

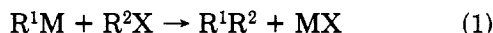
Palladium- or Nickel-Catalyzed Cross Coupling. A New Selective Method for Carbon-Carbon Bond Formation

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The cross-coupling reaction of organometallic species with organic halides and related electrophiles represents one of the most straightforward methods for carbon-carbon bond formation (eq 1). Despite its inherent

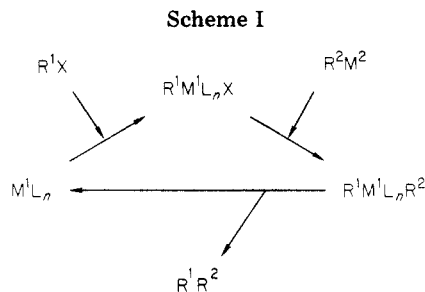


simplicity and significance, however, its synthetic utility had been severely limited until the mid-1960s due mainly to (a) the inability of Grignard reagents and organolithiums to undergo direct substitution with aryl, alkenyl, and alkynyl halides, (b) the general lack of chemoselectivity associated with these conventional organometallics, (c) competitive eliminations, and (d) cross-homo scrambling via halogen-metal exchange.

Although advances in organocopper chemistry¹ over the past two decades have solved many of the above-mentioned difficulties, a large number of other problems still persist. For example, the Cu-promoted coupling of two different alkenyl or aryl groups is very sluggish and/or involves extensive cross-homo scrambling,^{1,2} and the reaction of alkynylcoppers with organic halides generally is very sluggish, requiring drastic reaction conditions.³

About 10 years ago, we became interested in directly generating alkenylcopper reagents from either alkenylboranes or alkenylalanes, many of which are readily available by the respective hydrometallation of alkynes,⁴ but our attempts were unsuccessful.^{5,6} In 1972, Kumada⁷ and Corriu⁸ independently reported that the reaction of Grignard reagents with alkenyl or aryl halides could be markedly catalyzed by certain Ni-phosphine complexes, e.g., $Cl_2Ni(PPh_3)_2$. Although many other transition-metal-catalyzed reactions of Grignard reagents with organic halides were known, the so-called Kharasch-type reactions,⁹ with the exception of the Cu-catalyzed procedures,¹⁰ are not well suited for cross coupling due to extensive cross-homo scrambling and other complications.

Although the unique synthetic advantages of the Ni-catalyzed reaction were unknown, we were strongly attracted by the possibility that the suggested mechanistic scheme⁷ (Scheme I) might represent a general and useful approach to selective carbon-carbon bond for-



mation. One of our specific goals was to come up with a satisfactory solution to the above-mentioned problem of directly transferring stereo- and regiodefined alkenyl groups from boron or aluminum to carbon via a transition metal, e.g., Ni. However, we also became interested in the scope of Scheme I with respect to M^1 , M^2 , R^1 , and R^2 . We were particularly attracted by the possibility of utilizing metals that are less electropositive than alkali metals and Mg, such as Zn, Cd, B, Al, Si, Sn, and Zr. Organometallics containing these metals are known to be more compatible with various electrophiles, such as esters, amides, nitriles, and nitro compounds, than those containing Li and Mg. More exciting to us was the possibility of generating stereo- and regiodefined alkenylmetals containing B,^{4b} Al,^{4c} Si,¹¹ Sn,¹² and Zr¹³ via hydrometalation or carbometalation¹⁴

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(2) See, for example, House, H. O. *Proc. R. A. Welch Found. Conf. Chem. Res.* 1974, 17, 101.

(3) Castro, C. E.; Havlin, R.; Honwad, V. K.; Malte, A.; Mojé, S. *J. Am. Chem. Soc.* 1969, 91, 6464.

(4) (a) For a general review of the subject, see: Negishi, E. "Organometallics in Organic Synthesis"; Wiley-Interscience: New York, 1980. (b) B: For a review, see: Brown, H. C. "Hydroboration"; Benjamin: New York, 1962. (c) Al: For a review, see: Mole, T.; Jeffery, E. A. "Organometallic Compounds"; Elsevier: Amsterdam, 1972.

(5) Unpublished results of T. Yoshida and E. Negishi.

(6) For more recent and successful results, see: (a) Yamamoto, Y.; Yatagai, H.; Maruyama, K.; Sonoda, A.; Murahashi, S. I. *J. Am. Chem. Soc.* 1977, 99, 5652; *Bull. Chem. Soc. Jpn.* 1977, 50, 3427. (b) Brown, H. C.; Campbell, J. B., Jr. *J. Org. Chem.* 1980, 45, 389, 549, 550. (c) Uchida, K.; Utimoto, K.; Nozaki, H. *Ibid.* 1976, 41, 2941.

(7) (a) Tamo, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* 1972, 94, 4374. (b) For a review, see: Kumada, M. *Pure Appl. Chem.* 1980, 52, 669.

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(9) Kharasch, M. S.; Reinmuth, O. "Grignard Reactions of Nonmetallic substances"; Prentice-Hall: New York, 1954; Chapter 16.

(10) (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* 1971, 93, 1483. (b) For a review, see: Kochi, J. K. *Acc. Chem. Res.* 1974, 7, 351.

(11) For reviews, see: (a) Lukevits, E. Ya.; Voronkov, M. G. "Organic Insertion Reactions of Group IV Elements"; Consultants Bureau: New York, 1966. (b) Benkeser, R. A. *Pure Appl. Chem.* 1966, 13, 133.

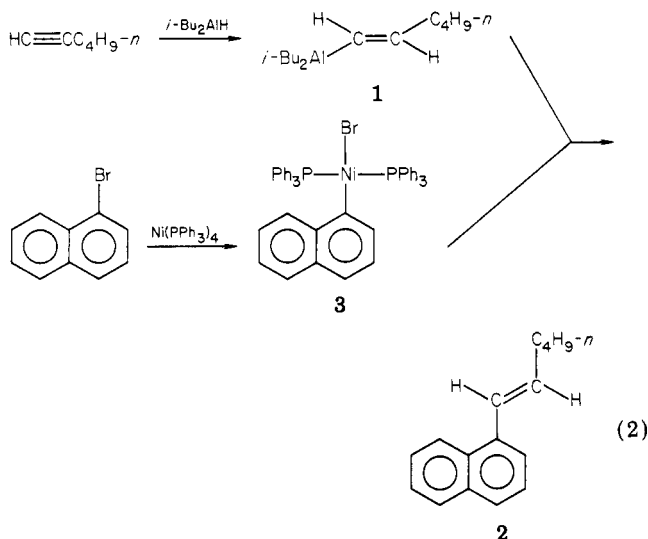
(12) In addition to ref 11a, see the following. (a) Leusink, A. J.; Budding, H. A.; Marman, J. W. *J. Organomet. Chem.* 1976, 9, 285. (b) Leusink, A. J.; Budding, H. A.; Dreuth, W. *Ibid.* 1976, 9, 295. (c) Corey, E. J.; Wollenberg, R. H. *J. Am. Chem. Soc.* 1974, 96, 5582; *J. Org. Chem.* 1975, 40, 2265.

Ei-ichi Negishi obtained his baccalaureate degree from the University of Tokyo in 1958. After working 2 years with Teijin, Ltd., as a research chemist, he came to this country as a Fulbright scholar and obtained a Ph.D. degree from the University of Pennsylvania in 1963. After spending 3 more years at Teijin, he joined Herbert C. Brown's research group at Purdue University as a postdoctoral associate and then served as his personal assistant. In 1972 he moved to Syracuse University as an Assistant Professor and was promoted to an Associate Professor in 1976. He moved back to Purdue University in 1979 as Professor. His research interests range from C, chemistry to the selective synthesis of natural products involving the use of organometallics, especially bimetallic and multimetallic catalytic systems. Besides the Pd- or Ni-catalyzed cross coupling discussed here, he takes pride in the recent discovery and development of Zr- or Ti-catalyzed carbometalation of alkynes.

and transferring the alkenyl groups from these metals to carbon under the influence of transition-metal catalysts.

Pd- or Ni-Catalyzed Cross Coupling of Two Unsaturated Carbon Groups

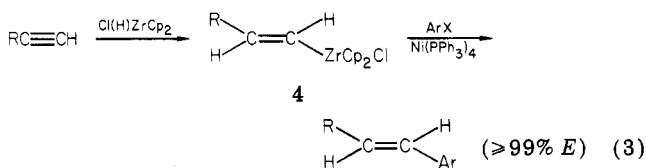
With the above-mentioned objectives in mind we reacted (*E*)-1-hexenyldisiamylborane, its ate complex with *n*-butyllithium, or (*E*)-1-hexenyldiisobutylalane (1) with 1-bromonaphthalene in THF in the presence of 5 mol % of Ni(PPh₃)₄, prepared by reacting anhydrous Ni(acac)₂ with 1 molar equiv of diisobutylaluminum hydride (DIBAH) in the presence of 4 equiv of PPh₃ in THF.¹⁵ Whereas no cross coupling was observed with the boron compounds at room temperature, the reaction of alkenylalane 1 gave 2 in 73% yield with ≥99% retention of the *E* geometry (eq 2). Since no



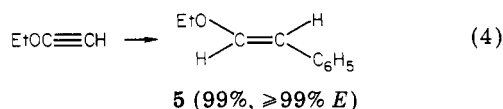
reaction occurs in the absence of the Ni complex, the reaction is catalyzed by the Ni complex. Bromo(1-naphthyl)bis(triphenylphosphine)nickel (3) reacts with 1 to produce 2 in 65% yield after 1 h at 25 °C. It is therefore likely that 3 is an intermediate in the reaction. The product yields observed in the Ni-catalyzed reac-

tion of (*E*)-1-alkenylalanes with various aryl iodides and bromides were generally high (64–93%), and the stereoselectivity in each case was ≥99%.

(*E*)-1-Alkenylzirconium derivatives (4), obtained by hydrozirconation of alkynes, also undergo an analogous Ni-catalyzed cross-coupling reaction with aryl iodides and bromides¹⁶ (eq 3).

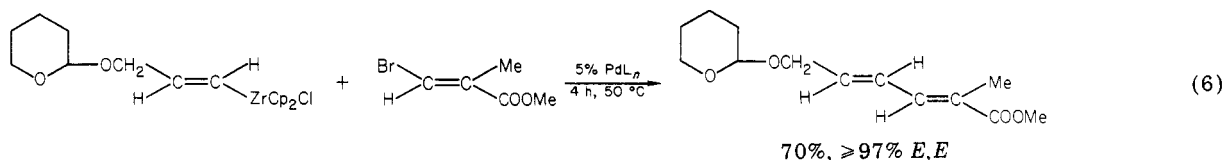
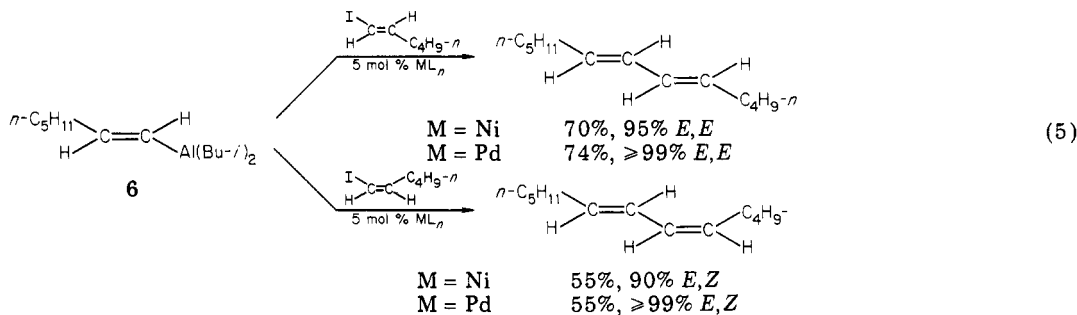


Since the scope of carbon-carbon bond formation involving organozirconium compounds was limited to only a few reactions, such as carbonylation¹⁷ and the reaction with acyl halides to form ketones,¹⁸ the Ni-catalyzed cross coupling represented a breakthrough in the application of organozirconium chemistry to organic synthesis. Hydrozirconation¹³ can tolerate certain functional groups, oxy functional groups in particular, that are incompatible with hydroalumination,¹⁹ and aryl-substituted (*E*)-alkenes containing ethereal groups, such as 5, can now be readily obtained.¹⁶ Various



functional groups, such as COOMe, CN, OMe, and Cl, in aryl halides can also be tolerated.

We then undertook to develop selective procedures for alkenyl-alkenyl cross coupling, for which there were essentially no general cross-coupling procedures. We found that, although the Ni-catalyzed reaction of (*E*)-1-alkenylalanes 6 with (*E*)-1-iodoalkenes produced the desired conjugated *E,E*-dienes of ca. 95% stereoisomeric purity, the stereospecificity in the corresponding reaction of 6 with (*Z*)-1-iodoalkenes was only ca. 90%²⁰ (eq 5). In search for a superior catalyst we have tested all three metals of the nickel triad and have



(13) (a) Wailes, P. C.; Weigold, H.; Bell, A. P. *J. Organomet. Chem.* 1971, 27, 373. (b) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* 1975, 97, 679. (c) For a review, see: Schwartz, J. *J. Organomet. Chem. Lib.* 1976, 1, 641.

(14) (a) Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* 1978, 100, 2252. (b) For a review, see: Negishi, E. *Pure Appl. Chem.* 1981, 53, 2333.

(15) Negishi, E.; Baba, S. *J. Chem. Soc., Chem. Commun.* 1976, 596.

(16) Negishi, E.; Van Horn, D. E. *J. Am. Chem. Soc.* 1977, 99, 3168.

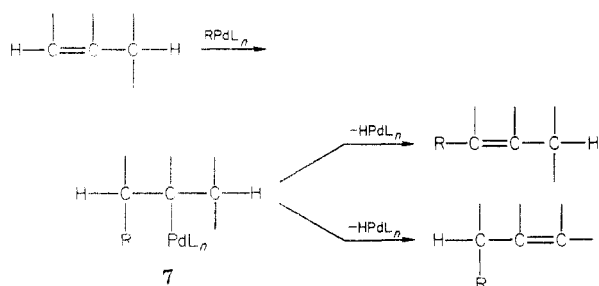
(17) Bertelo, C. A.; Schwartz, J. *J. Am. Chem. Soc.* 1975, 97, 228; 1976, 98, 262.

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(19) Collins, P. W.; Dajani, E. Z.; Bruhn, M. S.; Brown, C. H.; Palmer, J. R.; Pappo, R. *Tetrahedron Lett.* 1975, 4217.

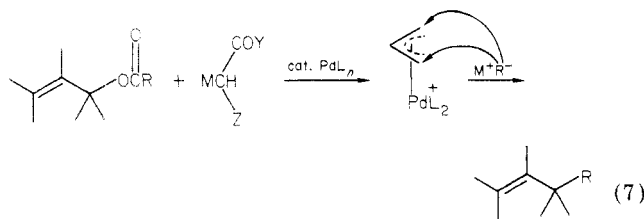
(20) Baba, S.; Negishi, E. *J. Am. Chem. Soc.* 1976, 98, 6729.

Scheme II



indeed found that the same alkenyl-alkenyl coupling can be achieved with $\geq 99\%$ stereospecificity if a Pd-phosphine catalyst, prepared by the reduction of $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ with 2 equiv of *i*- Bu_2AlH , is used in place of $\text{Ni}(\text{PPh}_3)_4$ (eq 5). The corresponding reaction of alkenylzirconium derivatives also proceeds with essentially complete retention of stereochemistry of the alkenyl groups,²¹ as exemplified by the results shown in eq 6.

At the time we observed the Pd-catalyzed alkenyl-aryl¹⁵ and alkenyl-alkenyl²⁰ coupling reactions, virtually nothing was known about the Pd-catalyzed cross coupling, even though a couple of papers describing the Pd-catalyzed cross-coupling reaction of Grignard reagents²² and of alkynylsodiums²³ appeared in the literature before our papers^{15,20} were published. The Pd-catalyzed alkenyl-alkenyl coupling reaction^{20,21} as well as Cassar's Pd-catalyzed alkyne synthesis²³ showed some distinct advantages of Pd catalysts over Ni catalysts. Prior to the development of these reactions, a few other types of Pd-promoted carbon-carbon bond-forming reactions had been developed. In 1965, Tsuji²⁴ reported a stoichiometric allylation of enolates with π -allylpalladium derivatives, which was developed into a catalytic reaction of considerable synthetic utility by Trost²⁵ (eq 7). Until recently, however, the synthetic



utility of the reaction had largely been limited to allylation of "stabilized" enolates. Another reaction developed primarily by Heck²⁶ involves substitution of either an alkenyl or allyl hydrogen by a carbon group of an organopalladium reagent, which is believed to proceed by an addition-elimination mechanism (Scheme II). Although the reaction proceeds selectively in favorable cases, it tends to lack stereo- and regioselectivity, since any hydrogen β to Pd in 7 can, in principle, participate in elimination. Thus, the new Pd-catalyzed cross coupling represented a general and

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(23) Cassar, L. *J. Organomet. Chem.* 1975, 93, 253.

(24) Tsuji, J.; Takahashi, H. *Tetrahedron Lett.* 1965, 4387.

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(26) Heck, R. F. *Acc. Chem. Res.* 1979, 12, 146.

Table I
Pd-Catalyzed Reaction of 1-Heptynylmetals
with *o*-Tolyl Iodide^a

metal	time, h	product yield (%)	unreacted <i>o</i> -tolyl iodide (%)
Li	1	trace	88
Na ^b	24 ^c	58	41
MgBr ^d	1	29	55
ZnCl	1	91	8
HgCl	1	<2	92
B(Bu- <i>n</i>) ₃	3	<2	76
	1 ^e	92	5
Al(Bu- <i>i</i>) ₂	3	49	46
SiMe ₃	1 ^e	<2	94
Sn(Bu- <i>n</i>) ₃	6	83	6

^a Unless otherwise stated, the reaction was run at 20–22 °C in THF in the presence of 5 mol % of a catalyst generated in situ by treating $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ with *i*- Bu_2AlH .

^b Generated in situ by treating 1-heptyne with NaOMe.

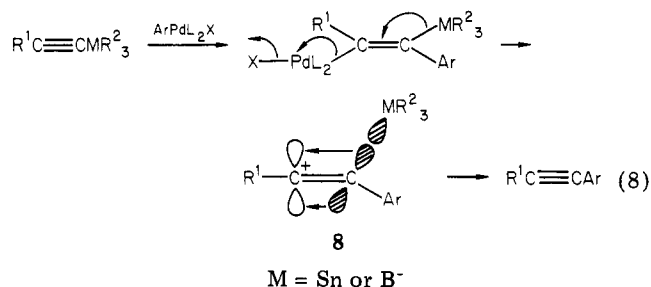
^c The reaction was carried out in DMF at 50 °C according to the procedure of Cassar.²³ ^d Prepared by treating 1-heptyne with *i*-PrMgBr. ^e The reaction mixture was refluxed.

selective method for carbon-carbon bond formation, different from either the Tsuji-Trost-type reaction of stabilized enolates²⁵ or the Heck-type reaction.²⁶

To further examine the scope of the Pd-catalyzed cross coupling, 1-heptynylmetal derivatives containing various metals were generated and reacted with *o*-tolyl iodide in the presence of 5 mol % of a Pd catalyst generated in situ by treating $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ with *i*- Bu_2AlH . The results summarized in Table I²⁷ reveal the following interesting features. First, contrary to our expectation, the reactions of 1-heptynylmetals containing Li and Na were quite sluggish at room temperature. Second, 1-heptynylmetals containing certain group 2 and 3 metals, e.g., Mg, Zn, and Al, are the most reactive group of reagents, and Zn appears to be by far the most satisfactory metal with respect to both reaction rate and product yield. Third, 1-heptynyltri-*n*-butyltin also show an unexpectedly high reactivity for a metal of relatively high electronegativity. Although lithium 1-heptynyltri-*n*-butylborate is less reactive, it cleanly produces the expected cross-coupling product in 92% yield in 1 h at 65–70 °C. Fourth, there is no indication of cross coupling with 1-heptynylmetals containing Hg or Si. The unexpectedly low reaction rates observed with Li and Na suggest that the organometallic compounds containing these metals exert some kind of retardation or inhibition of the Pd catalysis, e.g., conversion of Pd complexes to the corresponding ate complexes.²⁸ The unexpected high reactivity of the tin and borate derivatives is also puzzling in light of the relatively high electronegativity of Sn and B. It is conceivable that, with these reagents, the reaction proceeds by a mechanism other than that shown in Scheme I. One likely path, which might be viewed as the organometallic version of the Heck-type addition-elimination reaction, is shown in eq 8. The σ - π conjugation effect of group 4 and other heavy metals,⁴ as depicted in 8, should strongly favor the path shown

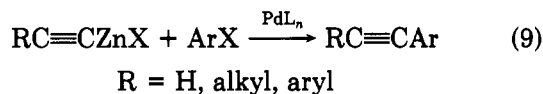
(27) King, A. O., Ph.D. Dissertation, Syracuse University, 1979. These results were presented at 174th National Meeting of the American Chemical Society, New Orleans, March 1977. See also: Negishi, E., in "Aspects of Mechanism and Organometallic Chemistry"; Brewster, J. H., Ed.; Plenum: New York, 1978; p 285.

(28) Clarification of the mechanism is in progress in our laboratories.



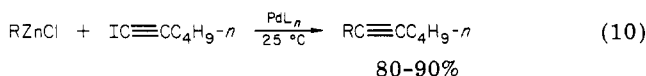
in eq 8. Although not well-established, ate complexes of group 3 metals, e.g., B and Al, should also participate in the σ - π conjugation.

The Pd-catalyzed reaction of alkynylzinc derivatives with aryl iodides or bromides (eq 9) proceeds readily

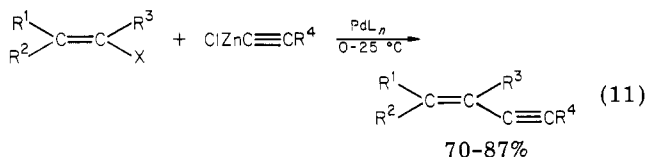


and selectively at or below room temperature and appears to be generally applicable, permitting even the direct synthesis of arylated ethynes.²⁹ These features appear to be unique among the known alkynyl-aryl coupling procedures.^{3,23,30}

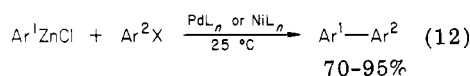
Having developed a highly efficient and selective procedure for coupling two unsaturated groups that involves the reaction of organozinc derivatives with organic iodides or bromides in the presence of Pd-phosphine complexes in THF, we then examined its scope with respect to the R¹ and R² groups in Scheme I. As indicated by the results shown in eq 10-12 as well as those already discussed above, the Zn-Pd method has proven to be general and selective, providing satisfactory procedures for alkenyl-alkynyl and aryl-aryl cases^{27,31,32} as well.



R = aryl, alkenyl



Rⁿ = H, or carbon group; X = I or Br



Ar¹, Ar² = aryl; X = I or Br

Phosphine complexes containing Ni and Pd can be used interchangeably in many instances. In such cases, the lower cost and the higher reactivity of Ni catalysts toward organic halides make them preferable to Pd catalysts. On the other hand, the product yields in Ni-catalyzed aryl-alkynyl and alkenyl-alkynyl coupling

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(30) (a) Dieck, H. A.; Heck, R. F. *J. Organomet. Chem.* **1975**, *93*, 259. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(31) (a) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683. (b) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.

(32) For related reactions involving Grignard reagents, see: (a) Fauvarque, J. F.; Jutand, A. *Bull. Soc. Chim. Fr.* **1976**, 765. (b) Sekiya, A.; Ishikawa, N. *J. Organomet. Chem.* **1976**, *118*, 349.

Table II
Scope of the Pd- or Ni-Catalyzed Cross Coupling
of Two Unsaturated Groups

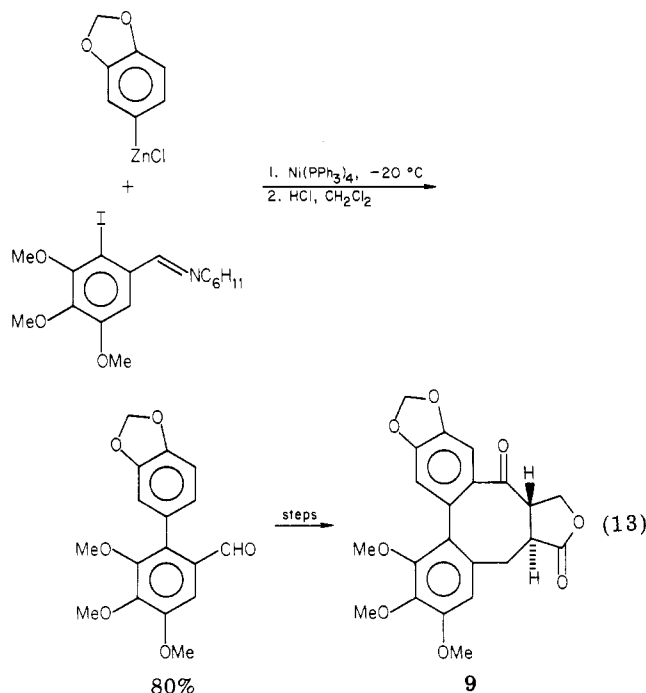
R ² of R ² M	aryl ^a		alkenyl ^a		alkynyl ^a	
	Pd	Ni	Pd	Ni	Pd	Ni
aryl	+ ^b	+	+	+	+	- ^c
alkenyl	+	+	+	- ^d	+	+ ^c
alkynyl	+	- ^c	+	- ^c	- ^e	- ^e

^a R¹ of R¹X. ^b The + sign indicates generally satisfactory results. ^c The product yield is generally very low.

^d Stereochemical scrambling occurs. ^e Nearly statistical mixtures of three possible diynes are formed in high combined yields.

reactions have been substantially lower than those realized with Pd catalysts, presumably because the acetylenic starting compounds and/or products tend to react with Ni catalysts more readily than with similar Pd catalysts to form polymers, most notably cyclic trimers and tetramers.³³ In general, Pd complexes appear to be more compatible with various functional groups than the corresponding Ni complexes. Triphenylphosphine is inexpensive and appears to be one of the most satisfactory ligands. Both Pd(PPh₃)₄³⁴ and a Pd(0)-PPh₃ complex generated in situ by treating Cl₂Pd(PPh₃)₂³⁵ with 2 equiv of *i*-Bu₂AlH or other suitable reducing agents work satisfactorily, although the latter has exhibited a greater reactivity in some instances. The current scope of the Pd- or Ni-catalyzed cross coupling of two unsaturated groups is indicated in Table II.

Although the number of papers reporting the use of these procedures in the selective synthesis of complex natural products is still very small, the synthesis of steganone³⁶ (9) shown in eq 13 demonstrates their synthetic potential.



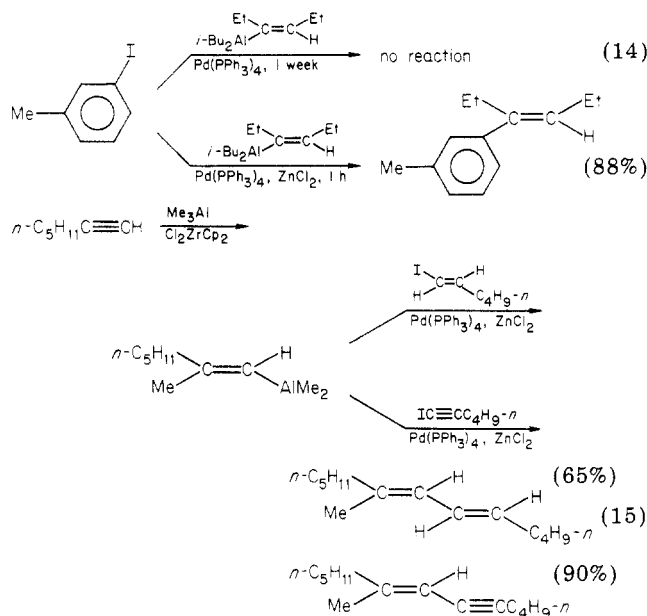
(33) For a review, see: Vollhardt, K. P. C. *Acc. Chem. Res.* **1977**, *10*, 1.

(34) Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.

(35) The preparation of Cl₂Pd(PPh₃)₂ involves treatment of PdCl₂ with 2.5 equiv of PPh₃ in DMF (6 ml/mmol of PdCl₂) at 140-150 °C, followed by cooling, filtration, and washing with ether.

(36) Larson, E. R.; Raphael, R. A. *Tetrahedron Lett.* **1979**, 5041.

Although the Pd- or Ni-catalyzed cross coupling of alkenylaluminum or alkenylzirconium derivatives with aryl, alkenyl, or alkynyl halides proceeds satisfactorily in cases where the alkenyl group is β -monosubstituted, the use of either α,β - or β,β -disubstituted alkenylmetals containing Al or Zr led to either no reaction or low product yields. Fortunately, we soon found that this difficulty could be readily overcome by adding catalytic amounts of zinc halides³⁷ (eq 14 and 15). These re-



actions are likely to be doubly catalyzed by Zn as well as Pd or Ni.

Similar reactions involving Cu-Zn-Pd mixed metal systems reported recently³⁸ also indicate the effectiveness of the double metal catalysis involving Zn and Pd. The scope of the Pd-catalyzed cross coupling of alkenylmetal derivatives has been further expanded so as to include the use of alkenylmetals containing Mg³⁹ and B.⁴⁰ The reaction of alkenylboron compounds was somewhat unexpected in light of our earlier failure to observe such reaction.^{15,20} However, the use of a base, e.g., NaOEt, which will convert the alkenylboranes into the corresponding ate complexes, and the high reaction temperatures not only are reminiscent of our alkynylborate reaction²⁷ (Table I) but also suggest that these alkenylboron reactions too might proceed by an addition-elimination mechanism similar to that shown in eq 8.

Organic halides, especially iodides and bromides, are the most reactive class of electrophiles. More recently, however, the use of other leaving groups, such as those containing O,^{41,42} S,⁴³ and Se,⁴⁴ has been investigated.

(37) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254.

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(40) (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, 3437. (b) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866. (c) Miyaura, N.; Sugimoto, H.; Suzuki, A. *Tetrahedron Lett.* **1981**, 22, 127. (d) Miyaura, N.; Suzuki, A. *J. Organomet. Chem.* **1981**, *213*, C53.

(41) Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* **1979**, *101*, 2246.

(42) (a) Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 2531. (b) Sato, M.; Takai, K.; Oshima, K.; Nozaki, H. *Ibid.* **1981**, *22*, 1609.

(43) (a) Okamura, H.; Miura, M.; Takei, H. *Tetrahedron Lett.* **1979**, 43. (b) Takei, H.; Miura, M.; Sugiura, H.; Okamura, H. *Chem. Lett.* **1979**, 1447.

In cases where these derivatives are more readily available than the corresponding halides, their use will prove to be a valuable extension of the Pd- or Ni-catalyzed cross coupling using organic halides.

Pd-Catalyzed Allylation, Benzylolation, and Propargylation

In addition to alkenyl, aryl, and alkynyl halides, allyl, benzyl, and propargyl halides as well as related species containing other heteroatom groups, such as O, S, and Se, are known to readily participate in the oxidative addition with Pd(0) and Ni(0) complexes.⁴⁵ The use of allyl, benzyl, and propargyl electrophiles in the Pd- or Ni-catalyzed cross coupling was therefore of interest to us. In 1967, Corey⁴⁶ introduced the reaction of π -allylnickel derivatives with organic halides. The reaction is regioselective but not stereoselective. A few years later, Felkin⁴⁷ developed the Ni-catalyzed reaction of Grignard reagents with allylic alcohols. Although this reaction too is nonselective, it is unique in that it tends to involve attack by a Grignard reagent at the more hindered of the two equilibrating allylic carbon atoms. A closely related Ni-catalyzed reaction of Grignard reagents with allylic sulfides⁴⁸ is also nonselective. Yet another approach to the Ni-catalyzed allylation is the reaction of allylmagnesium halides with aryl halides in the presence of Ni-phosphine complexes.^{49,50} Unlike these Ni-promoted allylation reactions, the Tsuji-Trost-type allylation involving Pd^{24,25} is reasonably selective. Until recently, however, its applicability had largely been limited to allylation of "stabilized" enolates, although more recent results indicate that appropriate modifications permit the use of simple ketone enolates.⁵¹⁻⁵³ Typical alkylmetals containing Li, Mg, Cu, etc., were reported to be ineffective.²⁵ Several relatively electronegative metals, such as Hg,⁵⁴ B,⁵⁵ Si,⁵⁶ and Sn,⁵⁷ are known to undergo the Pd-catalyzed allylation. However, their utility in the selective synthesis of olefins is still very limited.

We have found that the Pd-catalyzed allylation of alkenyl- and arylmetals containing Al, Zn, and Zr can

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(48) Okamura, H.; Takei, H. *Tetrahedron Lett.* **1979**, 3425.

(49) Thorsett, E.; Stermitz, F. R. *Heterocycl. Chem.* **1973**, *10*, 243.

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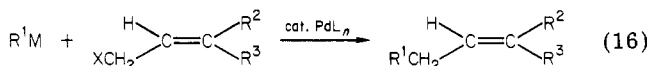
(55) Miyaura, N.; Yano, T.; Suzuki, A. *Tetrahedron Lett.* **1980**, *21*, 2865.

(56) Yoshida, J.; Tamao, K.; Takahashi, M.; Kumada, M. *Tetrahedron Lett.* **1978**, 2161.

(57) (a) Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301. (b) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2595.

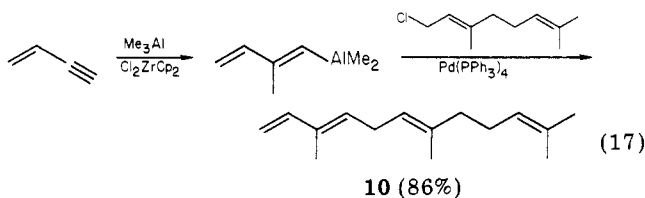
(c) Stille, J. K.; Goldschalx, J. *Ibid.* **1980**, *21*, 2599.

proceed with essentially complete retention of the stereo- and regiochemistry of certain allylic electrophiles^{58,59} (eq 16). A wide variety of allylic derivatives



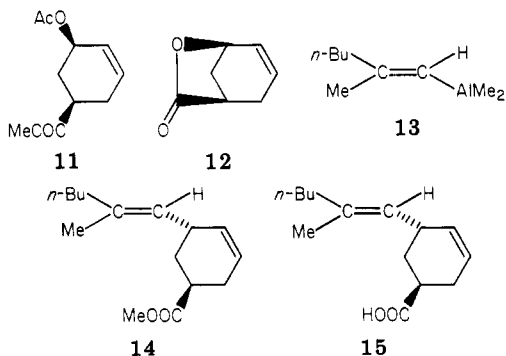
R^1 = alkenyl or aryl; R^2 and R^3 = two hydrogens or two carbon groups; M = Al, Zr, or Zn

containing halogens, OAc, OAlR₂, OP(O)(OR)₂, and OSiR₃ groups can participate in the reaction,⁶⁰ the order of their reactivity being halogen > OAc > OAlR₂ > OP(O)(OR)₂ > OSiR₃. When used in conjunction with the Zr-catalyzed carboalumination,¹⁴ the reaction provides a uniquely expeditious and selective route to 1,4-dienes of terpenoid origin, as indicated by the completely stereo- and regiospecific synthesis of α -farnesene (10)⁵⁸ shown in eq 17.



Besides being of considerable synthetic promise, the Pd-catalyzed allylation offers intriguing mechanistic problems. In principle, the Pd-catalyzed reaction of an organometallic reagent (RM) with allylic electrophiles may proceed by any of the following three mechanisms: (a) the Heck-type addition-elimination mechanism,^{54a} (b) the Trost-type mechanism²⁵ involving attack of π -allylpalladium species by a nucleophile on the side opposite to Pd (eq 7), and (c) the oxidative addition-transmetalation-reductive-elimination mechanism (Scheme I).

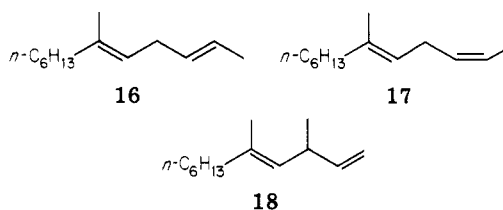
The regiochemistry shown in eq 16 and 17 seems to rule out the addition-elimination mechanism, which involves an allylic rearrangement. Treatment of the dimer of π -allylpalladium bromide with 4 equiv of PPh₃ (P/Pd = 2) has been reported to give σ -allylbromobis(triphenylphosphine)palladium.⁶¹ Its reaction with 1 equiv of alkenylalanes is at least as fast as the corresponding catalytic reaction. To further clarify its mechanism, cyclic allylic acetates 11 and 12 were re-



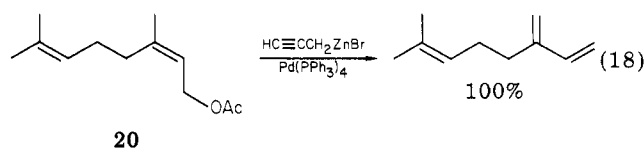
(58) Matsushita, H.; Negishi, E. *J. Am. Chem. Soc.* 1981, 103, 2882.
 (59) For related stoichiometric and catalytic reactions of alkenyl-zirconium derivatives, see: (a) Temple, J. S.; Schwartz, J. *J. Am. Chem. Soc.* 1980, 102, 7381. (b) Hayashi, Y.; Temple, J. S.; Schwartz, J. *Tetrahedron Lett.* 1981, 22. See also Castanet, J.; Petit, F. *Tetrahedron Lett.* 1979, 3221.
 (60) Negishi, E.; Chatterjee, S.; Matsushita, H. *Tetrahedron Lett.* 1981, 22, 3737.
 (61) Powell, J.; Shaw, B. L. *J. Chem. Soc. A* 1967, 1939. See also: Fitton, P.; Johnson, M. P.; McKeon, J. E. *Chem. Commun.* 1968, 6.

acted with 13 in the presence of Pd(PPh₃)₄ to give 14 and 15, whose stereochemical purities were 85 and 98%, respectively.⁶² The observed trans stereochemistry implies an overall inversion of configuration, which is entirely opposite to that observed in the Trost reaction of 11.⁶³ Since palladation of allylic esters, such as 11 and 14, has been reported to involve exclusive or predominant inversion,²⁵ the other microsteps in the reaction must proceed with overall retention. Thus, the Trost-type mechanism does not operate in this reaction. On the other hand, the results are consistent with the mechanism shown in Scheme I.

Unlike γ,γ -unsubstituted or γ,γ -disubstituted primary allylic derivatives, γ -monosubstituted allylic derivatives react with partial scrambling of the regio- and stereochemistry of the allyl group. Typically, the Pd-catalyzed reaction of (*E*)-crotyl acetate with (*E*)-(2-methyl-1-octenyl)dimethylalane gives an 80:10:10 mixture of 16, 17, and 18.⁶⁰ Clearly, further improvements are desirable.



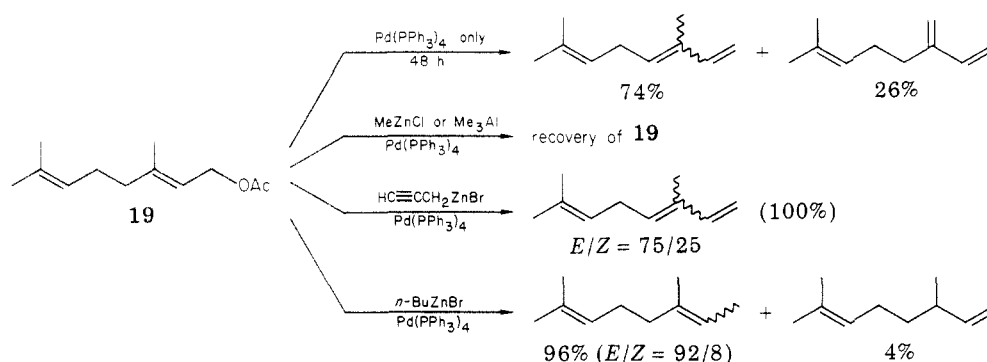
The use of other classes of organometallics does not readily induce the desired cross coupling. Specifically, the reaction of geranyl acetate (19) with MeZnCl or Me₃Al in the presence of Pd(PPh₃)₄ does not produce at 25 °C any product containing the geranyl moiety, resulting in essentially complete recovery of 19.⁶⁴ Since the reaction of 19 with Pd(PPh₃)₄ in the absence of any organometallic reagent does induce a slow 1,4 elimination,⁶⁵ MeZnCl or Me₃Al must be acting as an inhibitor.²⁸ Interestingly, the same 1,4 elimination can proceed far more readily and regioselectively in the presence of propargylzinc bromide.⁶⁴ Thus, 19 gives a 75:25 mixture of *trans*- and *cis*-ocimene without producing any myrcene, while neryl acetate gives pure myrcene. An exclusive anti 1,4 elimination is observed. Such a high regioselectivity has not been matched by any other class of organometallic reagents or bases so far tested. The use of alkylmetals containing β hydrogens, e.g., *n*-BuZnCl, leads to the reductive C-O cleavage of 19.⁶⁴ These results are summarized in Scheme III and eq 18.



The Ni-catalyzed reaction of benzylmetals containing Mg or Zn with aryl halides^{31b,49,66} gives high yields of diarylmethanes. On the other hand, the corresponding

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 (63) Trost, B. M.; Verhoeven, T. R. *J. Org. Chem.* 1976, 41, 215.
 (64) Matsushita, H.; Negishi, E. *J. Org. Chem.*, in press.
 (65) (a) Tsuji, J.; Yamakawa, T.; Kaito, M.; Mandai, T. *Tetrahedron Lett.* 1978, 2075. (b) Trost, B. M.; Verhoeven, T. R.; Fortunak, J. M. *Ibid.* 1979, 2301.
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Scheme III



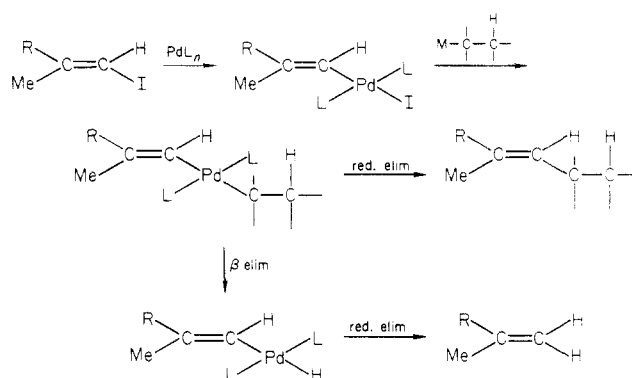
Ni-catalyzed reaction of alkenyl halides tends to induce isomerization of the alkene moiety to form styrene derivatives.⁶⁷ Here again, the use of Pd catalysts is advantageous.⁶⁷ The Ni-catalyzed asymmetric benzyl-alkenyl coupling initially resulted in low optical yields (<15% ee).⁶⁸ More recent results are, however, very promising (up to 94% ee).^{7b} Although the Pd-catalyzed benzylation of methyl derivatives⁶⁹ has been extensively studied primarily from the mechanistic viewpoint, the use of other types of organic derivatives, such as those containing alkynyl, allyl, benzyl, and propargyl groups, in the Pd-catalyzed benzylation remains essentially unexplored. Preliminary results obtained by us⁶⁴ and others⁷⁰ indicate that the Pd-catalyzed cross coupling involving either propargyl- or alkenylmetals, especially those containing Zn, readily produce allenes.

Pd-Catalyzed Alkylation. Efficient and Selective Syntheses of 1,5-Dienes and 1,5-Enynes

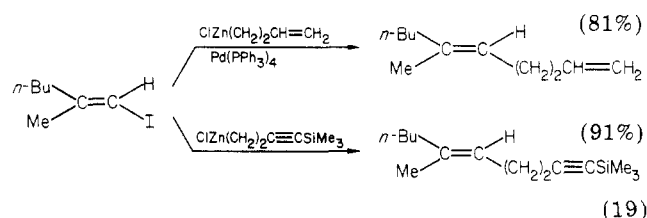
One of the major disadvantages of the Pd- or Ni-catalyzed cross coupling relative to the Cu-promoted cross coupling¹ is that alkyl halides containing sp^3 carbon-bound β hydrogens cannot be readily utilized, presumably because their oxidative addition with Pd(0) or Ni(0) complexes is in competition with β elimination of the resultant alkylmetal derivatives. Indeed, the same β elimination is presumably the product-forming step in the Pd-promoted Heck reaction.²⁶ In connection with our study directed toward the applications of the Zr-catalyzed carboalumination¹⁴ to the selective synthesis of 1,5-dienes of terpenoid origin, we hoped to develop selective procedures for alkenyl-homoallyl and alkenyl-homopropargyl coupling reactions involving Pd catalysts. We felt that, if transmetalation of alkylmetals containing β hydrogens as well as subsequent reductive elimination can be made much faster than β elimination of alkylpalladium intermediates, the Pd-catalyzed alkylation can be a satisfactory method (Scheme IV).

We were pleased to find that not only simple primary alkylzinc derivatives, e.g., *n*-BuZnCl, but also homoallylzinc and homopropargylzinc derivatives reacted with (*E*)-1-iodo-2-methyl-1-hexene in the presence of

Scheme IV



Pd(PPh₃)₄ to give the desired cross-coupled products in excellent yields⁷¹ (eq 19). The extent of β elimination



as judged by the amount of the deiodinated alkene was $\leq 2\%$. On the other hand, the corresponding Grignard reagents underwent extensive β elimination (30–50%), even though the Pd-catalyzed reaction of ethylmagnesium bromide with 1-octenyl iodide gives the cross-coupled product in 85% yield.³⁹ The use of *sec*-BuZnCl also gives high yields of cross-coupled products, but mixtures of *sec*-Bu- and *n*-Bu-substituted products were obtained. The yields of cross-coupled products observed with *t*-BuZnCl and Pd(PPh₃)₄ were <10%. However, recent results obtained by using PdCl₂(η^5 -Ph₂PC₅H₄)₂Fe in place of Pd(PPh₃)₄ are more promising, and the Pd-catalyzed alkyl-aryl or alkyl-alkenyl coupling involving secondary or even tertiary alkylmagnesium halides proceeds selectively.⁷²

The Pd-catalyzed homoallylation and homopropargylation⁷¹ used in conjunction with the Zr-catalyzed carboalumination¹⁴ provides an expeditious and

(67) Negishi, E.; Matsushita, H.; Okukado, N. *Tetrahedron Lett.* 1981, 22, 2715.

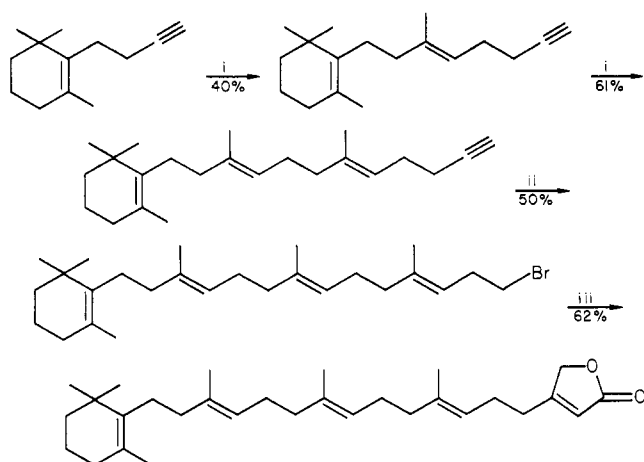
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(71) (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* 1980, 102, 3298. (b) Kobayashi, M.; Negishi, E. *J. Org. Chem.* 1980, 45, 5223.

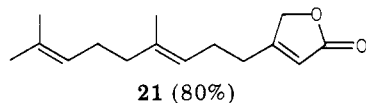
(72) (a) Hayashi, T.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* 1979, 1871; *J. Organomet. Chem.* 1980, 186, C1. (b) Hayashi, T.; Konishi, M.; Yokota, K.; Kumada, M. *Chem. Lett.* 1980, 767.

Scheme V^a

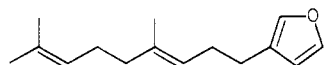
23

^a i: (1) $\text{Me}_3\text{Al}-\text{Cl}_2\text{ZrCp}_2$, (2) I_2 , (3) $\text{ClZn}(\text{CH}_2)_2\text{C}\equiv\text{CSiMe}_3$, (4) $\text{KF}\cdot 2\text{H}_2\text{O}$. ii: (1) $\text{Me}_3\text{Al}-\text{Cl}_2\text{ZrCp}_2$, (2) $n\text{-BuLi}$, (3) ethylene oxide, (4) TsCl , pyridine, (5) LiBr , acetone. iii: (1) Mg , THF, (2) ZnBr_2 , (3) 4-bromo-2(5H)-furanone, $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$, $i\text{-Bu}_2\text{AlH}$.

selective route to 1,5-dienes of terpenoid origin, as demonstrated by the syntheses of 21,⁷¹ which was



21 (80%)



22

readily convertible to dendrolasin (22), and of moku-palide⁷¹ (23) (Scheme V).

Other Cross-Coupling Reactions and Remaining Explorations

A large number of α - or β -heterosubstituted organometallics and organic electrophiles have been developed for organic synthesis.^{4a} Their synthetic utility, however, is restricted by the fact that organometallics containing Li and Mg do not readily form carbon-carbon bonds with alkenyl, aryl, and alkynyl electrophiles. The available data indicate that Pd and Ni complexes are effective in solving the above-mentioned problem, even though the current scope of such studies is still limited.

As mentioned earlier, the Pd-catalyzed allylation of "stabilized" enolates is now a well-established methodology.²⁵ More challenging are alkenylation, arylation, and alkynylation of enolates. The Ni-catalyzed cross coupling of lithium enolates with aryl halides has been studied^{73,74} and applied to the synthesis of a Cephalotaxus alkaloid. However, the reaction is reported to be inferior to the photoinduced arylation of enolates.⁷⁵ The Ni- or Pd-catalyzed arylation⁷⁶ and alkenylation⁷⁷ of the Reformatsky reagents have also been reported,

(73) (a) Semmelhack, M. F.; Stauffer, R. D.; Rogerson, T. D. *Tetrahedron Lett.* 1973, 4519. (b) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* 1975, 97, 2507.

(74) Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* 1977, 99, 4833.

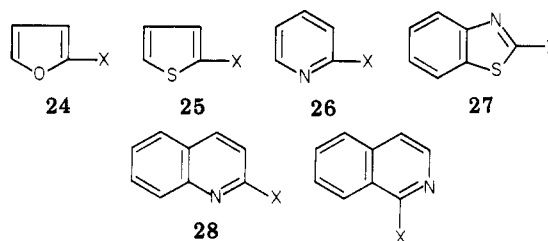
(75) Rossi, R. A.; Bunnett, J. F. *J. Am. Chem. Soc.* 1972, 94, 683; *J. Org. Chem.* 1973, 38, 1407.

(76) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* 1977, 132, C17; 1979, 177, 273.

(77) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* 1978, 209, 109.

but further developments of these reactions are desirable. An alternative approach to α arylation and α alkenylation of carbonyl compounds involves the use of β -heterosubstituted alkenyl or allyl electrophiles. The Ni-catalyzed reaction of β -alkoxy- or β -(silyloxy)-alkenyl bromides with arylmagnesium halides, after hydrolysis, produces α -arylated carbonyl compounds.⁷⁸

Turning our attention to α -heterosubstituted organometallics and organic electrophiles, the Pd- or Ni-catalyzed synthesis of aryl cyanides using metal cyanides appears to be well-developed and generally satisfactory.⁷⁹ A few studies deal with the Pd-catalyzed reaction of acyl halides with organometallics containing various metals, such as Zn,⁸⁰ Hg,⁸¹ and Sn.⁸² Various α -heteroaromatic reagents containing O, S, and N, such as 24-29 readily participate in the Pd- or Ni-catalyzed



X = metal, halogen, or S group.

cross coupling.^{30,43b,49,66,78,83,84} Some of these derivatives, e.g., 27, are known to act as masked carbonyl and carboxyl synthons. Thus, direct introduction of unsaturated organic groups under the influence of Pd or Ni catalysts can be of considerable synthetic interest. While various Grignard and/or organozinc reagents containing α -silyl^{78,85} or α -oxy⁸⁶ groups readily participate in the Pd- or Ni-catalyzed cross coupling, attempts at the use of various nonaromatic organometallics containing α -S groups, e.g., dithiane derivatives, have not so far been successful.

Mechanism

Since this Account primarily deals with synthetic aspects of the Pd- or Ni-catalyzed cross coupling, only a brief discussion of its mechanistic aspects is presented here. First, in cases where relatively electropositive metals, such as Mg, Zn, and Al, are used, the oxidative addition-transmetalation-reductive elimination mechanisms, i.e., Scheme I and its variations, appear to be generally plausible. With more electronegative metals, such as B and Sn, the metal version of the Heck-type addition-elimination mechanisms may operate in cases where α,β - or β,γ -unsaturated organometallics are used. The crucial carbon-carbon bond formation in the former occurs in the presumed reductive elimination step, whereas the latter involves carbometallation of the

(78) Tamao, K.; Zembayashi, M.; Kumada, M. *Chem. Lett.* 1976, 1237, 1239.

(79) (a) Cassar, L. *J. Organomet. Chem.* 1973, 54, C57. (b) Sekiya, A.; Ishikawa, N. *Chem. Lett.* 1975, 277.

(80) Sato, F.; Naruse, K.; Enokiya, M.; Fujisawa, T. *Chem. Lett.* 1981, 1135.

(81) Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Chem. Lett.* 1975, 951.

(82) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* 1978, 100, 3636.

(83) Isobe, K.; Nakamura, Y.; Kawaguchi, S. *Chem. Lett.* 1977, 1383.

(84) Negishi, E.; Luo, F. T.; Frisbee, R.; Matsushita, H. *Heterocycles* 1982, 18, 117.

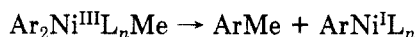
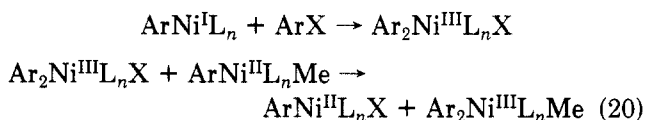
(85) Negishi, E.; Luo, F. T.; Rand, C. L. *Tetrahedron Lett.* 1982, 23, 27.

(86) Unpublished results of F. T. Luo and E. Negishi.

carbon-carbon double or triple bond, which is neither oxidative nor reductive.

Second, in both mechanisms discussed above, the oxidative addition of organic electrophiles to Pd or Ni complexes is a presumed key step. Indeed, in many instances, oxidative addition products have been isolated and have been shown to react with organometallic reagents to produce the expected cross-coupling products, indicating that they can be intermediates in the Pd- or Ni-catalyzed cross coupling.

Third, recent mechanistic studies indicate that various ramifications and/or modifications of the mechanisms presented above are possible. For example, although *o*-tolylmethylbis(triethylphosphine)nickel undergoes a thermal, intramolecular, first-order reaction to produce *o*-xylene in >90% yield in accordance with Scheme I, its reaction in the presence of an added aryl halide is a faster radical-chain process involving paramagnetic Ni(I) and Ni(III) species⁸⁷ (eq 20). On the



other hand, the Pd-catalyzed methyl-benzyl coupling^{69,88} most likely involves the intermediacy of a hexacoordinate Pd(IV) species formed by oxidative addition of an organic halide (RX) to a diorganopalladium (II) species. While these mechanisms appear plausible for the reactions studied, their generality remains to be established. It does not appear that the mechanism represented by Scheme I has not been ruled out for a number of synthetically useful Pd-catalyzed

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(88) Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* 1980, 102, 4933.

reactions, in which the thermal reductive elimination step appears to be very facile. Therefore, until the overall mechanistic picture of the Pd- or Ni-catalyzed cross coupling emerges, we may still use Scheme I as a working hypothesis, with the understanding that some reactions require modifications of this scheme.

Conclusions

A decade ago, copper was the only metal that would permit synthetic chemists to cope with unsaturated organic electrophiles in the cross-coupling reaction, and the use of nickel in this reaction has just been introduced. The unique capability of palladium began capturing the attention of synthetic chemists only as recent as the mid-1970s. Despite its short history, the Pd- or Ni-catalyzed cross coupling has already begun rivaling the Cu-promoted cross coupling in scope and synthetic utility. Perhaps more importantly, the two methods are often complementary, as discussed above. Despite the high cost of Pd, the Pd-catalyzed cross coupling, along with the Ni-catalyzed cross coupling, should find widespread use in synthesis because of its versatility and high selectivity. Finally, a number of papers related to the topics, most notably a series of pioneering works on the Ni-catalyzed cross coupling by Kumada, Tamao, Hayashi, and their co-workers, are not cited, since (a) this Account emphasizes the Pd-catalyzed cross coupling and (b) there is an excellent recent review^{7b} mainly describing their own contributions.

I am deeply indebted to my co-workers, whose names appear in our papers cited in this Account, especially Drs. S. Baba, A. O. King, D. E. Van Horn, N. Okukado, L. F. Valente, M. Kobayashi, and H. Matsushita. My current co-workers active in this area are C. L. Rand, S. Chatterjee, F. T. Luo, L. D. Boardman, A. T. Stoll, and M. Balestra. Our research has been supported mainly by the National Science Foundation, the National Institutes of Health, and the Petroleum Research Fund, administered by the American Chemical Society.

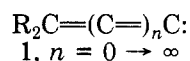
Recent Developments in Unsaturated Carbenes and Related Chemistry¹

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Received April 9, 1982

Carbenes are among the more useful and interesting intermediates in organic chemistry. Unsaturated carbenes, **1**, are members of an infinite homologous



series of reactive intermediates where the electron-deficient

carbenic carbon is an integral part of a π unsaturation. There has been much confusion in the literature on the proper nomenclature of these novel species. A consistent, logical system, in accord with current IUPAC rules, is presented, along with examples, in Table I.² This system is based upon the recommendation of Chemical Abstracts Service,³ with alkylidene-carbene **2** as a root for the first member of the ho-

(1) Presented at the 183rd National Meeting of the American Chemical Society, Las Vegas, NV, March 1982, as part of the James Flack Norris Award Symposium in Physical Organic Chemistry honoring A. Streitwieser, Jr.

(2) Fisk, T. E. Ph.D. Dissertation, The University of Utah, 1980.

(3) See footnote 2 in: Newman, M. S.; Patrick, T. B. *J. Am. Chem. Soc.* 1970, 92, 4312.

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