥ 98 %) in most of the critical respects. In approximately 20 other classes of cross-coupling, the reactions generally proceed in high overall yields, but some selectivity features need to be further improved. Only the remaining dozen or so classes of cross-coupling reactions either have remained largely unexplored or require major improvements. Fortunately, in most of these three dozen or so less-than-satisfactory cases, the Pd-catalyzed cross-coupling methodology offers satisfactory alternatives, requiring modifications as simple as a) swapping the metal (M) and the leaving group (X), b) shifting the position of the C–C bond formation by one bond, and c) using masked or protected carbon groups, as highlighted later.

Table 3: LEGO approach to C–C bond formation by Pd-catalyzed cross-coupling reactions.[a]



[a] R¹, R² = C group; **M** = Mg, Zn, B, Al, In, Si, Sn, Cu, Mn, Zr, etc.; **X** = I, Br, Cl, F, OTs, OTf, etc. **M** and **X** are regio- and stereospecifiers, which permit a genuine LEGO game that avoids addition/eliminiation.

At this point, it is useful to briefly discuss some of the fundamentally important factors that contribute to the current status of Pd-catalyzed cross-coupling.

Use of Metals of Moderate Electronegativity, as Represented by Zn

Transition-metal-catalyzed cross-coupling may have started as Grignard or organoalkali metal reactions with organic electrophiles to which transition-metal-containing compounds were added in the hope of catalyzing or promoting such reactions. The earlier, seemingly exclusive use of Grignard reagents and organoalkali metals as R^{1}M (Scheme 1) strongly suggests that their high intrinsic reactivity was most probably thought to be indispensable. In reality, however, there has been a rather limited number of publications on the reactions of organoalkali metals catalyzed by Pd complexes,[8b,22] and the results are mostly disappointing, except in some special cases. The current profile of the Pd- and Ni-catalyzed Grignard cross-coupling is considerably more favorable.[8,11] In the overall sense, however, its scope is significantly more limited than those employing Zn and B supplemented with Al and Zr. It has become increasingly apparent that Grignard reagents and organoalkali metals are intrinsically too reactive to allow Pd to efficiently participate in the putative three-step catalytic cross-coupling cycle (Scheme 3). Indeed, under the stoichiometric conditions, alkali metals and Mg are often as effective as or even more effective than Zn and other metals.[23] These results suggest that their excessive reactivity may serve as palladium-catalyst poisons. Another major difficulty with Grignard reagents and organoalkali metals is their generally low chemoselectivity in the conventional sense. As one of the important advantageous features of the Pd-catalyzed cross-coupling is that it permits preassembly of functionally elaborated R^{1}M and R^{2}X for the final or nearly final assemblage of R^1–R^2, the low chemoselectivity of Grignard reagents and organoalkali metals is a critically serious limitation. Despite these shortcomings, however, the Pd- or Ni-catalyzed Grignard cross-coupling[8,11] should be given a high priority in cases where it is competitively satisfactory in the overall sense, because Grignard reagents often serve as precursors to other organometals. In the other cases, metals of moderate electronegativity (Pauling electronegativity values 1.4–1.7), such as Zn (1.6), Al (1.5), In (1.7), and Zr (1.4), should offer a combination of superior reactivity under Pd-catalyzed conditions and high chemoselectivity. The surprisingly high chemoselectivity of Zn has made it desirable to prepare organozincs without going through organoalkali metals or Grignard reagents, and intensive explorations by Knochel[24] are particularly noteworthy. Although the B atom in boranes may be highly electronegative (2.0), rendering organoboranes rather non-nucleophilic, its electronegativity can be substantially lowered through borate formation. This dual character of B makes it an attractive metal in Pd-catalyzed cross-coupling.[4]

Pd as the Optimal Catalyst Component

Although Cu,[25] Ni,[11,15,26,27] Fe,[28] and even some other d-block transition metals have been shown to be useful elements in C–C cross-coupling, it is Pd that represents the currently most widely useful catalyst in catalytic cross-coupling. In a nutshell, it shares with other transition metals some of the crucially important features, such as an ability to readily interact with nonpolar π bonds, such as alkenes, alkynes, and arenes, leading to facile, selective, and often reversible oxidative addition, transmetalation, and reductive elimination, as shown in Scheme 3.

In contrast with the high reactivity of proximally π-bonded organic halides, most of the traditionally important heteroatom-containing functional groups, such as various carbonyl derivatives except acyl halides, are much less reactive toward Pd, and their presence is readily tolerated. These nonconventional reactivity profiles associated with some d-block transition metals have indeed provided a series of new and general synthetic paradigms involving transition-metal catalysts, such as Pd-catalyzed cross-coupling and olefin metathesis.[29]

But why is Pd so well suited for the transition-metal-catalyzed cross-coupling? If we compare Pd with the other two members of the Ni triad, the heavier and larger Pt is also capable of participating in the three microsteps in Scheme 3, but $R^1R^2PtL_n$ is much more stable than the corresponding Pd- or Ni-containing ones, and their reductive elimination is generally too slow to be synthetically useful, even though fundamentally very interesting.[30] On the other hand, the smaller Ni appears to be fundamentally more reactive and versatile than Pd. Whereas Pd appears to strongly favor the 0 and +2 oxidation states separated by two electrons, Ni appears to be more prone to undergoing one-electron-transferring redox processes in addition to the desired two-electron redox processes, thereby leading to less clean and more complex processes. Our recent comparisons of the TONs of various classes of Ni- and Pd-catalyzed cross-coupling reactions between two unsaturated carbon groups[31,32] have indicated that the Ni-catalyzed reactions generally display lower TONs by a factor of $\geq 10^2$ and lower levels of retention of stereo- and regiochemical details, readily offsetting any advantages stemming from the lower cost of Ni relative to Pd. On the other hand, the cleaner Pd-catalyzed cross-coupling reactions often display TONs of $\geq 10^6$. In some cases, TONs reaching or even surpassing 10^9 have been observed.[32] Thus, for example, the reactions of phenylzinc bromide with *p*-iodotoluene and of (*E*)-1-decenylzinc bromide with iodobenzene in the presence of $[Cl_2Pd(DPEphos)]$ in THF exhibited TONs of 9.7×10^9 and 8.0×10^7, respectively, while producing the desired products in ≥97% and 80% yields, respectively.[32] At these levels, not only cost issues but also some alleged Pd-related toxicity issues should become significantly less serious.

Critical Comparison of R^1M and R^1H

It is generally considered that the use of R^1H in place of R^1M would represent a step in the right direction toward "green" chemistry. This statement would be correct and significant provided that all of the other things and factors are equal or comparable. In reality, however, the other things and factors are rarely equal or comparable, and valid comparisons must be made by taking into consideration all the significant factors. In Pd-catalyzed alkenylation and also alkynylation, the development of Pd-catalyzed cross-coupling versions using Zn, B, Sn, and others as M in R^1M were, in fact, preceded by the R^1H versions, namely Heck alkenylation[33] and Heck–Sonogashira alkynylation.[34] Thus, evolution of the cross-coupling version took place in the R^1H to R^1M, rather than the R^1M to R^1H, direction. Despite some inherent advantages associated with the R^1H versions over the corresponding R^1M versions, the synthetic scopes of the R^1H versions are generally significantly more limited than the R^1M versions.[35] From the perspective of synthesizing conjugated di- and oligoenes in the $y(es)^2$ manner, the following difficulties and limitations of Heck alkenylation must be noted.

1) There is a need for certain activated and relatively unhindered alkenes, such as styrenes and carbonyl-conjugated alkenes, for satisfactory results.[36]

2) There is an inability to produce either pure (≥98%) *E* or *Z* isomers from a given alkene used as R^1H. This can be readily and fully overcome by the use of stereodefined isomerically pure (≥98%) alkenylmetals as R^1M.[37]

3) There is frequent formation of undesirable regioisomeric and stereoisomeric mixtures of alkenes,[33,37] which leads to lower yields of the desired alkenes.

4) Lower catalyst TONs (typically $\leq 10^2$–10^3) are obtained, except for the syntheses of styrenes having an additional aryl, carbonyl, or proximal heterofunctional group,[33c] as compared with those often exceeding 10^6 for the corresponding R^1M version, especially with Zn as M,[32] which significantly affects the cost and safety factors.

Both the fundamental and practical merits of using metals (M) as a) regio- and stereospecifiers, b) kinetic activators, and c) thermodynamic promoters are abundantly clear, and these differences must not be overlooked. Of course, in those specific cases where the R–H versions of alkenylation and alkynylation are more satisfactory than the R^1M version in the overall sense, including all $y(es)^2$ factors, their use over the R^1M versions would be well justified. Thus, it would still remain important and practically useful to continuously seek and develop additional R^1H processes that would proceed in the $y(es)^2$ manner and would be considered superior to the

R^1M version for a given synthetic task. After all, when one specific chemical transformation is desired, it is the best optimal process for that case rather than the process of the widest scope and general superiority that should be chosen.

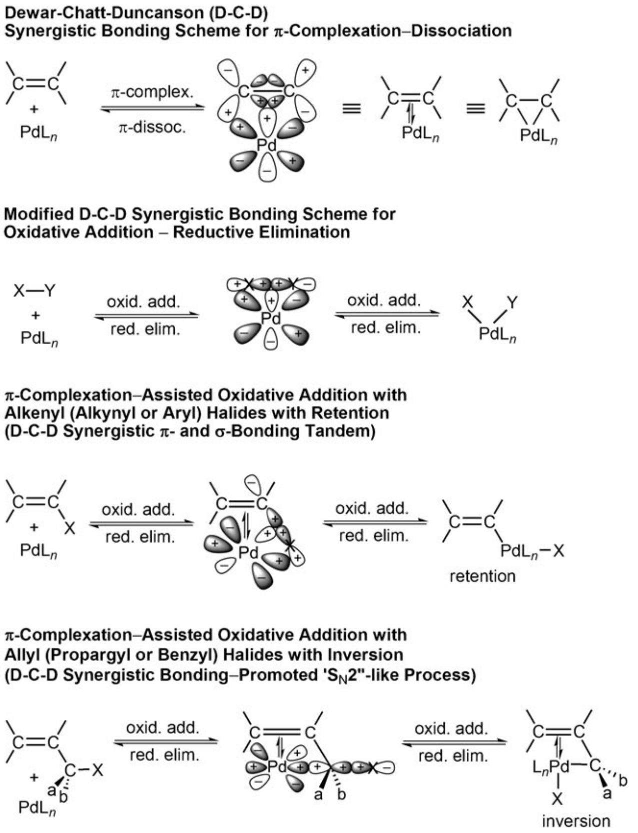
Advantage Associated with the Two-Stage (LEGO) Processes of the Pd-Catalyzed Cross-Coupling

In the Pd-catalyzed cross-coupling, the step of the final molecular assembly involves formation of a C–C single bond. As long as it proceeds with full retention of all the structural details of the R^1 and R^2 groups of R^1M and R^2X, an isomerically pure single product (R^1–R^2) would be obtained, except in those cases where formation of atropisomers are possible. While the majority of R^1 and R^2 groups do retain their structural details during Pd-catalyzed cross-coupling, allylic groups, especially allylic R^1 in R^1M, and propargyl groups as R^1 and/or R^2 may lose their regio- and/or stereochemical identities through allyl and propargyl–allenyl rearrangement, respectively. Secondary and tertiary alkyl groups are also prone to both stereoisomerization and β elimination. However, some Pd- and Ni-catalyzed asymmetric alkylations has been reported to proceed stereoselectively.[38] Furthermore, the preparation of R^1M and R^2X can be performed in totally separate steps by using any known method and, for that matter, any satisfactory method yet to be developed in the future as well. Significantly, a wide range of R^1M and R^2X with "sensitive" functional groups in a conventional sense, such as amides, esters, carboxylic acids, ketones, and even aldehydes, may be prepared and directly cross-coupled, as eloquently demonstrated by both the regio- and chemoselective preparation and Pd-catalyzed cross-coupling of a wide range of aryl and related compounds, notably by Knochel[24] and Snieckus.[39]

As such, the two-stage processes for the synthesis of R^1–R^2 offer certain distinct advantages over other widely used processes in which some critical structural features, such as chiral asymmetric carbon centers and geometrically defined C=C bonds, are to be established in the very steps of the skeletal construction of the entire molecular framework. Such processes include an ensemble of conventional carbonyl addition and condensation (olefination) reactions as well as modern olefin metathesis.[29] For example, the synthesis of (Z)-alkenes by intermolecular cross-metathesis has just made its critical first step[40] towards becoming a generally satisfactory route to (Z)-alkenes in the y(es)^2 manner.

Why d-Block Transition Metals? Some Fundamental and Useful Structural as well as Mechanistic Considerations

The three-step mechanistic hypothesis shown in Scheme 3 has provided a reasonable base not only for understanding various aspects of the seemingly concerted Pd-catalyzed cross-coupling but also for making useful predictions for exploring various types of concerted Pd-catalyzed cross-coupling reactions. Of course, what is shown in Scheme 3, which evolved from those seminal studies with Ni,[11,41] may be applicable to other transition-metal-catalyzed processes. At the same time, it is important to remember that few mechanistic schemes have ever been firmly established and that they are, in most cases, not much more than useful working hypotheses for rational interpretations and predictions on the basis of the numbers of protons, electrons, and neutrons as well as space for accommodating them, including orbitals accommodating electrons, which bring yet another fundamentally important factor, namely symmetry. The fundamental significance of the molecular orbital (MO) theory represented by the frontier orbital (HOMO–LUMO) theory of Fukui,[42] synergistic bonding of Dewar,[43] exemplified by the so-called Dewar–Chatt–Duncanson (DCD) model (Scheme 4), and the orbital symmetry theory of Woodward and Hoffmann[44] can never be overemphasized.



Scheme 4.

In the area of C–C cross-coupling in the y(es)^2 manner with Pd and other d-block transition metals as the central catalyst components, the following two factors, at least, are critically important:

1) the ability to provide simultaneously one or more each of the valence-shell empty orbitals that serve as LUMOs and filled nonbonding orbitals that serve as HOMOs (Scheme 4) and

2) the ability to participate in redox processes that occur simultaneously in both oxidative and reductive directions under one set of reaction conditions in one vessel.

The first of the two is partially shared by singlet carbenes and related species and, therefore, termed "carbene-like". With one empty and one filled nonbonding orbital, carbenes are known to readily interact with nonpolar π bonds and even with some σ bonds. The mutually opposite directions of HOMO–LUMO interactions, which significantly minimize the effect of activation energy boosting polarization in each HOMO–LUMO interaction, should be firmly recognized. These features readily explain the facile and selective formation of stable π complexes with d-block transition metals, which is not readily shared by main group elements, such as B and Al, as they cannot readily provide a filled nonbonding orbital together with an empty orbital.

Despite the above-discussed similarity between carbenes and transition metals, there are some critically significant differences between them. Thus, many transition-metal-centered "carbene-like" species are not only of surprising thermal stability, and are even commercially available with long shelf-lives at ambient temperatures, e.g., $[ClRh(PPh_3)_3]$ and $[Cl_2Pd(PPh_3)_2]$, they are also reversibly formed in redox processes, thus permitting high catalyst TONs that often exceed a million or even a billion.[31,32] The authors are tempted to call such species "super-carbenoidal". Significantly, the "super-carbenoidal" properties of d-block transition metals do not end here. In addition to numerous 16-electron species with one empty valence-shell orbital, there are a number of 14-electron species, including surprisingly stable and even commercially available ones, such as $[Pd(tBu_3P)_2]$. In the oxidative addition step in Scheme 3, Pd must not only act like singlet carbene to generate π complexes for binding, it must also interact with the proximal C–X bond with either retention or inversion, presumably in a concerted manner, for which a σ-bond version of the synergistic bonding may be envisioned (Scheme 4). For such processes of low activation barriers, an "effective" 14-electron species may be considered to be critically desired. Although the transmetalation step in Scheme 3 is not limited to transition metals, the reductive elimination step, for which a concerted microscopic reversal of oxidative addition discussed above appears to be a reasonable and useful working hypothesis, must once again rely on the "super-carbenoidal" transition metals to complete a redox catalyst cycle. Of course, many variants of the mechanism shown in Scheme 3 are conceivable, and they may be useful in dealing with some finer details.

Alkyne Elementometalation/Pd-Catalyzed Cross-Coupling Routes to Alkenes

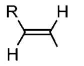
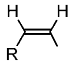
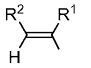
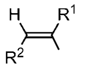
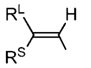
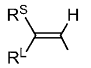
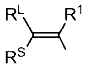
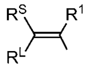
Historical Background of Alkene Syntheses

Before the advent of Pd-catalyzed alkenylation[15,45] and alkynylation[35] in the 1970s, the synthesis of regio- and stereodefined alkenes had been mostly achieved by a) carbonyl olefination which proceeds via addition/elimination processes, such as the Wittig reaction[46] and its variants, such as the Horner–Wadsworth–Emmons reaction[47] and its later modifications, including *Z*-selective Still–Gennari[48] and Ando[49] versions; b) Peterson olefination[50] and its variants including the Corey–Schlessinger–Mills methacrylaldehyde synthesis;[51] and c) Julia[52] and related olefination reactions. Even today, many of these reactions collectively represent the mainstay of alkene syntheses. From the viewpoint of alkene syntheses in the y(es)^2 manner, however, these conventional methods have been associated with various frustrating limitations that need to be overcome. With the exception of the alkyne addition routes, many of which can proceed in high (≥ 98 %) stereoselectivity, most of the widely used conventional methods, including all of the carbonyl olefination reactions mentioned above, must involve β elimination, which fundamentally lacks high (≥ 98 %) stereoselectivity and often tends to be regiochemically capricious as well.

As discussed earlier, the Pd-catalyzed alkenylation is thought to proceed generally via reductive elimination, although some involving the use of relatively nonpolar C–M bonds, such as C–B, C–Si, and C–Sn, are known to proceed at least partially via carbometalation/β elimination. In sharp contrast to β elimination, reductive elimination, which is predominantly a σ-bond process, can proceed in most cases with full retention of all the alkenyl structural details. Moreover, the scope of Pd-catalyzed alkenylation is fundamentally limited only by the availability of the required alkenyl precursors, as either R^1M or R^2X, and a wide range of methods for their preparation—both known and yet to be developed—may be considered and utilized. As discussed in detail, many of the Pd-catalyzed alkenylation reactions have displayed highly favorable results, as judged by the y(es)^2 criteria. Thus, Pd-catalyzed alkenylation has evolved since the mid-1970s into arguably the most general and highly selective (≥ 98 %) method of alkene synthesis known to date.

At this point it is both useful and important to classify the alkenyl groups, R^1 and/or R^2 in R^1M and/or R^2X, into ten structural types (Table 4). Since our attention is mainly

Table 4: Classification and definition of ten types of alkenyl groups

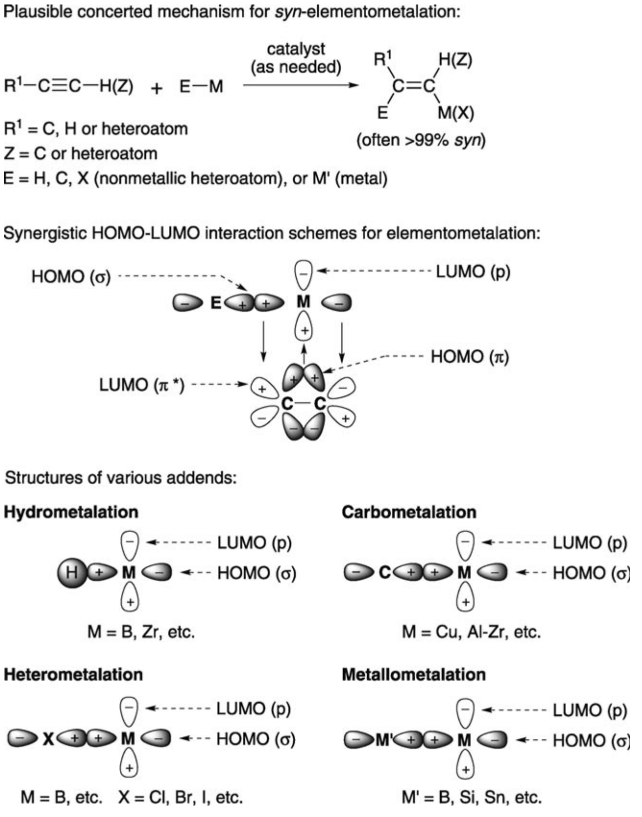
Type	Alkenyl descriptor	Structure	Regio-defined?	Stereo-defined?
I	vinyl	$H_2C{=}CH{-}$	no	no
II	α-monosubstituted	$H_2C{=}\overset{R}{\overset{\vert}{C}}{-}$	yes	no
III	(*E*)-β-monosubstituted		yes	yes
IV	(*Z*)-β-monosubstituted		yes	yes
V	α,β-cis-disubstituted		yes	yes
VI	α,β-trans-disubstituted		yes	yes
VII	(*E*)-β,β′-disubstituted[a]		yes	yes
VIII	(*Z*)-β,β′-disubstituted[a]		yes	yes
IX	(*E*)-α,β,β′-trisubstituted[a]		yes	yes
X	(*Z*)-α,β,β′-trisubstituted[a]		yes	yes

[a] R^L takes a higher priority than R^S according to the Cahn–Ingold–Prelog rule.

focused on those cases where both regio- and stereochemical details critically matter, no intentional discussion of Types I and II alkenyl groups is presented.

Elementometalation

The addition of element–metal bonds (E–M), where E is H, C, a heteroatom (X), or a metal (M′), to alkynes and alkenes may be collectively termed "*elementometalation*". As long as M is coordinatively unsaturated, providing one or more empty valence-shell orbitals, *syn*-elementometalation should, in principle, be feasible and facile, as suggested by the synergistic bonding scheme involving the bonding and antibonding orbitals of an E–M bond as a HOMO and LUMO pair for interacting with a π*- and π-orbital pair of alkynes and alkenes, as shown in Scheme 5 for hydrometalation, carbometalation, "heterometalation", and metallometalation. As such, these processes are stoichiometric, and the metals (M and M′) must be reasonably inexpensive. Besides this practically important factor, there are other chemical factors limiting the available choices of M. Thus, the generally high lattice energies of hydrides and other EMs of alkali metals and alkaline-earth metals make it difficult to observe their favorable elementometalation reactions. In reality, B and Al are just about the only two reasonably inexpensive and nontoxic main group metals capable of readily participating in highly satisfactory uncatalyzed elementometalation reactions. Among the d-block transition metals, Zr and Cu readily participate in stoichiometric *syn*-elementometalation reactions and nicely complement B and Al. For cost reasons, Ti, Mn, and Fe are also attractive, but their elementometalation reactions need further exploration. Likewise, transition-metal-catalyzed elementometalation reactions of Si, Ge, and Sn are promising,[53] but their adoption will have to be fully justified through objective overall comparisons with B, Al, Zr, and Cu. In this Review, no specific discussion of alkyne metallometalation is given.



Scheme 5.

Importantly, the four metals mentioned above are mutually more complementary than competitive. As summarized briefly in Table 5, hydroboration is the broadest in scope and the most highly chemoselective in the "conventional" sense among all the currently known alkyne hydrometalation reactions. Although somewhat more limited in scope and chemoselectivity, Zr tends to display the highest regioselectivity. More significantly, its reactivity in the subsequent Pd-catalyzed cross-coupling is considerably higher than that of B. In many cases where Zr works well, it therefore tends to be the metal of choice. Overall, B and Zr are the two best choices for hydrometalation. Difficulties associated with the relatively high cost of commercially available [$HZrCp_2Cl$] and its relatively short shelf-life have been finally resolved by the development of an operationally simple, economical, clean, and satisfactory reaction of [$ZrCp_2Cl_2$] with one equivalent of $i$$Bu_2AlH$ in THF to generate genuine [$HZrCp_2Cl$] (Scheme 6).[54]

In marked contrast, direct and uncatalyzed four-centered carboboration is still essentially unknown. This may tentatively be attributed to the very short, sterically hindered C–B bond. Currently, alkylcopper compounds[57] appear to be the only class of organometals that undergo satisfactory uncatalyzed, stoichiometric, and controlled single-stage carbometalation with alkynes. Although trialkylaluminums do react with terminal alkynes at elevated temperatures, it is complicated by terminal alumination.[58] This difficulty was overcome for the single-most important case of alkyne methylalumination through the discovery and development of the Zr-catalyzed methylalumination of alkynes with Me_3Al (ZMA reaction).[26a,59,60] Ethyl- and higher alkylaluminum compounds[60,61] as well as those containing allyl and benzyl groups[62] react readily but display disappointingly low regioselectivity ranges due mainly to the intervention of cyclic carbozirconation,[61] which must be further improved.

Despite such limitations, the ZMA reaction has proved to be highly useful because of the special significance of methyl-branched *E*-trisubstituted alkenes as a widely occurring structural unit in many isoprenoids. Detailed mechanistic studies have established that it involves an Al-promoted *syn*-carbozirconation of alkynes (Scheme 7). In the interaction with alkynes, the active Zr–Al species must act as a "superacidic" methylzirconium reagent through its interaction with an alane, i.e., operation of the "two-is-better-than-one" principle.[63] (*E*)-β,β-Disubstituted trisubstituted (Type VIII) alkenylaluminum derivatives thus generated can be in situ converted to a wide range of the corresponding trisubstituted alkenes (Scheme 7).

Table 5: Current profiles of hydro-, carbo-, and halometalation reactions with B, Zr, Al, and Cu

syn-Elementometalation	B	Zr	Al	Cu
syn-Hydrometalation (Types III-VI)	• Widest scope and applicablity. • Most tolerant of carbonyl and other heterofunctional groups. • Relatively slow in Pd-cat. cross-coupling. • Prone to π-addition–elimination leading to regio- and stereo-scrambling. • Recent cross-coupling procedures increasingly satisfactory.	• Reasonable scope. • Highly regioselective with R^1—≡—H, esp. with conjugated terminal enynes and some internal alkynes, etc. • Recent preparative procedure of $HZrCp_2Cl$ very convenient. • Highest reactivity in Pd-cat. cross-coupling among the four metals listed.	• More limited than B or Zr. • Alkynyl H or halogen abstraction problematic.	• Relatively little developed.
syn-Carbometalation (Types VII&VIII)	• Uncatalyzed four-centered carboboration essentially unknown.	• Zr alone tends to undergo cyclic carbozirconation, but it is a good metal as catalyst for carboalumination.	• Zr-cat. methylalumination (ZMA) is of broad scope with respect to R^1 of R^1—≡—H and of very high synthetic value. • Some benzyl, allyl, and higher *n*-alkylaluminums also react readily, but selectivity problematical. • >150 complex natural products prepared. • Al used together with Zn in some cases is very satisfactory in Pd-cat. cross-coupling.	• Primary alkyl-cupration useful. • Types VII and VIII as well as IV alkenyl derivatives accessible. • Methylcupration sluggish. Use ZMA instead. • Cu-Zn combination very good in Pd-cat. cross-coupling.
syn-Halometalation (Types VII&VIII)	• Bromoboration of alkynes facile and broadly applicable. • A wide reange of Type VII and VIII alkenyl derivatives are accessible. • With ethyne Type III alkenyl derivatives are accessible, but its use needs justification. • Recent procedures for both bromoboration and subsequent Pd-cat. cross-coupling very promising (see Scheme 9).	• Appears to be unknown.	• Appears to be unknown.	• Appears to be unknown.

For the selective synthesis of (*Z*)-β,β-disubstituted Type VIII alkenyl derivatives, alkyne haloboration reactions discovered by Lappert[64] in the early 1960s and developed by Suzuki[65] in the 1980s are of considerable interest. In particular, the alkyne bromoboration/Negishi couping tandem process[66] promised to provide a broadly applicable method for the head-to-tail (H-to-T) construction of various types of trisubstituted alkenes (Scheme 8). In reality, however, there were a number of undesirable limitations, of which the following were some of the most critical:

1) formation of (*E*)-β-haloethenylboranes through essentially full stereoisomerization,[67]

2) partial stereoisomerization (≥10%) in the arguably single most-important case of propyne haloboration,[68]

3) competitive and extensive β-dehaloboration to give the starting alkynes in cases where 1-alkynes contain unsaturated aryl, alkenyl, and alkynyl groups.

4) sluggish second Pd-catalyzed cross-coupling reactions under the reported Suzuki coupling conditions.[66] To avoid this difficulty, the use of the second Negishi coupling via B→I[69–71] and even B→I→Li[71] transformations have been reported as more satisfactory, if circuitous, alternatives.

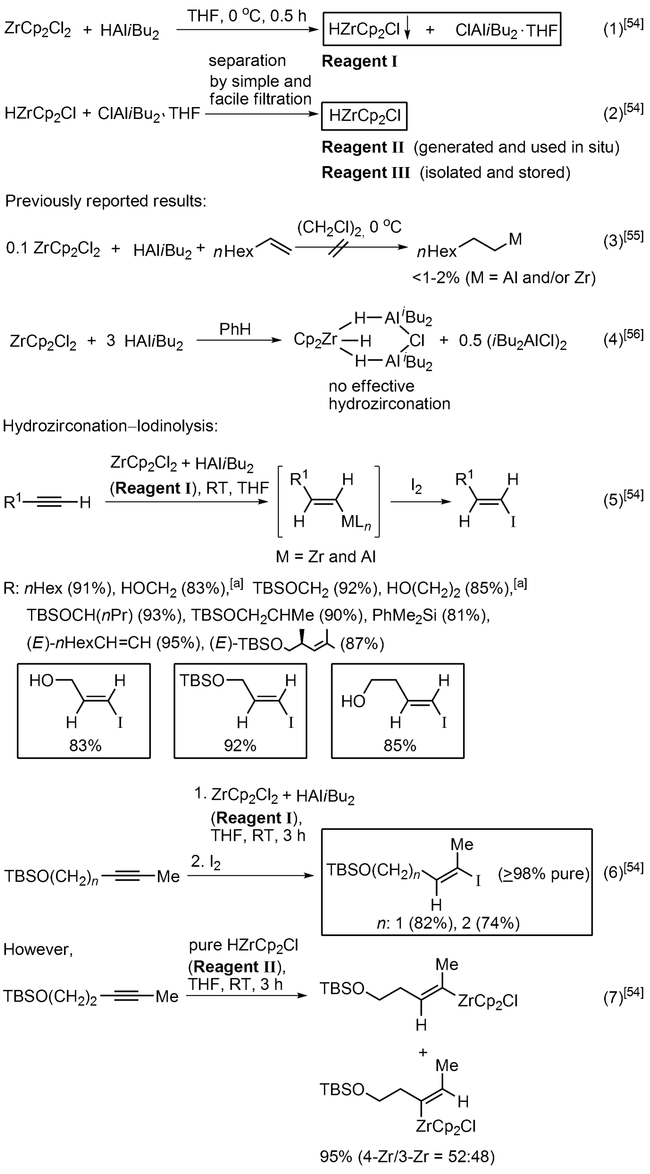
Although no investigation of point (1) has been attempted, highly satisfactory procedures have been developed to fully avoid the difficulty described in point (2)[70a] [Eq. (1) in Scheme 8] and substantially improving the second-stage Pd-catalyzed cross-coupling by the direct use of alkenylborane intermediates[72] [Eq. (2) in Scheme 8]. Additionally, a major step towards the establishment of highly general and satisfactory alkene synthetic methods based on elementometalation/Pd-catalyzed cross-coupling has been taken with the recent development of an hitherto unknown tandem arylethyne bromoboration/Pd-catalyzed cross-coupling process[71b] [Eqs. (4)–(7) in Scheme 8]. At present, however, the use of conjugated enynes and diynes in place of arylethynes appears to be even more challenging than the cases of arylethynes, and it is currently under investigation.

Even at the current stage, the alkyne elementometalation/Pd-catalyzed cross-coupling tandem processes summarized in Table 5 collectively provide by far the most widely applicable and satisfactory routes to various types of acyclic alkenes.

Alkyne syn-Elementometalation Followed by Stereo- and/or Regioisomerization

syn-Hydroboration of 1-Halo-1-alkynes

syn-Hydroboration of internal alkynes tends to give a mixture of two possible regioisomers. In cases where 1-halo-1-alkynes are used as internal alkynes, the reaction is nearly 100% regioselective in placing B at the halogen-bound carbon atom. The resultant (*Z*)-α-haloalkenylboranes can



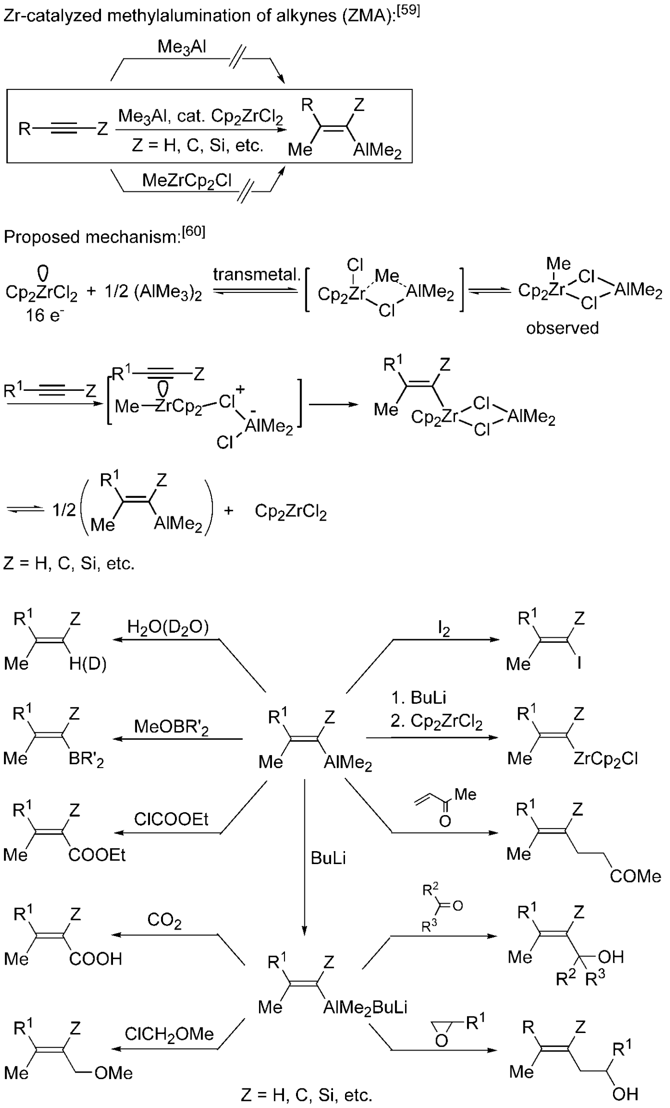
[a] Additional one equivalent $HAl\textit{i}Bu_2$ was used to metalate the OH group.

Scheme 6.

be used to prepare 1) (*Z*)-1-alkenylboranes (Type IV),[73] 2) (*Z*)-α,β-disubstituted alkenylboranes (Type V),[76] and 3) (*E*)-α,β-disubstituted alkenylboranes (Type VI),[74,75] as summarized in Scheme 9.

syn-Hydroboration of 1-Alkynes Followed by Halogenolysis with Either Retention or Inversion

The hydroboration of 1-alkynes followed by iodinolysis proceeds with retention to give (*E*)-1-iodoalkenes (Type III) of > 99 % purity,[77] whereas the corresponding brominolysis in the presence of NaOMe in MeOH produces the stereo-inverted *Z* isomer (Type IV) of > 99 % purity[78] (Scheme 10).



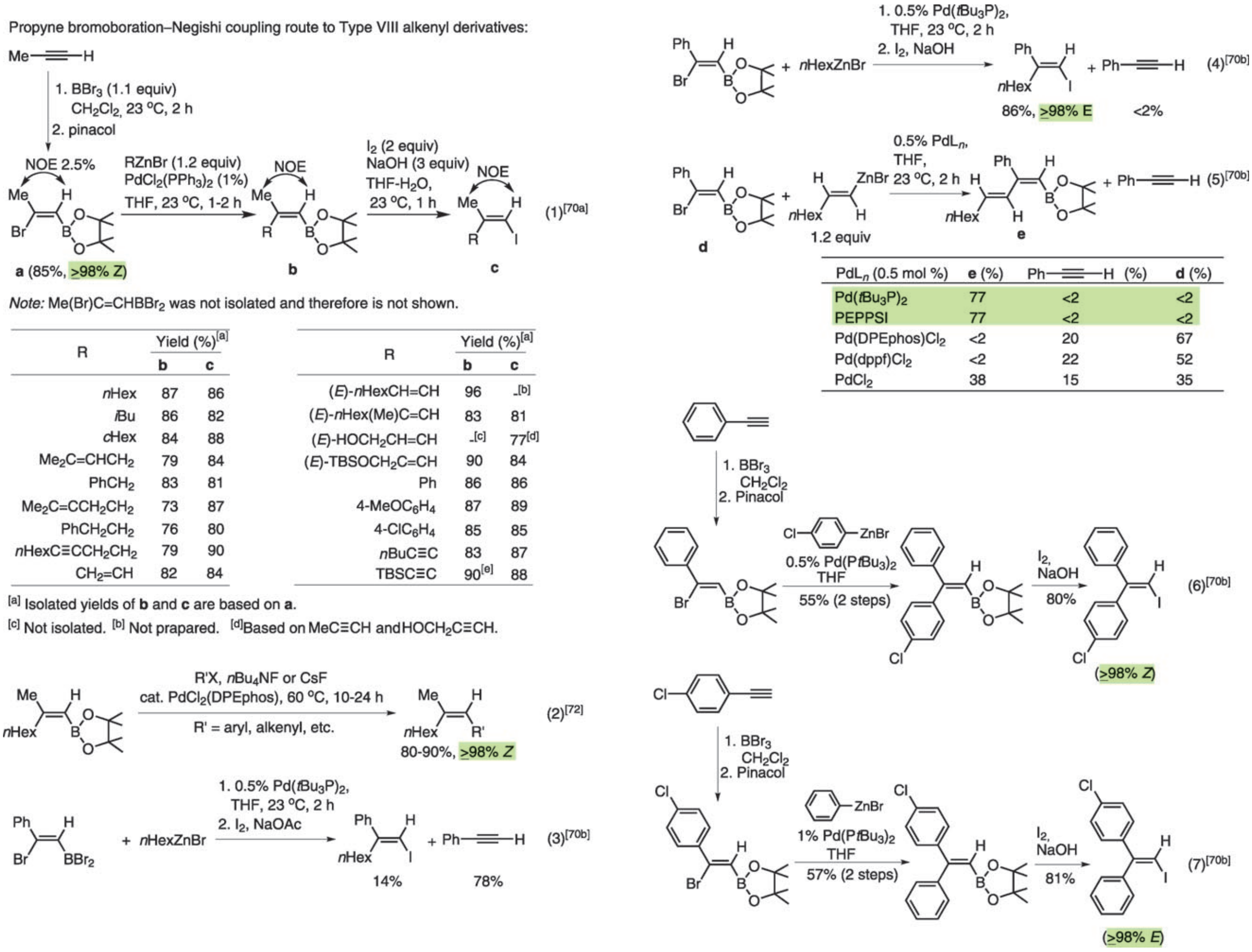
Scheme 7.

syn-Zr-Catalyzed Carboalumination (ZMA) of Proximally Heterofunctional Alkynes Followed by Stereoisomerization

The ZMA reaction of homopropargyl alcohol followed by treatment with $AlCl_3$ at 50 °C for several hours provides the corresponding *Z* isomer.[79,80] Its mono- and diiodo derivatives have proven to be useful Type VIII alkenyl reagents for the synthesis of a variety of *Z*-alkene-containing terpenoids, as discussed later in detail (Scheme 11).

Magical Power of Transition Metals: Present and Future Outlook

As a LEGO-like tool for synthesizing all conceivable types of organic compounds, the Pd-catalyzed cross-coupling between R^1M (M = Zn, Al, B, Zr, etc.) and R^2X (X = halogen, etc.) for producing R^1–R^2 as organic products has emerged as the currently most widely applicable and satisfactory method in the y(es)^2 manner. A glance at Table 3 might give us the



Note: Me(Br)C=CHBBr$_2$ was not isolated and therefore is not shown.

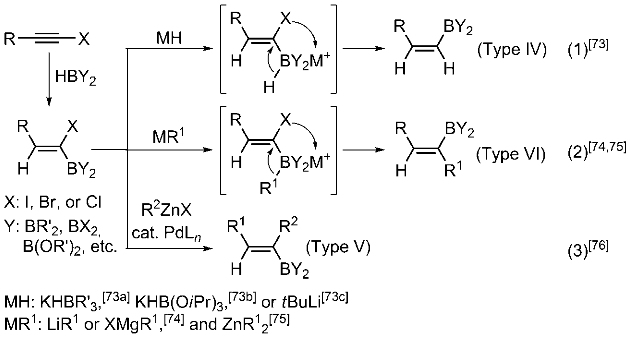
R	Yield (%)[a] b	Yield (%)[a] c
*n*Hex	87	86
*i*Bu	86	82
*c*Hex	84	88
Me$_2$C=CHCH$_2$	79	84
PhCH$_2$	83	81
Me$_2$C=CCH$_2$CH$_2$	73	87
PhCH$_2$CH$_2$	76	80
*n*HexC≡CCH$_2$CH$_2$	79	90
CH$_2$=CH	82	84

R	Yield (%)[a] b	Yield (%)[a] c
(*E*)-*n*HexCH=CH	96	–[b]
(*E*)-*n*Hex(Me)C=CH	83	81
(*E*)-HOCH$_2$CH=CH	–[c]	77[d]
(*E*)-TBSOCH$_2$C=CH	90	84
Ph	86	86
4-MeOC$_6$H$_4$	87	89
4-ClC$_6$H$_4$	85	85
*n*BuC≡C	83	87
TBSC≡C	90[e]	88

[a] Isolated yields of **b** and **c** are based on **a**.
[c] Not isolated. [b] Not prapared. [d] Based on MeC≡CH and HOCH$_2$C≡CH.

PdL$_n$ (0.5 mol %)	**e** (%)	Ph–≡–H (%)	**d** (%)
Pd(*t*Bu$_3$P)$_2$	77	<2	<2
PEPPSI	77	<2	<2
Pd(DPEphos)Cl$_2$	<2	20	67
Pd(dppf)Cl$_2$	<2	22	52
PdCl$_2$	38	15	35

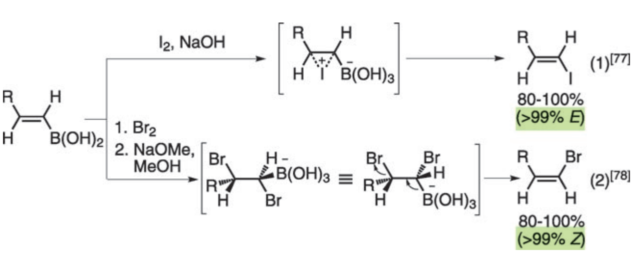
Scheme 8.



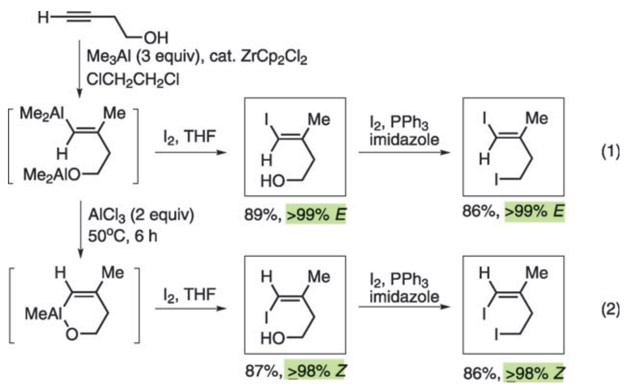
X: I, Br, or Cl
Y: BR'$_2$, BX$_2$, B(OR')$_2$, etc.

MH: KHBR'$_3$,[73a] KHB(O*i*Pr)$_3$,[73b] or *t*BuLi[73c]
MR^1: LiR^1 or XMgR^1,[74] and ZnR$^1_2$[75]

Scheme 9.



Scheme 10.



Scheme 11.

impression that our task in the "LEGO game" might be a little more than halfway complete, provided that both R^{1}M and R^{2}X are available in the desirable forms. At present, one may state that the overall scope of the syntheses of R^1–R^2 is limited more by the availability of appropriately structured R^{1}M and R^{2}X. One of the most challenging aspects of organic syntheses is to be able to synthesize not only all the conceivable types of monoenes shown in Table 4, for which various types of alkyne elementometalation reactions

(Schemes 5–Scheme 11 and Table 5) are indispensable, but also any of their desired combinations, such as all the conceivable types of di-, tri-, and higher oligoenes, and so on. Although no details are presented here, it is gratifying that through the use of various combinations of alkyne elementometalation reactions and the Pd-catalyzed alkenyl–alkenyl cross-coupling procedures, mostly Negishi supplemented with Suzuki coupling, we have just synthesized four possible types of conjugated dienes and eight possible types of conjugated trienes in high overall yields and in $\geq 98\,\%$ stereoselectivities throughout the syntheses, in other words, without generating detectable amounts of any stereoisomers.[37a]

Although there are some pending issues, such as alkynyl–alkynyl cross-coupling, which is prone to produce mixtures of all three possible conjugated diynes ($R^1C{\equiv}C{-}C{\equiv}CR^2$, $R^1C{\equiv}C{-}C{\equiv}CR^1$, and $R^2C{\equiv}C{-}C{\equiv}CR^2$), the Pd-catalyzed cross-coupling reactions between two unsaturated carbon groups, i.e., aryl, alkenyl, and alkynyl groups are generally well-behaved (Table 3). Even in the cases of conjugated diyne syntheses, indirect but efficient and selective routes are available.[19b,81]

As we turn our attention to Pd-catalyzed cross-coupling involving alkylmetals and/or alkyl electrophiles, including allyl, benzyl, propargyl, and their higher homologues, it can be readily noted from Table 3 that the use of alkyl electrophiles lacking proximal π bonds is considerably more challenging, although some notable progress has been made in recent years. On the other hand, alkylmetals and proximally π-bonded alkyl electrophiles display sufficiently high reactivities, as illustrated for the cases of allylic electrophiles (Scheme 4). Clearly, this is one large area of Pd-catalyzed cross-coupling, corresponding to nearly 30 out of the 72 cases of cross-coupling combinations shown in Table 3 and requires major attention. As many of these cases are being further investigated, it should be clearly noted that the following satisfactory options do exist: 1) Those nine cases of cross-coupling involving two allyl, benzyl, and/or propargyl cross-coupling partners are at best capricious, but the same desired products may be obtained in the y(es)^2 manner by shifting the point of C–C bond formation by one[17,82,83] (Table 3). 2) For alkyl–alkyl coupling without the involvement of proximal π bonds, the reaction of alkyl Grignard reagents with alkyl halides and related electrophiles catalyzed with Li_2CuCl_4 or other related Cu catalysts still appears to be the current best option.[25]

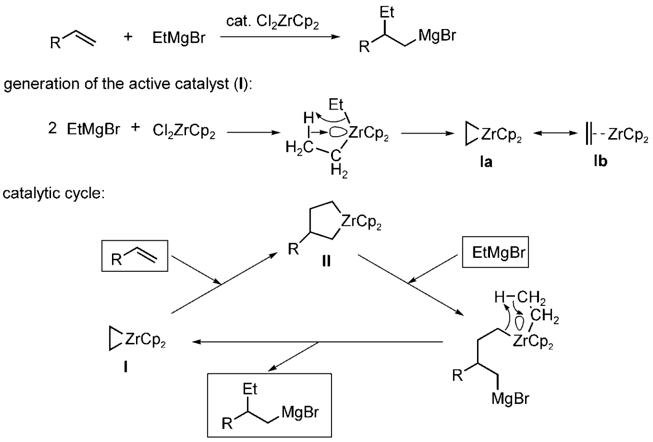
Zirconium-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA Reaction)

At the time we discovered the Zr-catalyzed carboalumination of alkynes (ZMA) in 1978 (Scheme 7),[59] a dream of expanding the scope of this reaction so as to embrace its alkene version for asymmetric C–C bond formation, which would amount to the single-step version of the Ziegler–Natta alkene polymerization, captured my mind. However, this seemingly easy task proved to be quite challenging, and several intermittent attempts over 17 years, heavily supported by our ongoing systematic investigations on zirconocene chemistry, were needed to finally discover in 1995 the zirconium-catalyzed asymmetric carboalumination of alkenes (ZACA reaction hereafter),[84] as detailed below.

Historical and Mechanistic Background of Carbometalation of Alkenes and Alkynes with Alkylzirconocene Derivatives

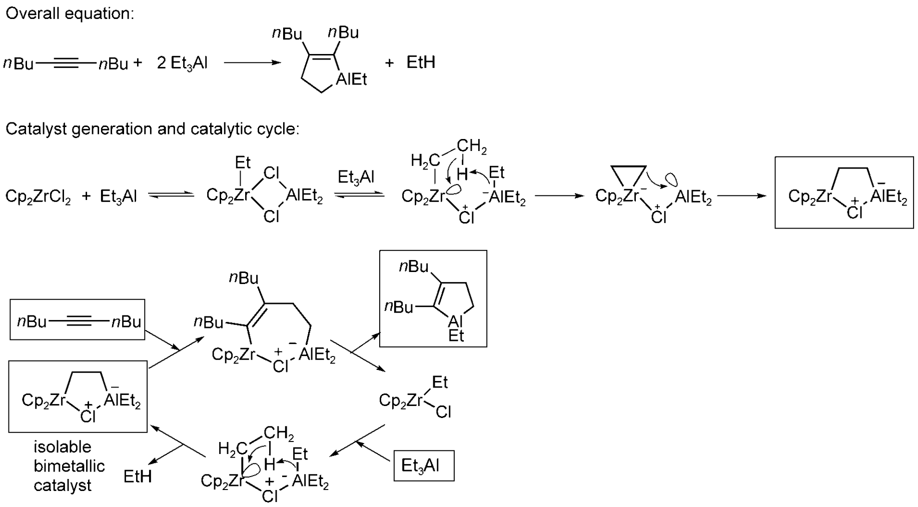
The Zr-catalyzed methylalumination of alkynes (ZMA reaction) was shown to involve one-step *syn*-addition of a Me–Zr bond to 1-alkynes in an *anti*-Markovnikov manner followed by Zr-to-Al transmetalation on the resultant carbon group.[60] This reaction involves acyclic carbometalation of a "super-acidic"[63,85] Zr–Al bimetallic system (Scheme 7).

Several years later, Dzhemilev reported a seemingly analogous reaction of Zr-catalyzed carbomagnesiation of alkenes with EtMgBr (Scheme 12).[86] There did not appear to be any apparent reasons to suspect that the mechanisms of these two closely analogous reactions should be radically different. Through our systematic investigations of "$ZrCp_2$" chemistry,[87] however, we accidentally clarified that the Dzhemilev ethylmagnesiation of alkenes actually proceeded through a highly intricate series of transformations via 1) formation of Et_2ZrCp_2, 2) β-agostic interaction induced intramolecular "acid–base" interaction producing a zirconacyclopropane (**Ia**) which may also be viewed as a zirconocene–ethylene π complex (**Ib**), 3) cyclic carbozirconation of an alkene with **I** to give, typically a 3-substituted zirconacyclopentane (**II**), 4) subsequent reaction of **II** with another molecule of EtMgBr leading to a β-agostic interaction induced "acid–base" interaction producing a 2-ethyl-1-alkylmagnesium bromide with regeneration of ethylene–$ZrCp_2$ π complex (**I**). All of the steps proposed above have been independently and amply supported (Scheme 12).[87,88]



Scheme 12. Cyclic carbozirconation mechanism for the Dzhemilev ethylmagnesiation.

We believe that both the discovery of the Dzhemilev ethylmagnesiation and our mechanistic clarification[88] have not only clearly established the existence of both acyclic and cyclic carbozirconation processes, but also enabled us to carefully distinguish some seemingly analogous carbometalation reactions of zirconocene derivatives. We were later further surprised by the existence of bimetallic (involving both Zr and Al) cyclic carbozirconation of alkynes and alkenes, which may be viewed as a hybrid of acyclic and cyclic carbozirconation[61] (Scheme 13). We also noted that our bimetallic (Zr–Al) cyclic carbozirconation process closely resembled the corresponding carbotitanation of alkenes with titanium–carbene species, which can be viewed as a two-membered titanacycle (Tebbe reagent) generated from a Ti–Al bimetallic system.[89] Without going into detailed mechanistic discussions, the following brief summary can be presented: 1) The formation of metallacycles including metal–carbene complexes (two-membered metallacycles) is a widely observable phenomenon with coordinatively unsaturated organotransition-metal complexes, especially in those cases where coordinatively unsaturated dialkylated organotransition-metal species that are readily prone to β- or even α-agostic interaction induced cyclization are generated.[90] 2) The propensity for generating the requisite "coordinatively unsaturated dialkyltransition-metal species" rests on a delicate balance between the alkylating power of alkylmetal reagents, e.g., RLi > RMgX > $RAlX_2$, and their ability to avoid formation of coordinatively saturated "ate" complexes. Thus, for example, trialkylalanes, e.g. Et_3Al, do not dialkylate $[ZrCp_2Cl_2]$ to give $[Et_2ZrCp_2]$. On the other hand, Grignard reagents, e.g. EtMgBr, readily dialkylate to give the $16e^-$ $[Et_2ZrCp_2]$. Triethylation does proceed, but it is readily reversible. All these make alkylmagnesium derivatives some of the optimal reagents for converting $[ZrCp_2Cl_2]$ into zirconacycles. 3) Even with alkylalanes, however, zirconacycles may still be formed via the "bimetallic intramolecular acid–base interactions" discussed above.



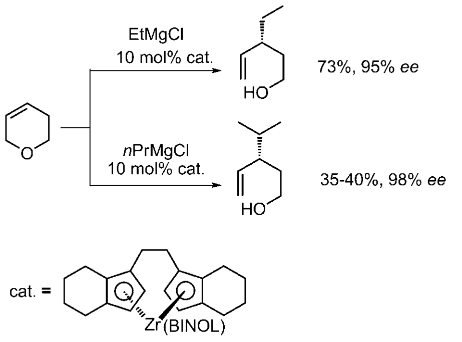
Scheme 13. Bimetallic cyclic carboalumination mechanism.[61]

Catalytic Asymmetric Carbometalation of Alkenes Proceeding via Dzhemilev Ethylmagnesiation

The first catalytic and highly enantioselective alkene carbometalation with zirconocene derivatives was reportd by Hoveyda in 1993.[91] Highly satisfactory results have been obtained through the use of Dzhemilev ethylmagnesiation of allyl ethers and allylamines (Scheme 14). Similar developments were also made later.[92]

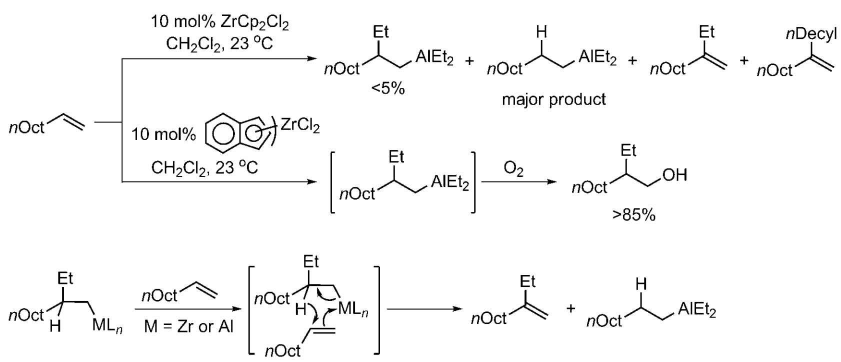
Although the enantioselectivity in some cases are spectacularly high, a few critical limitations should be noted. As might be expected from mechanistic details of the Dzhemilev carbomagnesiation discussed above, the introduction of the singularly important Me group is not readily feasible. While the introduction of Et is satisfactory, that of *n*Pr and longer alkyl groups is accompanied by regioisomerization, leading to the formation of unattractive product mixtures.[91–93] Clearly, new alternative reactions not requiring zirconacycles were needed, especially for the most highly desirable case of enantioselective methylmetalation.

In the meantime, our own efforts toward this goal were failing miserably. We then noted that all of our very tentative feasibility investigations that led to negative results were conducted with the parent $[ZrCp_2Cl_2]$. We finally decided to commit ourselves to the following two studies: 1) a detailed fact-finding investigation of the reaction of 1-decene with 10 mol% of $[ZrCp_2Cl_2]$ in CH_2Cl_2 and 2) a search for satisfactory procedures based on (1). These studies immediately led to some most useful results (Scheme 15). With $[(Me_5C_5)_2ZrCl_2]$, no reaction was observed under the same conditions.[84] Clearly, zirconocene derivatives with sufficiently, but not excessively, bulky ligands to suppress unwanted side reactions, most notably β-H transfer hydrometalation, while promoting the desired carbometalation, were needed to realize our goal.



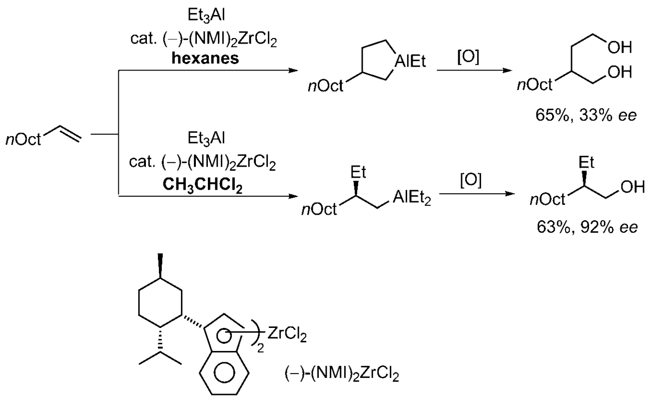
Scheme 14. Catalytic asymmetric carbometalation/elimination of allyl ethers with ethylmagnesium and chiral zirconocene derivatives.

Yet another ambush we briefly encountered was the initially unexpected Al-Zr bimetallic cyclic carbometalation of alkenes. Before 1995, we believed that dialkylation of zirconocene derivatives would be mandatory to observe the



Scheme 15. Reaction of 1-decene with Et_3Al in the presence of various zirconocene derivatives.

formation of zirconacyclopropanes via β-agostic interaction induced cyclization. We were, however, surprised to find out that the reaction of 1-decene with Et_3Al in the presence of $[(NMI)_2ZrCl_2]$[94a] (NMI = neomenthylindenyl) in hexanes would proceed by cyclic carbometalation[84b] (Scheme 16), even though there were ample indications that trialkylalanes

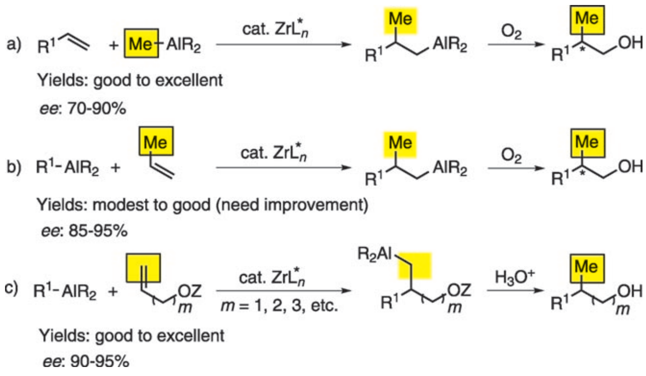


Scheme 16. Marked solvent effect in the reaction of 1-decene with Et_3Al in the presence of $[(NMI)_2ZrCl_2]$.

do not lead to the dialkylation of zirconocene derivatives. It was indeed this surprising finding that led to the clarification and establishment of the bimetallic cyclic mechanism for carbozirconation of alkynes mentioned earlier (Scheme 13).[61] Fortunately, we soon learned that the use of more polar solvents including CH_2Cl_2, CH_3CHCl_2, and $(CH_2Cl)_2$ almost totally suppressed the undesired cyclic carbometalation process, thereby promoting formation of the desired products (Scheme 16).[84]

Throughout our investigations we were very much concerned about the third potential side reaction, i.e., Zr-catalyzed alkene polymerization of Ziegler and Natta.[95] However, this has not been of any serious concern. In retrospect, this is not surprising, if one considers the 1) essentially 1:1 alkene/alane ratios and 2) the absence of highly efficient polymerization promotors, such as methylaluminoxane (MAO), which are typically required in large quantities relative to trialkylalanes. In our ZACA reaction, the use of MAO and other promoters is not mandatory and typically not necessary, although the addition of one equivalent or less of water or the corresponding amount of preformed MAO can significantly promote otherwise slow ZACA reactions,[96] such as that of styrenes.

Having learned about three major pitfalls, namely 1) cyclic carbometalation, 2) H-transfer hydrometalation, and 3) Ziegler–Natta-type alkene polymerization as well as how to avoid them, our remaining major task was to find some satisfactory chiral zirconocene catalysts. In this respect, we have not yet made a systematic optimization by catalyst design. Instead, we have merely screened a dozen to 15 known chiral zirconocene complexes. In our cases, the widely used $[(ebi)ZrCl_2]$[94b] (ebi = ethylenebis(indenyl)) and its partially hydrogenated derivatives[94c] were less effective. The most effective among those tested thus far is Erker's $[(NMI)_2ZrCl_2]$.[94a] By using either the *R* or *S* isomer of commercially available $[(NMI)_2ZrCl_2]$,[94d] the approximate ranges of enantiomeric excesses observed in the three mutually complementary ZACA reactions shown in Scheme 7 are 70–95 % *ee* and the product yields are generally satisfactory, although there clearly exists room for improvement (Scheme 17).



Scheme 17. Three protocols for the enantioselective synthesis of methyl-substituted 1-alkanols.

Current Summary of the Development and Application of the ZACA Reaction and Conclusions

Although no detailed discussion on the applications of the ZACA reaction is intended here, the following favorable features of this novel asymmetric C–C bond-forming reaction may be noted and exploited. In the interest of providing a full list of the publications on the ZACA reaction by the author's group, all the original papers and pertinent reviews and so on are listed in the references.[63,69,75,84,87,97–120]

1) The ZACA reaction is a novel and rare catalytic asymmetric C–C bond-forming reaction of terminal alkenes of one-point-binding without requiring any other functional groups, even though various functional groups may be present.

Table 6: Natural products and related compounds of biological and medicinal interest synthesized by the ZACA reaction by the author's group.

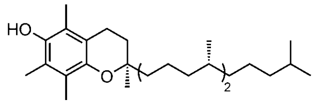
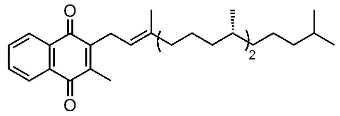
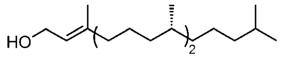
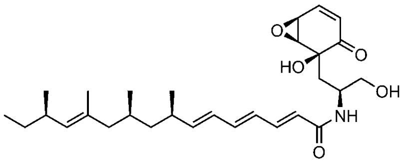
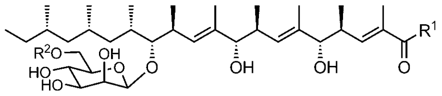
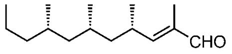
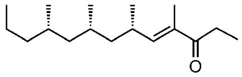
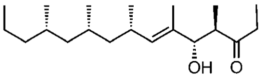
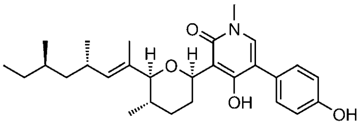
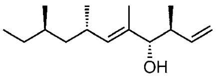
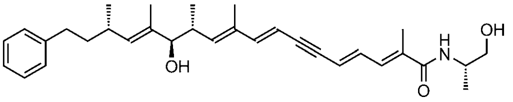
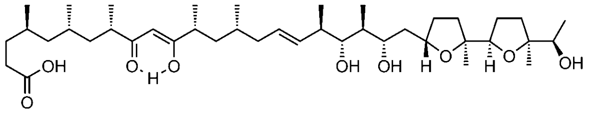
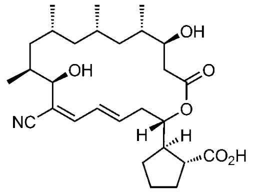
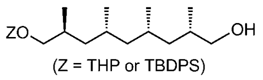
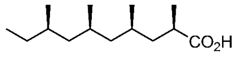
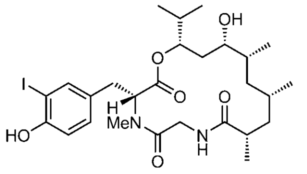
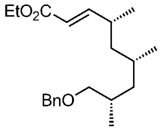
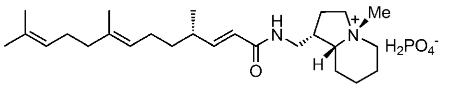
Entry	Compound (publication year)	Structure	Kind of synthesis
1	vitamin E (2001, 2002)[97,98]		total synthesis
2	vitamin K (2001)[97,106]		total synthesis
3	phytol (2001)[97]		total synthesis
4	scyphostatin (2004, 2010)[99,111]		side chain[99] and total synthesis[111]
5	TMC-151A-F C11–C20 fragment (2004)[100]	 $R^1 = C_6H_8O(OH)_5$ or $C_5H_7O(OH)_4$ R^2 = H or Ac	C11–C20 fragment
6	siphonarienal (2004)[101]		total synthesis
7	siphonarienone (2004)[101]		total synthesis
8	siphonarienolone (2004)[101]		total synthesis
9	(+)-sambutoxcin C9–C18 fragment (2004)[101]	 	C9–C18 fragment
10	6,7-dehydrostipiamide (2004)[102]		total synthesis
11	ionomycin C1–C10 fragment (2005)[103]		C1–C10 fragment
12	borrelidin C3–C11 fragment (2005)[103]	 	C3–C11 fragment
13	preen gland wax of the graylag goose, *Anser anser* (2006)[104]		total synthesis
14	doliculide C1–C9 fragment (2006)[104]	 	C1–C9 fragment
15	(+)-stellattamide A (2007)[106]		sidechain

Table 6: (Continued)

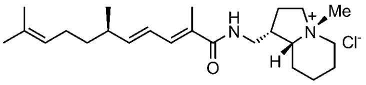
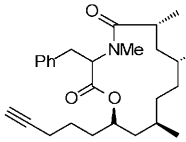
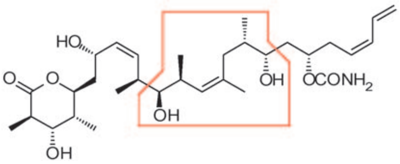
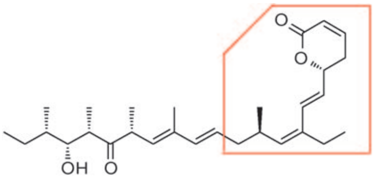
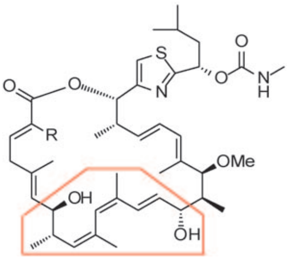
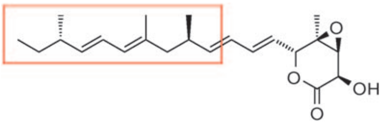
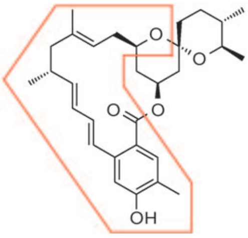
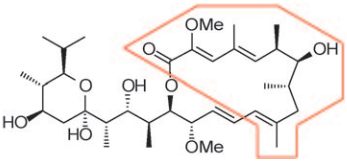
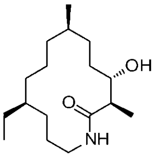
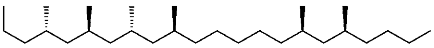
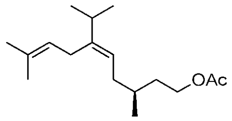
Entry	Compound (publication year)	Structure	Kind of synthesis
16	(+)-stellattamide B (2007)[106]		C5–C11 sidechain
17	(−)-spongidepsin (2007)[107]		total synthesis
18	(+)-discodermolide (2007)[75]		C11–C17 fragment
19	(−)-callystatin A (2007)[75]		C1–C11 fragment
20	archazolides A and B (2007)[75] A: R=Me, B: R=H		C7–C15 fragment
21	nafuredin (2008)[108]		C9–C18 fragment (formal total synthesis)
22	milbemycin β_3 (2008)[108]		C1–C13 fragment
23	bafilomycin A_1 (2008)[108]		C1–C11 fragment
24	fluvirucinin A_1 (2008)[109]		total synthesis
25	4,6,8,10,16,18-hexamethyldocosane (2008)[110]		total synthesis

Table 6: (Continued)

Entry	Compound (publication year)	Structure	Kind of synthesis
26	yellow scale pheromone (2008)[69]		total synthesis

2) There are a few or possibly more alternative and mutually complementary procedures to choose from, allowing the highly flexible design for the syntheses of chiral organic compounds[98,100] (Scheme 17).

3) In cases where the ZACA products are obtained as 2-chirally branched 1-alcohols via simple oxidation, typically with O_2, of alanes, lipase-catalyzed acetylation with ordinary column chromatography provides a widely applicable and convenient method of purification by taking advantage of the sufficiently high ZACA-generated 70–95 % enantiomeric excess of the crude products.[106]

4) In more demanding cases, proximally (γ- or δ-) heterofunctional and hence readily purifiable 2-chiral 1-alcohols may be prepared first, purified, and further converted.[120]

5) In the syntheses of compounds with two or more chiral centers, the principle of statistical enantiomeric amplification is operative. For the syntheses of deoxypolypropionates, for example, homologation by one 1,2-propylidene unit can be performed in one pot by a tandem ZACA and Pd-catalyzed vinylation process.[103] At a realistic average enantioselectivity of 80 % *ee*, di-, tri-, and tetrameric deoxypolypropionates are reliably predicted to be about 98, 99.9, and 99.99 % *ee*, respectively.[99,100] The only remaining task for preparing ultrapure deoxypolypropionates is the ordinary and very facile chromatographic purification of newly formed 2,4-dimethyl-1-hydroxybutyl moieties one at a time.[99–101,103,104]

We believe that the ZACA reaction is a widely applicable, high-yielding, efficient and selective method for asymmetric C–C bond formation that is potentially economical. As of today, however, it has not yet been widely embraced by the organic synthetic community, although its application to natural products synthesis by other workers is known.[96] In the meantime, our own efforts to apply it to catalytic asymmetric syntheses of chiral natural products have been very enjoyable and most rewarding. In this Review, only the names and structures of natural products and related compounds, including about a dozen that have been synthesized through the use of the ZACA reaction, are presented in Table 6. It is indeed gratifying to note that the ZACA/Pd- or Cu-catalyzed cross-coupling synergy does provide, in most cases, substantial improvements in efficiency and selectivity, leading to significant increases in overall yields of the pure desired compounds over the previous syntheses of the same or related compounds. Coupled with various flexible options for purifying optically active products to ultrahigh ($\geqslant 99\,\%$) purity levels, its wide-spread application in the near future may be anticipated.

Future Outlook

Aside from the finer aspects of mechanisms, all of the d-block transition-metal-catalyzed processes discussed above may be considered to proceed by two-electron transfer processes. As we pursue d-block transition-metal-catalyzed processes involving photochemical and other related processes, their catalytic activities through one-electron transfer processes would seem to be similarly important. From the nonbiological organic synthetic viewpoint, it still appears to be a largely unexplored field of vast potential.

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