REYES & REYES
A B O G A D O S

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-019204- -00006-0000
Fecha: 2008-02-25 15:49:01 Dep: 2020 NUECREACIONL
Tra: 11 PATENTES II Eve: 379 FASENACIONALII
Act: 525 OTROINFORMACION Folios: 45

SEÑOR
SUPERINTENDENTE DE INDUSTRIA Y COMI
E. S. D.

REF: **EXPEDIENTE 06-019-204**

TÍTULO SOLICITADO: **"PROCESO DE PURIFICACIÓN."**

PUBLICACIÓN: **Gaceta 579 de 31 de Agosto de 2007, número de publicación 308.**

SOLICITANTE: **NOVARTIS AG.**

PRIORIDAD: **GB 0320312.2 de 29/08/2003.**

APODERADO: **JIMENA ESCOBAR URIBE**

TRÁMITE: **SUSTENTACION DE OPOSICIÓN**

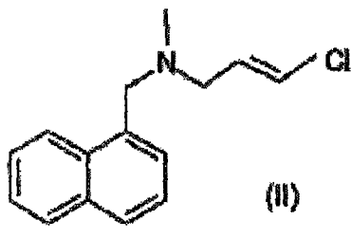
JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 28 de Noviembre de 2007, en los siguientes términos:

I. RATIFICACIÓN

Comedidamente me permito sustentar los argumentos planteados en la oposición referida, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia, incumple los requisitos de patentabilidad establecidos por los artículos 14, 16, 18 y 19 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

- En primer termino, la destilación de vía corta o camino corto con aplicación de vacío (Short Path Vacuum Distillation (SPVD)) es un proceso extensamente aplicado y ampliamente reconocido como una técnica de separación utilizada con frecuencia en la purificación de compuestos de baja volatilidad y termosensibles, la descripción de la misma en el año de 1969 por R. Habendorff et al., tal como consta en la patente americana US 3,434,935 publicada el 25 de Marzo del mismo año y titulada "APPARATUS FOR VACUUM AND SHORT-PATH DISTILLATION" y lo consignado en Lanzani y Bondioli, 1994; Cvengros, 1995; Hernandez y Rathbone, 1998; Ooi et al., 1994, en donde las sustancias a destilar se exponen un tiempo más corto y a temperaturas más bajas. Además, existe una gran cantidad de referencias de estos destiladores que permiten un proceso continuo, lo que los hace útiles a nivel industrial[1], específicamente en la industria farmacéutica y química.

- La patente europea EP 1 236709 titulada "A PROCESS FOR THE PREPARATION OF TERBINAFINE" revela un proceso para la preparación de Terbinafina (E)-N-(6,6-dimethyl-2-hepten-4-ynyl) -N-methyl-1- naphtalene methanamine, que comprende la reacción de Tert butilacetileno con un compuesto de fórmula (II)



(II)

y que se caracteriza por que la reacción se lleva a cabo en presencia de cobre (I) sale o base en ausencia de paladio, lo que hace posible que el trabajo y los pasos de purificación sean más fáciles, previniendo que el producto final esté contaminado con paladio, además, es ventajoso en términos de rendimiento y selectividad.

---

[1] http://www.avta-us.com/index.html,
http://www.technoforce.net/design/short_path.htm
http://www.chem-group.com/processing/short-path.tpl
http://209.85.165.104/search?q=cache:4kO4hcQ1Gj8J:www.oiltek.com.my/process-equip.html+short+path+distillation&hl=en&ct=clnk&cd=8
http://209.85.165.104/search?q=cache:6p_cNVDr15sJ:www.reactorvessels.demon.co.uk/Short_Path_Distillation/short_path_distillation.html+short+path+distillation&hl=en&ct=clnk&cd=13

106

Este documento también ilustra la forma de preparación y el uso de Terbinafina Cruda como material de partida la cual es preparada según su capítulo reivindicatorio y tal como se mencionó antes, por reacción del compuesto (II) que podría llamarse (E)-N-(3-Chloro-2-propenyl)-N-methyl-N-(1-naphthyl methyl) amine con Tert-butilacetileno (que también podría llamarse 3,3-dimethyl-1-butyne), y que si se compara con la solicitud colombiana en trámite, estaríamos hablando de procesos idénticos. Entonces, es evidente que las características asignadas al proceso de síntesis de terbinafina de la solicitud colombiana en tramite, específicamente lo que se refiere con los materiales de partida, intermediarios, reactivos utilizados y los catalizadores de la reacción ya habían sido revelados en la **EP 1 236709,** además, y es importante resaltar que dicha anterioridad describe que su proceso **no** utiliza catalizadores de paladio en el proceso y por tanto **no requiere de una posterior etapa de purificación**, con lo que aventaja al proceso de la solicitud colombiana ya que en ella si se incluye una etapa de purificación, (implicaría más tiempo y más costos en comparación con lo revelado en la EP 1 236709) y, que como se demostró anteriormente, dicha forma de purificación (mediante short path distillation) ahora incluida en esta solicitud en colombiana y conocida en el estado del arte, nos permiten afirmar que lo que ahora se pretende patentar en la actual solicitud en trámite no cumple con los requisitos de patentabilidad.

- Como se observa, la solicitud colombiana en tramite da una solución menos practica que sus anterioridades a un problema técnico ya resuelto, utiliza un proceso de obtención de terbinafina descrito con anterioridad en el estado de la técnica en todas sus características y además, busca reivindicar un proceso de purificación reconocido y estandarizado en su uso, y que resulta obvia su aplicación en el caso.

II. COMPLEMENTO DE INFORMACIÓN.

Por si no fuesen suficientes los argumentos expuestos en la oposición presentada en su momento, se puede demostrar que existe aun más información de carácter

científico que incluye las mismas características del proceso de obtención que busca reivindicar la solicitud colombiana en trámite, veamos:

- La publicación científica "PALLADIUM-CATALYZED ALKYNYLATION[2]" revela absolutamente todo lo relacionado a las posibles reacciones de alquinilación entre diversos compuestos, con la participación de catalizadores de paladio y relacionados; además de revelar información de los antecedentes de este tipo de reacciones, se encuentran varios protocolos en donde se ha utilizado la alquinilación catalizada por paladio; comparaciones entre diversas de estas reacciones de alquinilación contra las planteadas por Sonogashira et al.; síntesis de alquinos terminales a partir de etino o etinilmetales; R-alquinilación de compuestos de carbonilo R-halo R-alfa-insaturados; alquinilación de 1,2-dihaloetilenos; alquinilación de electrófilos organicos; **procesos en cascada que involucran una alquinilación catalizada por paladio; alquinilación catalizada por paladio con 1-halo-1-alquinos** y recientes modificaciones a los protocolos de alquinilación de Negishi et al. Y Sonogashira et al.

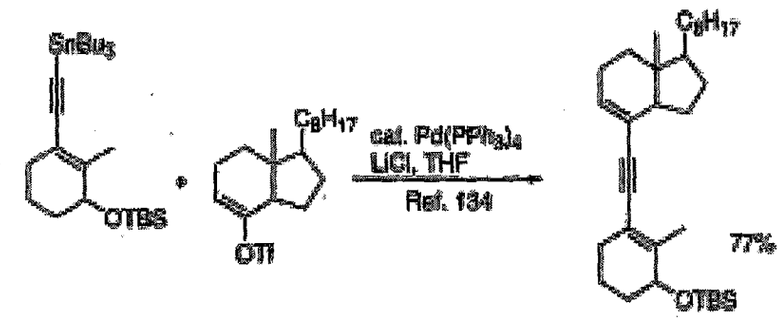
Además revela explícitamente:

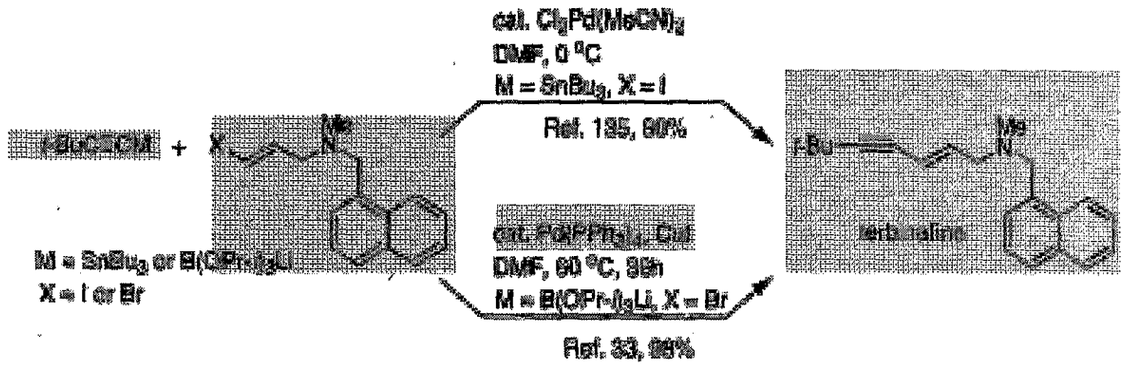
> *As in most of the other cases, the Pd-catalyzed alkynylation of alkenyl electrophiles were initially achieved by and large by using the Sonogashira coupling and the Negishi coupling with alkynylzincs, as indicated by the results shown in Table 7. The use of Mg was also introduced in the late 1970s. Although the Pd-catalyzed alkynylation of aryl halides with alkynyltins was reported as early as 1978, its earliest application to alkynylation of alkenyl electrophiles was most probably that reported in 1986 and shown in Scheme 15. Also shown in Scheme 15 is another earlier example in the **synthesis of terbinafine**.*

[2] Ei-ichi Negishi* and Luigi Anastasia. Palladium-Catalyzed Alkynylation. 2003 American Chemical Society Received July 29, 2002 Published on 04/15/2003.

108

Scheme 15





Este esquema permite tal como se mencionó antes, observar un proceso de síntesis de la sustancia Terbinafina, en donde se emplea un compuesto de tipo (E)-N-(3-halo-2-propenyl)-N-methyl-N-(1-naphthyl methyl) amine con un terbutilacetileno en presencia de catalizadores de Paladio y cobre para obtener Terbinafina como producto final, en consecuencia, se puede inferir que la síntesis planteada por la solicitud Colombiana en trámite involucra reactivos e intermediarios ampliamente descritos en el estado de la técnica y cuyas condiciones y mecanismos de reacción pueden derivarse obviamente a partir de la información suministrada en esta anterioridad.

En conclusión, el método de obtención y purificación de Terbinafina que contiene la solicitud Colombiana en trámite carece por completo de novedad y de nivel inventivo, si se tiene en cuenta que los intermediarios empleados ((E)-N-(3-halo-2-propenil)-N-metil-N-(1-naftilmetil)amina y 3,3-dimetil-1-butino) se encuentran descritos con anterioridad en el estado de la técnica, así como los catalizadores (de paladio o similares) empleados para la reacción que se describe; y ya que finalmente utiliza una técnica de purificación (destilación de vía corta) ampliamente utilizada en la industria farmacéutica y descrita con anterioridad para procesos químicos del mismo tipo, con el agravante que se conocen métodos que no

109

requieren de dicha etapa de purificación, con lo cual, además de todo, dicha solicitud da una solución a un problema técnico de una manera menos eficiente que otros procesos incluidos en el mismo estado de la técnica.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

III. ANEXOS

- La publicación científica "PALLADIUM-CATALYZED ALKYNYLATION".

Señor Superintendente,

JOSE LUIS REYES VILLAMIZAR
C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.

Palladium-Catalyzed Alkynylation

Ei-ichi Negishi* and Luigi Anastasia

Herbert C. Brown Laboratories of Chemistry, Purdue University, West Lafayette, Indiana 47907-2084

Received July 29, 2002

Contents

I. Introduction: Historical Perspective and Overview of the Scope with Respect to Metal Countercations

Over the past few decades, the Pd-catalyzed alkynylation has emerged as one of the most general and reliable methods for the synthesis of alkynes.[1,2] Currently, the most widely used by far is a hybrid of the Cu-promoted Castro–Stephens reaction[3] and the alkyne version of the Heck reaction,[4] which is known as the Sonogashira reaction[5–10] originally reported in 1975[5] (Scheme 1). The latter reaction has been cited well over 1000 times.[11] This reaction is considered generally superior to either the Castro–Stephens reaction[3] or the Heck protocol[4] without the use of a Cu salt, and it is normally used without checking the comparative merits among them, even though the Heck protocol, which is inherently simpler than the Sonogashira reaction, has been shown to be highly satisfactory in a number of cases.[12] Moreover, despite its wide applicability, convenience, and overall excellence, the Sonogashira reaction has also revealed some significant limitations.

Scheme 1

Castro-Stephens reaction

$$R^1C{\equiv}CCu + XR^2 \longrightarrow R^1C{\equiv}CR^2$$

Heck alkynylation reaction

$$R^1C{\equiv}CH + XR^2 \xrightarrow{\text{cat. } PdL_n,\ \text{base}} R^1C{\equiv}CR^2$$

Sonogashira alkynylation reaction

$$R^1C{\equiv}CH + XR^2 \xrightarrow[\text{base}]{\text{cat. } PdL_n,\ \text{cat. CuI}} R^1C{\equiv}CR^2$$

During the 1977–1978 period, Negishi and coworkers reported the Pd-catalyzed alkynylation reactions of alkynylzincs[13–17] (Scheme 2) and of 1-halo-1-alkynes.[18] Although the Pd-catalyzed alkynylation with alkynylsodiums has been known since 1975,[19] it is a sluggish reaction of limited scope, requiring refluxing MeOH, and relatively little use of this reaction has been reported. Similarly, alkynylmetals containing other alkali metals, e.g., Li, are generally unsatisfactory. It has been demonstrated that alkynyllithiums are at least as reactive as the corresponding alkynylzincs, if the stoichiometric amount of a Pd complex, such as $Cl_2Pd(PPh_3)_2$, is used, but that they hardly produce the desired alkynylation products in the presence of a catalytic amount of the same Pd complex. At least in one case, the formation

10.1021/cr020377i CCC: $44.00
Published on Web 04/15/2003

Ei-ichi Negishi grew up in Japan and received his baccalaureate degree in 1958 from the University of Tokyo. He first worked as a research chemist at a Japanese chemical company, Teijin, Ltd. He came to the USA as a Fulbright scholar in 1960 and earned a Ph.D. in organic chemistry in 1963 from the University of Pennsylvania. Negishi resumed his post at Teijin but returned to the United States in 1966 for postdoctoral work in organoboranes chemistry in Professor Brown's laboratories at Purdue University. After holding a series of academic positions at Purdue and Syracuse, Negishi became a chemistry professor at Purdue in 1979. In 1999 he became the inaugural Herbert C. Brown Distinguished Professor. Negishi's research has earned him numerous awards and honors, including the Chemical Society of Japan Award (1977), the American Chemical Society Organometallic Chemistry Award (1998), Alexander von Humboldt Award, Germany (1998–2001), and Sir Edward Frankland Prize Lectureship, the Royal Society of Chemistry (2000). He has given lectures throughout the world. He has published about 350 scientific papers, several patents, and a few dozen essays.

Luigi Anastasia was born in Mede (Pavia), Italy. He received a Laurea degree with honors in chemistry from the Università degli Studi di Pavia, Italy, in 1998, under the supervision of Prof. Giovanni Vidari. He was also presented the Best Graduating Student in Chemistry of the Year Award in Italy by Federchimica. He then received a Ph.D. degree in chemistry from Purdue University in 2002, under the direction of Prof. Ei-ichi Negishi. His graduate studies focused on the development of new Pd-catalyzed cross-coupling reactions and their applications to organic synthesis. In 2002 he received the H. C. Brown Graduate Research Award for his research at Purdue. He currently holds a position at Università degli Studi di Milano as Research Associate, and his research interests are now focused on enzymology and molecular biology of mammalian sialidases.

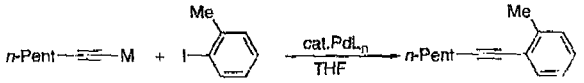
of a palladate, which is best represented by $Li_2Pd(C{\equiv}CR)_4$, was observed (Scheme 3).[20] Evidently, the excessively nucleophilic alkynyllithiums serve as catalyst poisons by displacing phosphine ligands. Similar difficulties may be anticipated with Na, K, and other alkali metals.

The Pd-catalyzed alkynylation reactions with alkynylmetals containing Mg,[15,21] B,[15] Al,[15,22,23] and Sn[15]

Scheme 2

$$R^1C{\equiv}CM + XR^2 \xrightarrow{\text{cat. } PdL_n} R^1C{\equiv}CR^2$$

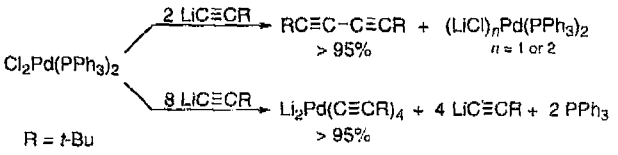
M = Zn, Mg, B, Al, Sn, etc.



Entry	M of n-PentC≡CM	Reaction Cond.[a] Temp (°C)	Time (h)	Product Yield (%)	Residual Ar-I (%)
1	Li	22	1	trace	88
2	Li	22	24	30	80
3	Na	reflux	24	58	41
4	MgBr	22	1	29	65
5	MgBr	22	24	49	33
6	ZnCl	22	1	91	8
7	ZnCl	22	3	88	2
8	HgCl	22	1	trace	92
9	HgCl	reflux	6	trace	88
10	BBu_3Li	22	3	10	76
11	BBu_3Li	reflux	1	92	5
12	$AlBu_3Li$	22	3	4	80
13	$AlBu_3Li$	reflux	1	38	10
14	$AlBu_2$	22	3	49	46
15	$SiMe_3$	reflux	1	trace	94
16	$SnBu_3$	22	1	75	14
17	$SnBu_3$	22	6	83	6
18	$ZrCp_2Cl$	reflux	3	0	80

[a] In all cases except entry 3, 5 mol % of $Cl_2Pd(PPh_3)_2$ treated with 10 mol % of i-Bu_2AlH was used as the catalyst. In entry 3, 5 mol % of $Pd(PPh_3)_4$ was used as the catalyst.

Scheme 3



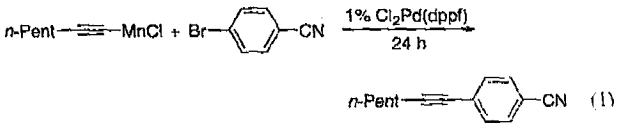
were also reported by Negishi in 1978, even though the B[15,24–27] and Sn[15,28,29] versions have sometimes been labeled as the Suzuki and Stille alkynylation reactions, respectively. More systematic investigations of Pd-catalyzed alkynylation with alkynylstannanes were performed in the early 1980s by Bumagin, Beletskaya, and their co-workers[28] and later by Stille.[29] Boron and aluminum were hardly used for alkynylation for almost two decades after the initial discovery.[15] In the meantime, the Pd-catalyzed reaction of haloalkynes with alkenylalanes and alkenylboranes were also reported by Negishi[18] and Suzuki–Miyaura,[30] respectively. More recently, the Pd-catalyzed alkynylation with alkynylboron derivatives has been further investigated.[24–27,31,32] While the reported results are generally satisfactory, essentially all of the products that have thus far been prepared by the alkynylboron reaction are also readily preparable by either the Sonogashira reaction or the alkynylzinc reaction. Further investigation of the Pd-catalyzed alkynylations with alkynylmetals containing B and Al would be necessary to delineate their scopes, especially their special merits relative to the others.

As indicated earlier, magnesium is often inferior to Zn for a variety of reasons, including its significantly lower chemoselectivity, lower catalytic reactivity, and lower "pair" selectivity in the direct ethynylation[32] (vide infra). In a number of less demanding cases, however, it is as satisfactory as any others, including Zn. Inasmuch as most of the other alkynylmetals are prepared via alkynylmetals containing Mg, Li, or Na, the reaction of alkynylmagnesium derivatives in particular should be considered first before converting them into other derivatives. It should also be noted that some alkynylmagnesium derivatives including HC≡CMgBr are commercially available.

Among other main group metals tested in the initial investigation,[15] Hg and Si were totally ineffective probably for very different reasons (Scheme 2). Although there are some Pd-catalyzed cross-coupling reactions of organomercurials known in the literature,[33] their scope is very limited. In view of the relative ease of Hg(II)-to-Hg(0) reduction,[34] organomercurials may interfere with Pd catalysis involving shuttle between Pd(0) and Pd(II) complexes. The inherent toxicity associated with Hg is another serious concern. The inability of alkynylsilicon derivatives to undergo facile alkynylation[15,16] must be due to their intrinsically low reactivity. In fact, Si has been used as part of alkyne protecting groups, such as Me_3Si, and of precursors to alkynylmetals containing other metal countercations. In some cases where fluoride and oxy bases are used as activators, however, it is likely that alkynylsilicon compounds containing a hypervalent Si are generated as actual reactants.[35-45]

Over the past few years, the Pd-catalyzed cross-coupling reaction of tris(alkynyl)indiums to give disubstituted alkynes in excellent yields has been reported.[46,47] All three alkynyl groups participate in the reaction. Thus, despite its limited current scope, the reaction appears to be rather promising. Although several other main group metals, such as Cd,[48] Ge[48,50] Pb,[51-53] and Bi,[54] have been employed in the Pd-catalyzed cross-coupling, little or nothing appears to be known about their use in the Pd-catalyzed alkynylation.

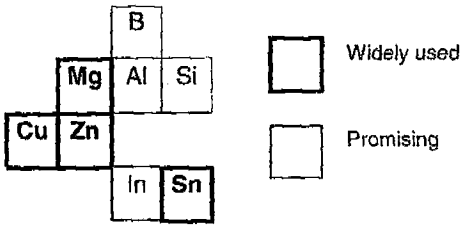
In the countercation screening reported in 1978,[15] Zr failed to serve as an effective metal countercation. As mentioned earlier, the stoichiometric amount of Cu has been used in the Castro–Stephens reaction[3] without the use of Pd catalysts, while a catalytic amount of Cu is used in the Sonogashira reaction.[5-10] Recently, the corresponding Pd-catalyzed reaction of preformed alkynylsilvers with alkenyl triflates has been reported.[55,56] In view of the relatively high cost of Ag vis-à-vis other less expensive metals mentioned above, the practical synthetic value of the Pd-catalyzed alkynylsilver reaction may be questionable. Among relatively inexpensive transition metals, Mn and some other first transition series metals, such as Ti, Cr, Mo, Fe, Co, and Ni, as well as some lanthanide metals might be shown to be useful. Indeed, one reaction of an alkynylmanganese with an aryl bromide catalyzed by $Cl_2Pd(dppf)$ has recently been reported as shown in eq 1.[57] However, little or nothing appears to be known about the use of other transition metal countercations in the Pd-catalyzed alkynylation.



(1)

In summary, Zn, Mg, and Sn, in addition to Cu used in catalytic quantities, have been widely used as part of alkynylmetals, while B, Al, In, and Si have been shown to be of promise, although their use has thus far been rather limited (Scheme 4).

Scheme 4



In the following section, a brief overview of the scope of the four major protocols, i.e., the Sonogashira reaction and those involving Zn, Sn, and Mg, with respect to the electrophilic cross-coupling partners will be presented first somewhat irrespective of relative merits and demerits among these protocols. It will be followed by discussions of some noteworthy recent advances in which more critical comparisons among the four protocols mentioned above will be made. The topics to be discussed in these critical comparisons include (a) direct ethynylation for preparing terminal alkynes, (b) use of electron-deficient alkynes, (c) use of sterically demanding organic electrophiles, (d) selective monoalkynylation of dihaloalkenes and di- and polyhaloarenes, (e) α-alkynylation of α-haloenones and related derivatives, (f) strictly pair-selective synthesis of conjugated diynes, (g) β-haloalkenoic acids and related reactions, (h) use of 1-haloalkynes, and (i) in situ generation of alkynylzincs. Also discussed briefly will be some recent methodological developments with emphasis on searches for superior phosphine and other ligands as well as some mechanistic aspects of the Pd-catalyzed alkynylation.

II. Scope with Respect to Organic Electrophiles

A. Overview

Since the Pd-catalyzed alkynylation is thought to be initiated by oxidative addition of Pd to organic halides and related electrophiles, one may readily expect that its scope would be limited to those cases where the above-mentioned oxidative addition can occur to synthetically useful extents. In this context, organic electrophiles may be classified as follows according to the hybridization state of the carbon

Table 1. The Current Scopes of the Pd-Catalyzed Alkynylation and Other Methods of Alkynylation with Respect to Organic Electrophiles

Class of RX	R of RX	Current Scope: Pd-Catalzyed Alkynylation	Current Scope: Cu-Catalzyed or Uncatalzyed Alkynylation without Pd Catalysts
C_{sp^2}–X	Aryl	• Widely applicable and satisfactory	• Generally inferior or unapplicable
	Alkenyl	• Widely applicable and satisfactory	• Generally inferior or unapplicable
	Acyl	• Widely applicable and satisfactory	• Alkynylcopper reactions may be competitive
C_{sp}–X	Alkynyl	• Not widely investigated • Cross-homo scrambling is a potential problem. • cf. Indirect alternative[59,60]	• The Cadiot-Chodkiewicz reaction[58] is currently most widely used but often problematic.
C_{sp^3}–X	Allyl	• Little appears to be known	• The Cu-Catalyzed alkynylmagnesium reaction is generally satisfactory.
	Benzyl	• Benzylation of alkynylindiums is promising.[47]	• See above
	Propargyl	• Appears to be widely applicable, producing selectively allenynes.	• See above
	Alkyl	• Generally not applicable due to slow oxidative addition	• Primary and some secondary alkyl halides can be alkynylated with alkynylmetals containing Li and other electropositive metals. • Some tertiary alkyl halides react well with alkynylalanes.[66]

atom bonded to a halogen or a related leaving group (X):

Class C_{sp^2}–X: aryl, alkenyl, and acyl

Class C_{sp}–X: alkynyl

Class C_{sp^3}–X: allyl, benzyl, propargyl, and alkyl

Of these, alkyl electrophiles lacking a β,γ-unsaturated bond are the only subclass of organic electrophiles that do not generally undergo synthetically useful oxidative addition with Pd. As detailed below, the Pd-catalyzed alkynylation has been shown to be widely applicable and generally satisfactory in cases where class C_{sp^2}–X electrophiles are employed.

Although alkynyl halides, i.e., class C_{sp}–X electrophiles, readily undergo oxidative addition with Pd, the scope of their Pd-catalyzed alkynylation has been surprisingly limited due in part to the formation of mixtures of cross- and homo-coupled diynes. Another reason for the fact mentioned above might be that the alkynyl–alkynyl coupling has traditionally been achieved often satisfactorily by the Cadiot–Chodkiewicz reaction involving the use of Cu catalyst.[58] It should also be pointed out here that an alternative Pd-catalyzed route to conjugated diynes via alkynyl–alkenyl coupling with ICH=CHBr or ICH=CHCl[59,60] provides a widely applicable and selective method for the synthesis of conjugated diynes, as detailed later.

Whereas the Pd-catalyzed alkynylation of propargyl and allenyl electrophiles with alkynylmetals, especially those containing Zn or Cu, is generally satisfactory, relatively little has been reported on the Pd-catalyzed alkynylation of allyl and benzyl electrophiles, which are known to readily undergo not only oxidative addition with Pd but also cross-coupling with organometals containing aryl,[61–63] alkenyl,[61–63] and other groups, including metal enolates.[64] Fortunately, alkynylation of allyl, benzyl, and propargyl electrophiles can often be satisfactorily achieved by the Cu-catalyzed reaction of alkynylmagnesium derivatives with these electrophiles.[65–67]

In summary, the Pd-catalyzed alkynylation is largely complementary with the previously developed alkynylation methods involving Cu-catalyzed or uncatalyzed reactions of alkynylmetals containing Mg and alkali metals, such as Li, Na, and K, as well as the Cu-catalyzed Cadiot–Chodkiewicz reaction of terminal alkynes with alkynyl halides, as indicated in Table 1. Currently, its main usefulness lies in the alkynylation of aryl, alkenyl, and acyl halides as well as their related electrophiles. The Pd-catalyzed alkynyl–alkynyl coupling remains to be systematically investigated, but cross-homo scrambling appears to be a problem to be overcome. In the meantime, the alternate method involving Pd-catalyzed alkynyl–alkenyl coupling mentioned above[59,60] has been shown to be superior to the Cadiot–Chodkiewicz reaction[58] in various cases. The Pd-catalyzed alkynylation of allyl and benzyl electrophiles remains as a puzzle to be solved by future investigations, even though that of propargyl and allenyl electrophiles is generally satisfactory for the synthesis of allenynes but not 1,4-diynes.

As in the other Pd-catalyzed cross-coupling reactions, the general order of reactivity of organic

Table 2. Some Representative Procedures and Reaction Conditions for the Sonogashira Alkynylation and the Pd-Catalyzed Alkynylation with Zn, Sn, and Mg

reaction symbol[a]	catalyst(s)	added reagent	solvent and others
Sonogashira			
Cu-Ia	$Cl_2Pd(PPh_3)_2$-CuI[b]	Et_2NH and other R_2NH[c]	Et_2NH, etc.[c]
Cu-Ib	$Cl_2Pd(PPh_3)_2$-CuI[b]	Et_3N and other R_3N[c]	Et_3NH, etc.[c]
Cu-Ic	$Cl_2Pd(PPh_3)_2$-CuI[b]	*n*-$BuNH_2$ and other RNH_2[c]	*n*-$BuNH_2$, etc.[c]
Cu-Id	$Cl_2Pd(PPh_3)_2$-CuI[b]	piperidine and other cyclic amines	piperidine, etc.[c]
Cu-Ie	$Cl_2Pd(PPh_3)_2$-CuI[b]	K_2CO_3	*d*
Cu-If	$Cl_2Pd(PPh_3)_2$-CuI[b]	Cs_2CO_3	*d*
Cu-Ix	$Cl_2Pd(PPh_3)_2$-CuI[b]	others to be specified	*d*
Cu-IIa	$Pd(PPh_3)_4$-CuI[b]	Et_2N and other R_2NH[c]	Et_2NH, etc.[c]
Cu-IIb	$Pd(PPh_3)_4$-CuI[b]	Et_3N and other R_3N[c]	Et_2N, etc.[c]
Cu-VIa	$Cl_2Pd(RCN)_2$-CuI[b]	*i*-Pr_2NH and other R_2NH[c]	R_2NH, dioxane, toluene, etc.[c]
Alkynylation with Zn			
Zn-I	$Cl_2Pd(PPh_3)_2$	none	THF, DMF, etc.
Zn-Ia	$Cl_2Pd(PPh_3)_2$	DIBAH[e]	THF, DMF, etc.
Zn-Ib	$Cl_2Pd(PPh_3)_2$	*n*-BuLi	THF, DMF, etc.
Zn-II	$Pd(PPh_3)_4$	none	THF, DMF, etc.
Alkynylation with Sn			
Sn-I	$Cl_2Pd(PPh_3)_2$	none	THF, toluene, etc.
Sn-Ia	$Cl_2Pd(PPh_3)_2$	DIBAH[e]	THF, toluene, etc.
Sn-II	$Pd(PPh_3)_4$	none	THF, toluene, etc.
Sn-VIII	$RPd(PPh_3)_2I$[f]	none	THF, DMF, $(CH_2Cl)_2$ etc.
Alkynylation with Mg			
Mg-I	$Cl_2Pd(PPh_3)_2$	none	THF, etc.
Mg-Ia	$Cl_2Pd(PPh_3)_2$	DIBAH[e]	THF, etc.
Mg-II	$Pd(PPh_3)_4$	none	THF, etc.

[a] The symbol indicates the metal countercation, the Pd complex, and one critical reagent, cocatalyst, or additive. The bold Roman numeral indicates one of the following Pd complexes.

Pd complexes containing monophosphines and those without phosphines	Pd complexes containing bidentate phosphines
I = $Cl_2Pd(PPh_3)_2$	**XI** = Cl_2Pd(dppf)
II = $Pd(PPh_3)_4$	**XII** = Cl_2Pd(dppp)
III = $Pd(OAc)_2$	**XIII** = Cl_2Pd(dppb)
IV = Li_2PdCl_4	**XIV** = Cl_2Pd(DPEphos)
V = $Pd(dba)_n$ (n = 1.5 or 2)	**XX** = other chelating phosphine-containing Pd complexes
VI = $Cl_2Pd(RCN)_2$	
VII = $Cl_2Pd(TFP_2)$, where TFP = tris(2-furyl)phosphine	
VIII = $RPd(PPh_3)_2X$, RX to be specified	
IX = $Pd(t\text{-}Bu_3P)_2$	
X = Other monophosphine-containing Pd complexes to be specified	

[b] The Pd/Cu ratio is typically 1/2. [c] Bases and solvents are often the same. In some cases, cosolvents, such as benzene and pyridine, are used. [d] For the definition of a-x, see **Cu-Ia**~**Cu-Ix**. [e] The Pd/Al ratio is 1/2. Use of DIBAH may be omitted, but some reactants and/or other reagents will be consumed to generate active Pd(0) catalysts. Other added reagetns, such as *n*-BuLi, may also be used. [f] R = Ar, such as Ph, Bn, etc., to be specificed in parentheses.

electrophiles with respect to (a) leaving groups (X) and (b) substituents is as shown below:

Reactivity of leaving group (X): I ≥ OTf ≥ Br > Cl

Reactivity of substituent: EWG > H > EDG

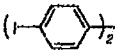
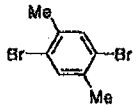
(EWG = electron-withdrawing group, EDG = electron-donating group)

These orders are in line with those observed in the oxidative addition of Pd(0) complexes to organic electrophiles. Recently, iodonium cations have been used as leaving groups of superior reactivity,[69-71] although their practical synthetic utility remains to be further delineated. Some other important features of organic electrophiles include steric effects and chelation. As important factors other than those associated with organic electrophiles, (a) substituents in alkynyl groups, (b) metal countercations discussed in the previous section, (c) cocatalysts, such as CuI, (d) ligands, (e) additives, (f) solvents, and (g) other reaction parameters, such as reaction temperature and time, must be considered.

As Pd catalysts or precatalysts to be exact, $Cl_2Pd(PPh_3)_2$ and $Pd(PPh_3)_4$ have been most frequently used. It has, however, become increasingly clear that the use of other Pd catalysts is desirable in some highly demanding cases. In the following discussions, the numerical symbols listed as the footnote a in Table 2 may be used for representing Pd catalysts. Various protocols and procedures may also be indicated by using the abbreviation symbols also shown in Table 2.

In this section, attention will be mainly focused on generally favorable cases of the Pd-catalyzed alkynylation without critical and detailed comparison among the widely used protocols primarily to catalog

Table 3. Early Investigations of the Pd-Catalyzed Alkynylation of Aryl Electrophiles with Cu, Zn, Sn, and Mg Countercations

$R^1C{\equiv}CH$ or $R^1C{\equiv}CM$	ArX	Reaction Conditions: Procedure[a]	Solvent	Temp, °C	Time, h	Product Yield, %[b]	Ref.
Sonogashira alkynylation							
$PhC{\equiv}CH$	o-$NO_2C_6H_4Br$	Cu-Ia	Et_2NH	rt	3	90	5
$HOCH_2C{\equiv}CH$	o-$NO_2C_6H_4Br$	Cu-Ia	Et_2NH	rt	3	80	5
$Me_3SiC{\equiv}CH$	o-$NO_2C_6H_4Br$	Cu-Ib	Et_3N	rt	4	70	8
$Me_3SiC{\equiv}CH$	p-$NO_2C_6H_4Br$	Cu-Ib	Et_3N	rt	4	88	8
$Me_3SiC{\equiv}CH$	p-NCC_6H_4Br	Cu-Ib	Et_3N	rt	4	82	8
$Me_3SiC{\equiv}CH$	p-$MeO_2CC_6H_4Br$	Cu-Ib	Et_3N	rt	4	89	8
$Me_3SiC{\equiv}CH$	p-$H_2NCC_6H_4I$	Cu-Ib	Et_3N	40	4	83	8
$Me_3SiC{\equiv}CH$	β-NaphI	Cu-Ib	Et_3N	rt	4	85	8
$Me_3SiC{\equiv}CH$		Cu-Ia	Et_2NH	rt	4	80	8
$Me_3SiC{\equiv}CH$		Cu-Id	piperidine	rt	4	85	8
$Me_3SiC{\equiv}CH$		Cu-Ia	Et_2NH, C_6H_6	rt	4	80	8
$Me_3SiC{\equiv}CH$		Cu-Id	piperidine	rt	4	85	8
Alkynylation with $RC{\equiv}CZnX$							
n-$PentC{\equiv}CZnCl$	o-MeC_6H_4I	Zn-Ia (DIBAH)	THF	rt	1	– (88)	14,15
n-$PentC{\equiv}CZnCl$	m-MeC_6H_4I	Zn-Ia (DIBAH)	THF	rt	1	79 (89)	15
n-$PentC{\equiv}CZnCl$	p-MeC_6H_4I	Zn-II	THF	rt	0.5	70 (92)	14
n-$PentC{\equiv}CZnCl$	p-NCC_6H_4I	Zn-II	THF	rt	4	– (93)	14
n-$PentC{\equiv}CZnCl$	p-$O_2NC_6H_4I$	Zn-Ia (DIBAH)	THF	rt	3	64 (94)	14
$PhC{\equiv}CZnCl$	PhI	Zn-II	THF	rt	0.5	74 (93)	14
$PhC{\equiv}CZnCl$	m-MeC_6H_4I	Zn-Ia (DIBAH)	THF	rt	1.5	80 (87)	14
Alkynylation with $RC{\equiv}CSnX_3$							
n-$PentC{\equiv}CSnBu_3$	o-MeC_6H_4I	Sn-Ia (DIBAH)	THF	rt	6	– (83)	15
Alkynylation with $RC{\equiv}CMgX$							
n-$PentC{\equiv}CMgBr$	o-MeC_6H_4I	Mg-Ia (DIBAH)	THF	rt	24	49	15

[a] See Table 2. An added reagent is indicated in parentheses. I = cat.$Cl_2Pd(PPh_3)_2$. II = cat.$Pd(PPh_3)_4$. Cu-I = cat.$Cl_2Pd(PPh_3)_2$ + cat.CuI. [b] Isolated yield. The numbers in parentheses are yields by GLC or NMR spectroscopy.

some representative examples and to thereby substantiate some of the generalizations presented in Table 1.

B. Aryl Electrophiles

1. Carbocyclic Aryl Electrophiles

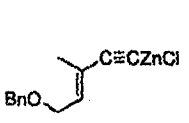
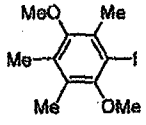
Some of the earliest prototypical examples of the Pd-catalyzed alkynylation of aryl electrophiles by the Sonogashira reaction[5,8] as well as by the reaction with alkynylmetals containing Zn[14-16] and Sn[15,16,28] reported in and before 1980 are shown in Table 3. These results indicate that the Pd-catalyzed alkynyl–aryl coupling may satisfactorily be achieved in many less demanding cases by using aryl iodides or bromides including those containing either electron-withdrawing or electron-donating substituents.

In fact, those reactions involving the use of Cu, Zn, and Sn have since been widely used to produce many satisfactory results, accounting for the great majority of the reported cases until the mid-1990s. Some of their representative examples reported since 1980 along with more recently reported results with B, In, and Si are shown in Table 4. Since most of the reported results are favorable, their comparative merits are not very clear. In addition to consideration of some of more obvious factors, such as cost, operational simplicity, and toxicity, investigation of comparative merits in chemically more demanding cases would be desirable.

An interesting application of the Pd-catalyzed alkynylation with alkynylstannanes is the synthesis of various alkynyl-substituted π-arene–metal complexes containing π-arenes of various ring sizes (Scheme 5).

A relatively few applications of the Pd-catalyzed alkynyl–aryl coupling to the natural products synthesis have been reported. Recent synthesis of dehydrotremetone[26] and lunularic acid[27] via Pd-catalyzed alkynylation of carbocyclic aryl bromides and triflates

Table 4. Representative Examples of the Pd-Catalyzed Alkynylation of Aryl Electrophiles Reported since 1981

$R^1C\equiv CH$ or $R^1C\equiv CM$	ArX	Reaction Conditions: Procedure[a]	Solvent	T, °C	Time, h	Product Yield, %[b]	Ref.
Sonogashira alkynylation							
$MeC\equiv CH$	o-MeC_6H_4Br	Cu-Ib	Et_3N	24	4-16	86	72
t-$BuC\equiv CH$	PhI	Cu-Ib (Et_3N)	MeCN	25	3	88	73
n-$BuC\equiv CH$	p-AcC_6H_4Br	Cu-Ib (Et_3N)	THF	25	16	91	74
n-$PentC\equiv CH$	p-$O_2NC_6H_4I$	Cu-VIIIb (Et_3N)	$CHCl_3$	60	1	100	75
n-$PentC\equiv CH$	p-$O_2NC_6H_4I$	Cu-IIb	Et_3N	90	24	85	76
$PhC\equiv CH$	p-MeC_6H_4I	Cu-X[1]b (Et_3N)	MeCN, H_2O	23	5	96	77
$PhC\equiv CH$	p-MeC_6H_4Br	Cu-Ib (Et_3N)	THF	25	16	87	74
$PhC\equiv CH$	2,6-$Me_2C_6H_3I$	Cu-VIa (i-Pr_2NH)	dioxane	23	0.5-15	63	78
$HOCH_2C\equiv CH$	p-$MeOC_6H_4I$	Cu-IIa (Et_2NH)	Et_2NH	25	2	92	12a
$MeCH(OH)C\equiv CH$	o-$MeOC_6H_4I$	Cu-VIa (i-Pr_2NH)	toluene	23	24	45	79
$HOMe_2C\equiv CH$	o-$MeOC_6H_4Br$	Cu-VIa (i-Pr_2NH)	dioxane	20	23	84	80
$HOMe_2C\equiv CH$	2,4,6-$(MeO)_3C_6H_2I$	Cu-Ib	DMF	80	21	67	81
$RSCH_2C\equiv CH$	o-$MeOC_6H_4I$	Cu-Ib (Et_3N)	MeCN	25	24	77	82
$MeHNCOC\equiv CH$	o-$MeOC_6H_4I$	Cu-X[2]b (Et_3N)	DMSO	23	16	95	83
$Me_3SiC\equiv CH$	o-MeC_6H_4I	Cu-IIx (TEBAC)	benzene, NaOH	40	48	46	84
$Me_3SiC\equiv CH$	p-AcC_6H_4Br	Cu-Ib (Et_3N)	THF	25	16	92	75
$Me_3SiC\equiv CH$	p-$MeOC_6H_4Br$	Cu-VIa (i-Pr_2NH)	dioxane	20	5-15	90	78
$Me_3SiC\equiv CH$	o-$C_6H_4(OTf)_2$	Cu-Ib (Et_3N, KI)	DMF	70	4	91	84
Alkynylation with $RC\equiv CZnX$							
t-$BuC\equiv CZnCl$	PhI	Zn-II	THF	22	0.1	92	85
t-$BuC\equiv CZnCl$	α-NaphBr	Zn-II	THF	reflux	6	67	86
$F_3CC\equiv CZnCl$	PhI	Zn-II	THF	50	4	96	87
$MeOCH_2C\equiv CZnCl$	PhOTf	Zn-II	DMB-benzene	90	8	67	88
$EtOC\equiv CZnCl$	PhI	Zn-I	THF	23	4	65	89
$EtOC\equiv CZnCl$	o-ClC_6H_4OTf	Zn-I	THF	23	4	65	89
		Zn-II	THF	50	7	73	90
Alkynylation with $RC\equiv SnX_3$							
n-$PrC\equiv CSnBu_3$	o-$AcNHC_6H_4Br$	Sn-II	toluene	100	2.5	77	91
$PhC\equiv CSnMe_3$	p-NCC_6H_4I	Sn-VIII[1]	DMF	20	0.17	95	92
$PhC\equiv CSnBu_3$	p-AcC_6H_4Br	Sn-X[3]	toluene	90	72	90	93
$PhC\equiv CSnBu_3$	o-$CF_3C_6H_4I$	Sn-X[3]	toluene	80	32	92	93
$PhC\equiv CSnMe_3$	p-$O_2NC_6H_4I$	Sn-VIII[1]	DMF	20	0.1	93	92
$PhC\equiv CSnBu_3$	2,4,6-$(O_2N)_3C_6H_2I$	Sn-VIII[2]	$(CH_2Cl)_2$	130	1.5	85	94
$EtO_2CC\equiv CSnBu_3$	PhI	Sn-I (Et_4NCl)	DMF	23	2	94	95
$Me_3Si(C\equiv C)_2SnBu_3$	o-$OHCC_6H_4Br$	Sn-I	toluene	110	2	91	96
$EtOC\equiv CSnMe_3$	PhI	Sn-I (Et_4NCl)	DMF	23	6	53	97
$EtOC\equiv CSnMe_3$	p-$O_2NC_6H_4I$	Sn-I (Et_4NCl)	DMF	20	0.1	80	97
$EtOC\equiv CSnMe_3$	p-$MeOC_6H_4I$	Sn-I (Et_4NCl)	DMF	23	1.5	66	97

14 116 117

Table 4 (Continued)

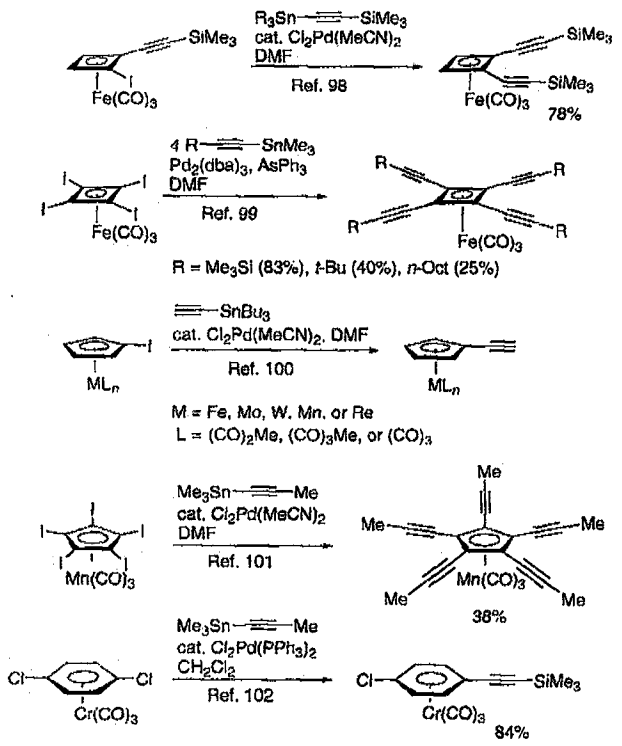
$R^1C{\equiv}CH$ or $R^1C{\equiv}CM$	ArX	Reaction Conditions: Procedure[a]	Solvent	T, °C	Time, h	Product: Yield, %[b]	Ref.
Alkynylation with RC≡CBX$_3$M							
n-PentC≡CBBu$_3$Li	*o*-MeC$_6$H$_4$I	B-I (DIBAH)	THF	reflux	1	– (92)	15
n-HexC≡CB(OPr-*i*)$_3$Li	*o*-MeC$_6$H$_4$I	B-II	THF	60	15	75	31
n-BuC≡CB(OPr-*i*)$_3$Li	*p*-MeC$_6$H$_4$I	B-II (CuI)	DMF	80	5	97	33
n-BuC≡CB(OPr-*i*)$_3$Li	*p*-O$_2$NC$_6$H$_4$I	B-II (CuI)	DMF	80	5	97	33
n-BuC≡CB(OPr-*i*)$_3$Li	2,4,6-(MeO)$_3$C$_6$H$_2$I	B-II (CuI)	DMF	80	48	27	33
PhC≡CB(OPr-*i*)$_3$Li	*o*-MeC$_6$H$_4$I	B-II (CuI)	DMF	60	15	96	33
PhC≡CB(OPr-*i*)$_3$Li	*p*-MeC$_6$H$_4$I	B-II (CuI)	DMF	23	24	90	33
PhC≡CB(OPr-*i*)$_3$Li	*p*-O$_2$NC$_6$H$_4$I	B-II (CuI)	DMF	60	15	98	33
PhC≡CBR$_2$(OMe)K[c]	*p*-OHCC$_6$H$_4$Br	B-XI	THF	reflux	1	77	26
PhC≡CBR$_2$(OMe)K[c]	*p*-NCC$_6$H$_4$Br	B-XI	THF	reflux	1	93	26
PhC≡CBR$_2$(OMe)K[c]	*p*-NCC$_6$H$_4$Br	B-XI	THF	reflux	1	89	26
Alkynylation with RC≡CAlX$_2$							
n-PentC≡CAlBu$_2$	*o*-MeC$_6$H$_4$I	Al-I (DIBAH)	THF	rt	3	– (49)	15
Alkynylation with (RC≡C)$_3$In							
(PhC≡C)$_3$In	*p*-MeC$_6$H$_4$I	In-I	THF	reflux	0.5	90	46,47
(PhC≡C)$_3$In	*p*-AcC$_6$H$_4$OTf	In-I	THF	reflux	1	94	46,47
(Me$_3$SiC≡C)$_3$In	*p*-MeC$_6$H$_4$OTf	In-I	THF	reflux	1	93	46,47
(Me$_3$SiC≡C)$_3$In	*p*-AcC$_6$H$_4$OTf	In-I	THF	reflux	1	91	46,47
Alkynylation with RC≡CSiX$_3$							
PhC≡CSiMe$_3$	*p*-AcC$_6$H$_4$I	Si-II (CuCl)	DMF	80	12	– (84)	38
PhC≡CSiMe$_3$	*p*-ArC$_6$H$_4$Br	Si-II (CuCl)	DMF	80	12	– (27)	38
PhC≡CSiMe$_3$	*p*-AcC$_6$H$_4$OTf	Si-II (CuCl)	DMF	80	24	89 (97)	37, 38
PhC≡CSiMe$_3$	*α*-NaphOTf	Si-II (CuCl)	DMF	80	14	– (84)	38
PhC≡CSiMe$_3$	*β*-NaphOTf	Si-II (CuCl)	DMF	80	12	– (65)	38
p-NCC$_6$H$_4$C≡CSiMe$_3$	*p*-AcC$_6$H$_4$OTf	Si-II (CuCl)	DMF	80	3-24	52 (98)	37
p-MeOC$_6$H$_4$C≡CSiMe$_3$	*p*-AcC$_6$H$_4$OTf	Si-II (CuCl)	DMF	80	3-24	65 (>99)	37
P-MeOC≡CsiMe$_3$	*p*-AcC$_6$H$_4$Cl	Si-XIII(CuCl)	DMF	120	12	56	38
	*p*-NCC$_6$H$_4$OTf	Si-II(CuCl)	DMF	80	3-24	52 (71)	37
PhC≡CSiMe$_2$OH	PhI	Si-II (CsF)	THF	60	12	<5	42
PhC≡CSiMe$_2$OH	PhI	Si-II (Ag$_2$O)	THF	60	2	78	42
PhC≡CSiMe$_2$OH	PhI	Si-II (TBAF)	THF	60	2	90	42
PhC≡CSiMe$_2$OH	*m*-MeC$_6$H$_4$I	Si-II (TBAF)	THF	60	2.5	95	42
PhC≡CSiMe$_2$OH	*p*-AcC$_6$H$_4$I	Si-II (TBAF)	THF	60	2	78	42
PhC≡CSiMe$_2$OH	*m*-BrC$_6$H$_4$I	Si-II (TBAF)	THF	60	2	73	42
PhC≡CSiMe$_2$OH	*β*-NaphI	Si-II (TBAF)	THF	60	3	71	42

[a] See Table 2. All Cu procedures use cat.CuI. An additional reagent is indicated in parentheses. **I** = cat.Cl$_2$Pd(PPh$_3$)$_2$. **II** = cat.Pd(PPh$_3$)$_4$. **VI** = cat.Cl$_2$Pd(RCN)$_2$. **VII**^{1} = cat.*p*-NO$_2$C$_6$H$_4$PdI(PPh$_3$)$_2$. **VIII**^{2} = cat.C$_6$H$_5$PdI(PPh$_3$)$_2$. **X**^{1} = cat.Pd(PPh$_3$)$_2$(*m*-C$_6$H$_4$SO$_3$Na).H$_2$O. **X**^{2} = cat.Pd(PPh$_3$)$_2$(OAc)$_2$. **X**^{3} = cat.PdCl(*π*-C$_3$H$_5$)$_2$. **XI** = cat.Cl$_2$Pd(dppf). [b] Isolated yields. The numbers in parentheses are GLC or NMR yields. [c] BR$_2$ = 9-BBN.

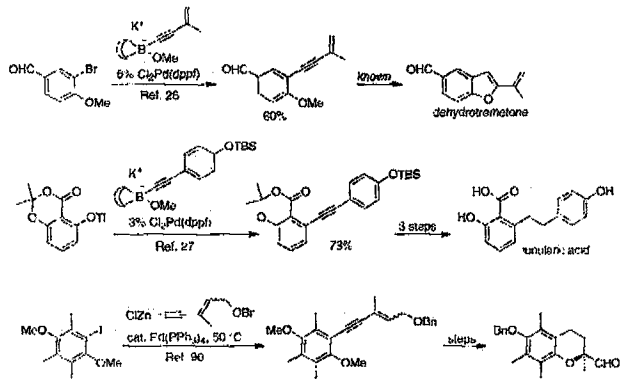
with alkynylborates shown in Scheme 6 are representative. Also noteworthy are the syntheses of enantiopure chromane moiety of vitamin E.[90]

On the other hand, a fair number of its applications to the synthesis of polymers and other compounds of material chemical interest have been reported[40,103–106]

Scheme 5



Scheme 6



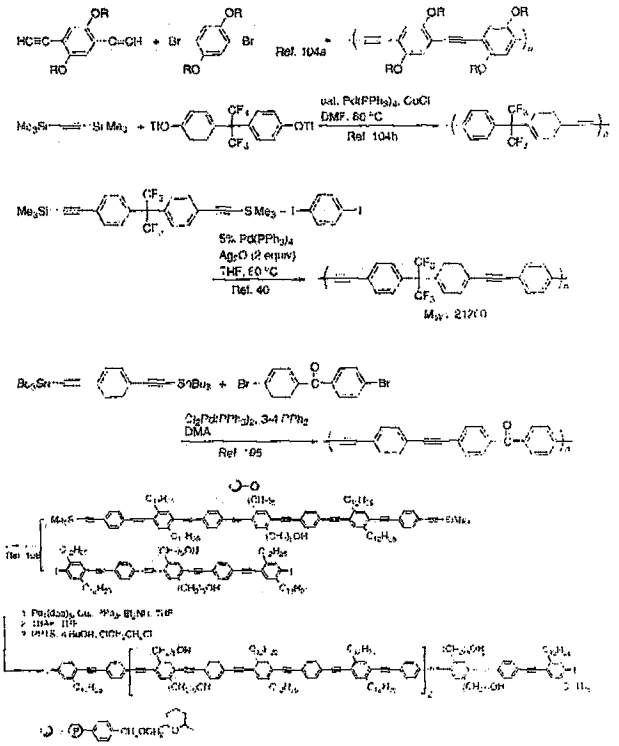
(Scheme 7). For the synthesis of polymers, the Sonogashira reaction and those employing thermally and hydrolytically stable alkynylmetals, such as alkylboranes, alkynylsilanes, and alkynylstannanes, may offer an advantage in terms of ability to purify alkynyl reagents.

2. Heteroaryl Electrophiles

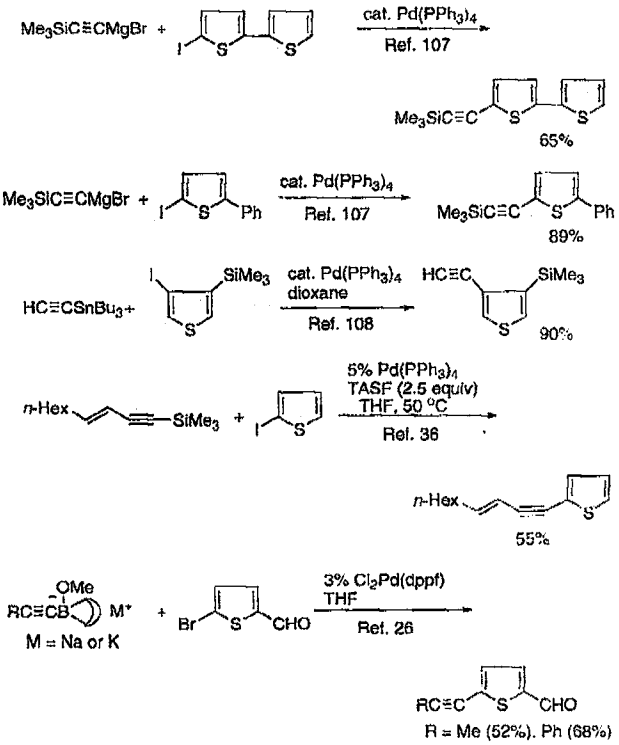
Despite the presence of proximal heteroatoms, including N, O, and S, that might be expected to significantly affect the course of the Pd-catalyzed alkynylation of heteroaryl electrophiles, a wide variety of heteroaryl electrophiles have been successfully alkynylated, as indicated by the results shown in Tables 5 and 6 as well as Schemes 8−13.

a. Five-Membered Heteroaromatic Electrophiles Containing One Heteroatom. Both α- and β-halo and related derivatives of pyrrole, furan, and thiophene have been satisfactorily alkynylated by using either the Sonogashira coupling or the Negishi

Scheme 7



Scheme 8

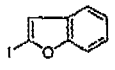
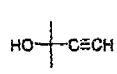
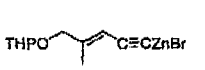
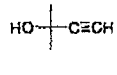
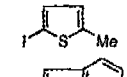
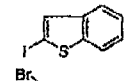
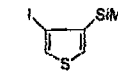


coupling with alkynylzincs. Although the number of examples involving the use of other metal countercations is limited, alkynylmetals containing Mg,[107] Sn,[108] Si,[36] and B[26] have also been employed in some cases (Table 5 and Scheme 8).

In the Pd-catalyzed alkynylation of α,β-dihalothiophenes and related furans, alkynylation can be achieved selectively in the α position, indicating that

16 119

Table 5. Pd-Catalyzed Alkynylation of Five-Membered Heteroaryl Electrophiles Containing One Heteroatom

$R^1C{\equiv}CH$ or $R^1C{\equiv}CM$	ArX	Reaction Conditions: Procedure[a]	Solvent	T, °C	Time, h	Product Yield, %[b]	Ref.
$Me_3SiC{\equiv}CH$		Cu-Ib (LiBr)	Et_3N/THF	70-75	3	79	2
$HC{\equiv}CZnBr$		Zn-II	THF	23	4	- (76)	109
$Me_3SiC{\equiv}CH$		Cu-Ib (LiBr)	Et_3N/THF	reflux	1	74	2
$HC{\equiv}CZnBr$		Zn-II	THF	23	4	- (92)	109
$HC{\equiv}CZnBr$		Zn-II	THF	23	4	72 (78)	109
		Cu-Ia (LiBr)	$(i\text{-}Pr)_2NH$/ piperidine/THF	reflux	5	77	2
		Zn-II	THF	23	1	- (82)	110
$Me_3SiC{\equiv}CH$		Cu-Ib (LiBr)	Et_3N/THF	90-95	2	75	2
		Cu-Ib (LiBr)	Et_3N/THF	90-95	2	86	2
$MeC{\equiv}CZnBr$		Zn-II	THF	rt	1	82 (92)	14
n-$PentC{\equiv}CZnBr$		Zn-Ia	THF	rt	2	70 (85)	14
n-$PentC{\equiv}CZnBr$		Zn-II	THF	rt	48	- (75)	14
$HC{\equiv}CZnBr$		Zn-II	THF	22-23	1	80 (87)	109
$HC{\equiv}CZnBr$		Zn-II	THF	22-23	1	71 (92)	109
$Me_3SiC{\equiv}CH$		Cu-IId (LiBr)	piperidine/THF	reflux	0.5	88	2
$Bu_3SnC{\equiv}CSnBu_3$		Sn-II	dioxane	reflux	6	56	108

[a] See Table 2. All Cu procedures us cat.CuI. An additional reagent is indicated in parentheses. I = cat.$Cl_2Pd(PPh_3)_2$. II = cat.$Pd(PPh_3)_4$. [b] Isolated yields. The numbers in parentheses are GLC or NMR yields.

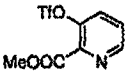
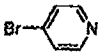
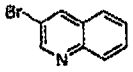
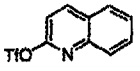
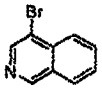
the α-carbon–halogen bond is substantially more reactive than that in the β position (Scheme 9). Also shown in Scheme 9 are a couple of examples of the use of heteroaryl triflates.[113]

b. Five-Membered Heteroaryl Electrophiles Containing Two or More Heteroatoms. The Pd-catalyzed alkynylation of five-membered heteroaryl electrophiles containing two or more heteroatoms have thus far been mostly achieved by the Sonogashira reaction, which appears to be satisfactory in a variety of cases. Although the currently available data on the use of alkynylzincs and other alkynylmetals are very limited, they might also be expected to be widely applicable, judging from the results shown in Table 5 and Scheme 8. Suffice it to indicate, most of the five-membered heteroaryl electrophiles containing (i) two nitrogens, (ii) one each of N and O, and (iii) one each of N and S have been alkynylated by using mainly the Sonogashira reaction. Those parent heteroaryl frameworks indicating the position of the leaving with X that are shown in Scheme 10 have been successfully alkynylated, and the readers are referred to some recent reviews for further details.[2,114] A few notable applications to the synthesis of structurally complex heteroarylalkynes containing two heteroatoms in a five-membered heteroaryl ring are shown in Scheme 11.

c. Six-Membered Heteroaryl Electrophiles. The Pd-catalyzed alkynylation of six-membered heteroaryl electrophiles has been mostly achieved by the Sonogashira reaction and the Negishi coupling with alkynylzincs. The electron-deficient nature of six-membered heteroaryl groups might be expected to favor the desired alkynylation. In reality, however, the heteroatoms can also exert rate retardation, as in the cases of other heteroaryl electrophiles. Despite these potential complications, a number of favorable results have been observed, as indicated by the results shown in Table 6. Additional results obtained with six-membered heteroaryl electrophiles containing two nitrogen atoms are shown in Scheme 12.

Although many alkyne-substituted heteroarenes have been synthesized as compounds of medicinal interest, the number of natural products containing

Table 6. Pd-Catalyzed Alkynylation of Six-Membered Heteroaryl Electrophiles Containing One N Atom

$R^1C{\equiv}CH$ or $R^1C{\equiv}CM$	ArX	Reaction Conditions: Procedure[a]	Solvent	T, °C	Time, h	Product Yield, %[b]	Ref.
2-Pyridyl							
PhC≡CH		Cu-Ia	Et_2NH	rt	3	99	5
$Me_3SiC{\equiv}CH$		Cu-Ib	Et_3N	120	12	80	117
HC≡CZnBr		Zn-II	THF	22	5	- (70)	109
n-HexC≡CZnBr		Zn-II	THF	23	5	79	118
BrZnO(CH$_2$)$_4$C≡CZnBr		Zn-II	THF	22	8	76 (83)	109
3-Pyridyl							
$Me_3SiC{\equiv}CH$		Cu-Ib	Et_3N	reflux	1	94	2
BrZnO(CH$_2$)$_4$C≡CZnBr		Zn-II	THF	22	8	83	109
EtOOCC≡CZnCl		Zn-I	THF-hexane	50	2	38	95
BnO(CH$_2$)$_4$C≡CZnCl		Zn-II	[c]	[c]	[c]	79	119
$Me_3SiC{\equiv}CSnBu_3$		Sn-II	dioxane	80	2	83	120
4-Pyridyl							
PhC≡CZnCl		Zn-II	THF	reflux	overnight	84	121
Quinolyl							
HC≡CZnBr		Zn-II	THF-DMF	50-55	24	55	109
$PhC{\equiv}CSnBu_3$		Sn-II(LiCl)	dioxane	90	16	65	122
Isoquinolyl							
HC≡CZnBr		Zn-II	THF-DMF	50-55	24	58 (62)	109

[a] See Table 2 for procedure symbols. [b] Isolated yields. The numbers in parentheses are GLC or NMR yields. [c] Not indicated.

heteroarenes synthesized by Pd-catalyzed alkynylation is still very small, and the target molecules have been largely limited to simple ones, such as 5-(3-buten-1-ynyl)-2,2-bithienyl,[107] junipal,[26] a thiophene-lactone,[109] and freelingyne[110] (Scheme 13).

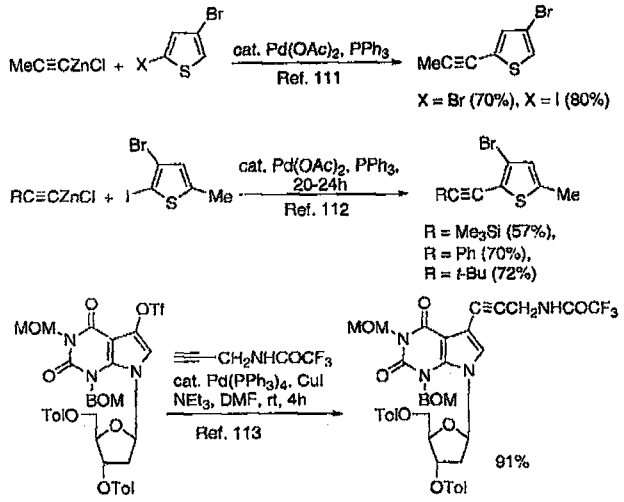
C. Alkenyl Electrophiles

1. Background and General Discussion

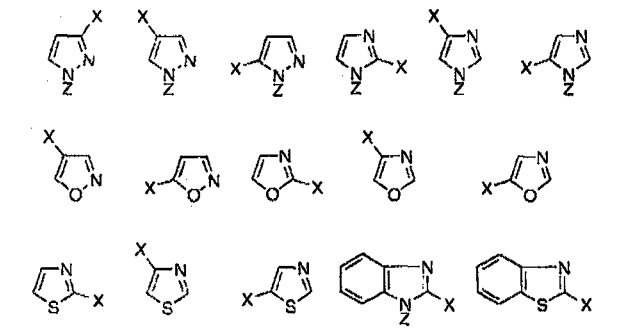
Alkenyl electrophiles are generally more reactive in Pd-catalyzed cross-coupling reactions than aryl electrophiles containing the same leaving groups.[131,132] Thus, not only alkenyl iodides, triflates, and bromides but even chlorides can often react readily and satisfactorily, as eloquently indicated by a synthesis of the sex pheromone of Egyptian cotton leafworm, *Spodoptera littoralis*,[133] shown in Scheme 14.

Along with many favorable consequences of the generally high reactivity of alkenyl electrophiles, however, there are a number of complicating and often negative consequences associated with alkenyl electrophiles, as discussed later. Their cross-coupling

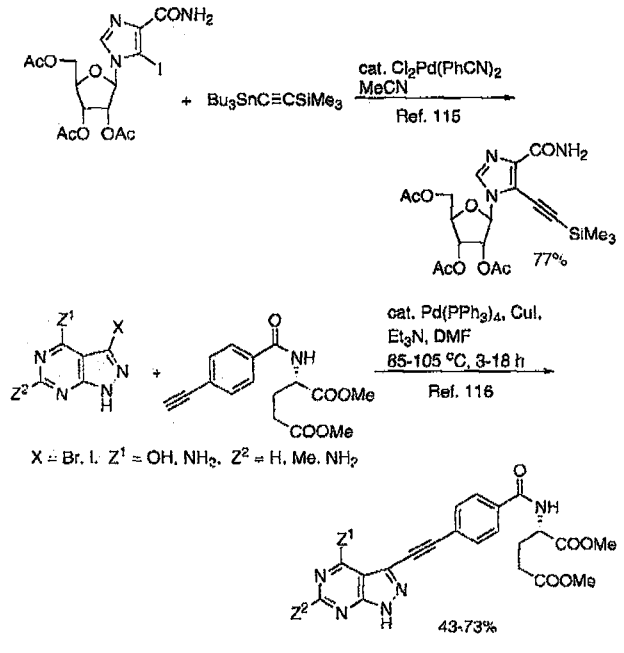
Scheme 9



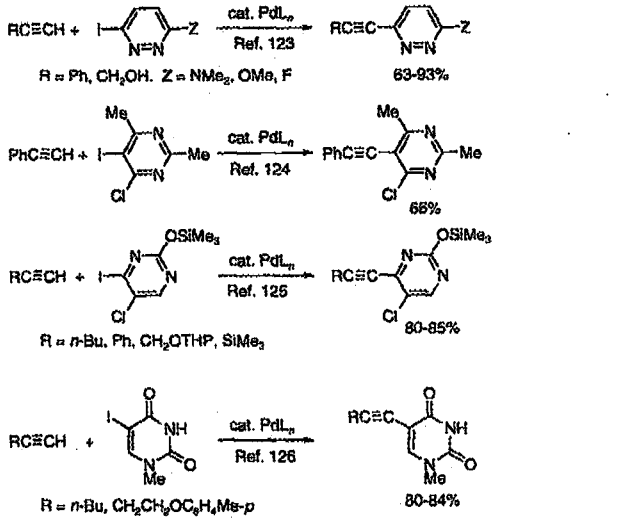
Scheme 10

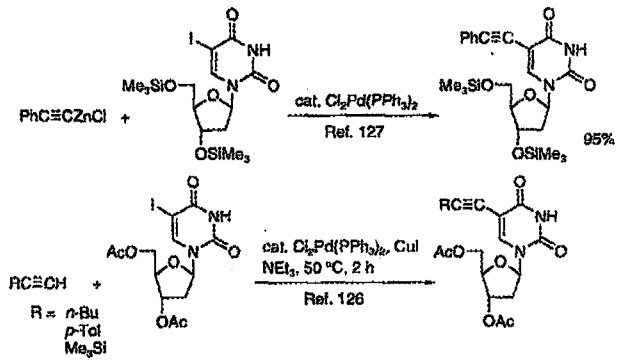


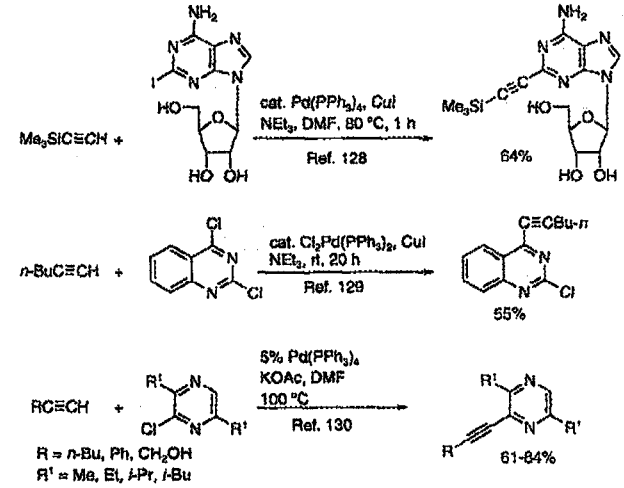
Scheme 11



Scheme 12







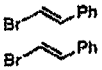
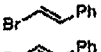
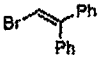
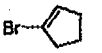
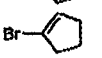
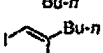
reactions are generally more varied, more sensitive to practically all factors pertaining to their reactions, and hence often more capricious and unpredictable than those of aryl electrophiles.

As in most of the other cases, the Pd-catalyzed alkynylation of alkenyl electrophiles were initially achieved by and large by using the Sonogashira coupling[5] and the Negishi coupling with alkynylzincs,[13] as indicated by the results shown in Table 7. The use of Mg was also introduced in the late 1970s.[21]

Although the Pd-catalyzed alkynylation of aryl halides with alkynyltins was reported as early as 1978,[15] its earliest application to alkynylation of alkenyl electrophiles was most probably that reported in 1986[134] and shown in Scheme 15. Also shown in Scheme 15 is another earlier example in the synthesis of terbinafine.[135]

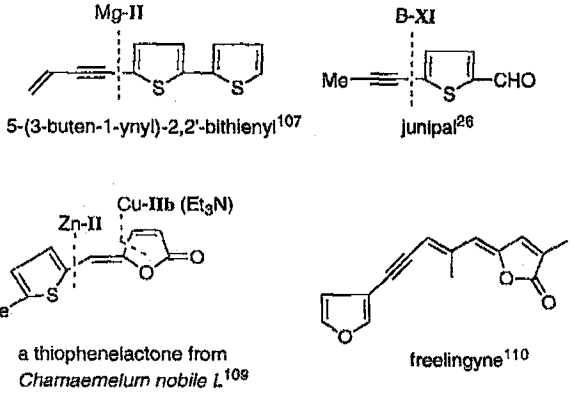
Activation of alkynylsilanes for the Pd-catalyzed alkynyl−alkenyl coupling with the stoichiometric

Table 7. Representative Early Examples of the Pd-Catalyzed Alkynyl–Alkenyl Coupling

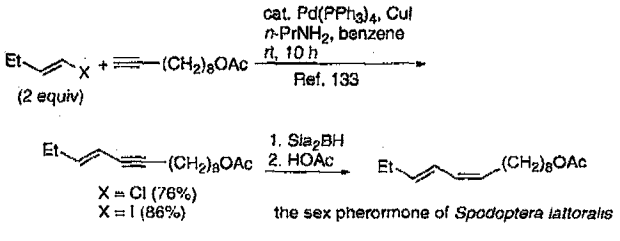
$R^1C{\equiv}CH$ or $R^1C{\equiv}CM$	ArX	Reaction Conditions: Procedure[a]	Solvent	T, °C	Time, h	Product Yield, %[b]	Ref.
Sonogashira coupling							
PhC≡CH	$BrCH{=}CH_2$	Cu-Ia	Et_2NH	rt	3	91	5
$HOH_2CC{\equiv}CH$	$BrCH{=}CH_2$	Cu-Ia	Et_2NH	rt	3	40	5
PhC≡CH		Cu-Ia	Et_2NH	rt	3	90	5
$HOH_2CC{\equiv}CH$		Cu-Ia	Et_2NH	rt	3	70	5
PhC≡CH		Cu-Ia	Et_2NH	rt	3	99	5
PhC≡CH		Cu-Ia	Et_2NH	rt	3	95	5
$HOH_2CC{\equiv}CH$		Cu-Ia	Et_2NH	rt	3	70	5
Negishi coupling with RC≡CZnX							
n-PentC≡CZnCl		Zn-II	THF	25	NA[c]	76 (87)	13
n-PentC≡CZnCl		Zn-II	THF	25	NA[c]	~ (82)	13
n-PentC≡CZnCl		Zn-Ia (DIBAH)	THF	25	NA[c]	~ (80)	13
n-BuC≡CZnCl		Zn-II	THF	25	NA[c]	65 (87)	13
Alkynylation with RC≡CMgX							
MeC≡CMgCl		Mg-II	THF	rt	2	83	21

[a] See Table 2 for procedure symbols. [b] Isolated yields. The numbers in parentheses are GLC yields. [c] Data not available.

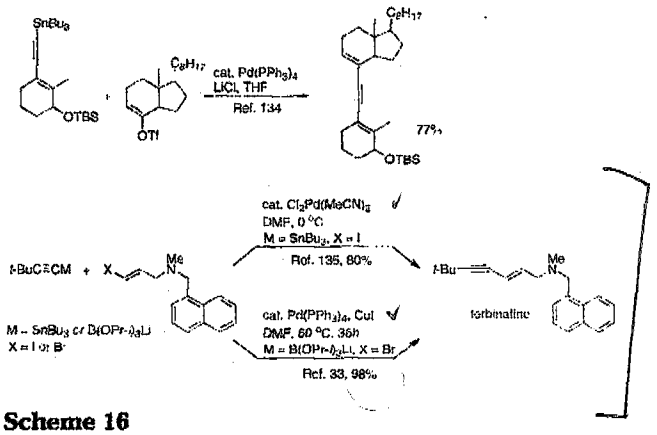
Scheme 13



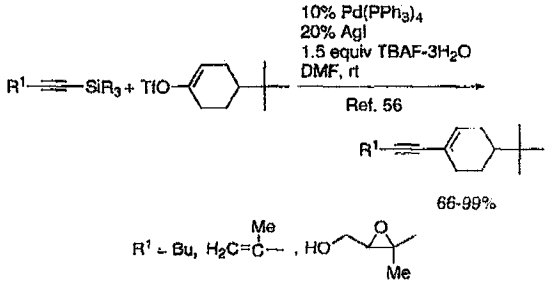
Scheme 14



Scheme 15



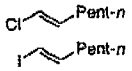
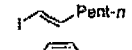
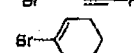
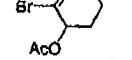
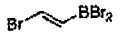
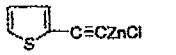
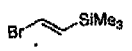
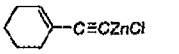
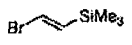
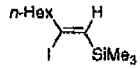
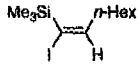
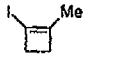
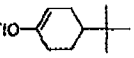
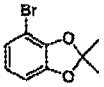
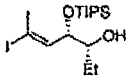
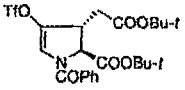
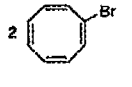
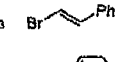
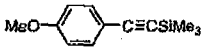
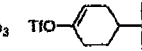
Scheme 16



amount of tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF) was reported in 1988.[35] Since then, attempts have been made to develop alternative procedures for the Pd-catalyzed alkynylation with alkynylsilanes. One recently reported procedure, for example, involves the use of 1.5 equiv of TBAF in place of TASF and 20 mol % of AgI as a cocatalyst[56] (Scheme 16). Since alkynylsilanes can be readily desilated by using inexpensive reagents, such as K_2-

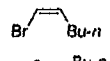
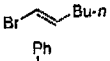
20 122 123

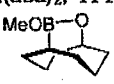
Table 8. Representative Examples of the Pd-Catalyzed Alkynylation of Alkenyl Electrophiles Reported since 1980

$R^1C{\equiv}CH$ or $R^1C{\equiv}CM$	Alkenyl Electrophile	Reaction Conditions: Procedure[a]	Solvent	T, °C	Time, h	Product Yield, %[b]	Ref.
Sonogashira alkynylation							
n-PentC≡CH		Cu-Id	piperidine	rt	20	93	136
$HO(H_2C)_2C{\equiv}CH$		Cu-IId	pyrrolidine	25	0.2	90	12a
$Me_3SiC{\equiv}CH$		Cu-IIb	i-Pr_2NEt	c	c	70	137
PhC≡CH		Cu-IId	pyrrolidine	c	c	67	138
$HOH_2CC{\equiv}CH$		Cu-IId	piperidine	c	c	62	139
Negishi coupling with RC≡CZnX							
n-HexC≡CZnCl		Zn-I	pentane-THF	rt	c	≥63	140
		Zn-II	THF	0	15	87	141
		Zn-II	THF	0	4	81	141
$Me_3SiC{\equiv}CZnCl$		Zn-II	THF	0	8	86	142
n-BuC≡CZnCl		Zn-II	THF	c	c	85	143
n-BuC≡CZnCl		Zn-II	THF	c	c	73	143
n-HexC≡CZnCl		Zn-II	THF	rt	c	78 (81)	144
n-HexC≡CZnCl	$ICF{=}CF_2$	Zn-II	THF	c	c	62	145
Alkynylation with RC≡CSnX₃							
$PhC{\equiv}CSnMe_3$		Sn-II	c	c	c	90	146
$PhC{\equiv}CSnMe_3$		Sn-II	c	c	c	90	147
t-BuC≡CSnBu₃		Sn-II	c	c	c	c	148
HC≡CSnBu₃		Sn-II	benzene	rfx	0.5	74	149
HC≡CSnBu₃		Sn-II	THF	c	c	91	150
$Me_3SiC{\equiv}CSnBu_3$		Sn-V[d] ($ZnCl_2$)	NMP-Et_2O	c	c	44	151
$Bu_3SnC{\equiv}CSnBu_3$		Sn-V	THF	rt	24	45	152
Alkynylation with RC≡CSiX₃							
n-Pent≡CSiMe₃		Si-X[e]	THF-HMPA	rt	c	86	35
		Si-IIa[f]	DMF	80	12	90 (>99)	37

21 193 124

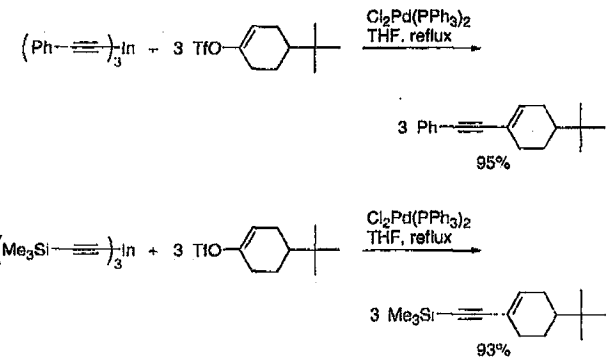
Table 8 (Continued)

$R^1C{\equiv}CH$ or $R^1C{\equiv}CM$	Alkenyl Electrophile	Procedure[a]	Reaction Conditions: Solvent	T, °C	Time, h	Product Yield, %[b]	Ref.
Alkynylation with RC≡CBX$_3$M							
t-BuC≡CBX$_3$Li[g]		B-II	THF-MeOH	rfx	[c]	56	24
Me$_3$SiC≡CBX$_3$Li[h]		B-II	THF	rfx	[c]	83	25
Me$_3$SiC≡CBX$_3$Li[g]		B-II	THF	rfx	[c]	55	24
Me$_3$SiC≡CBX$_3$Li[g]		B-II	THF	rfx	[c]	55	24

[a] See Table 2 for procedure symbols. [b] Isolated yields. The numbers in parentheses are GLC or NMR yields. [c] Data not available. [d] **V** = Pd(dba)$_2$, TFP, ZnCl$_2$. [e] **X** = (η^3-C$_3$H$_5$PdCl)$_2$, TASF (1.3 equiv), P(OEt)$_3$. [f] **IIa** = Pd(PPh$_3$)$_4$, CuCl. [g] BX$_3$ = *B*-MeO-9-BBN. [h] BX$_3$ = 

CO$_3$-MeOH, and can subsequently be used in the Sonogashira, Negishi, and other Pd-catalyzed alkynylation reactions, critical comparison among various available options would be desirable. Yet another notable recent development involves the use of tris(alkynyl)indiums[46,47] (Scheme 17).

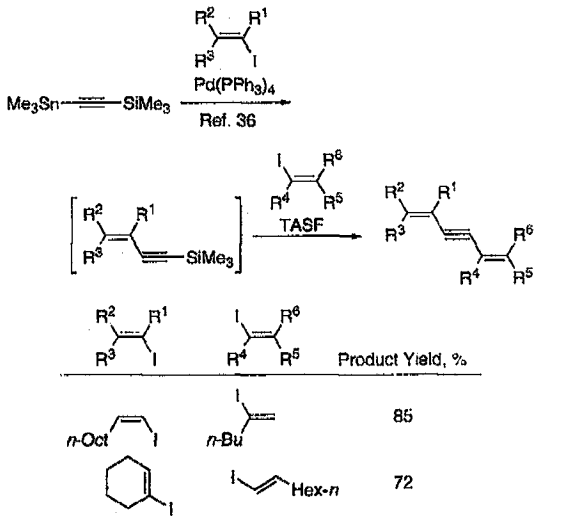
Scheme 17



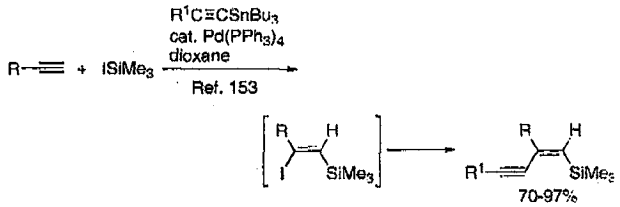
While recent developments involving the use of Si, B, In, and other metals are interesting and promising in some cases, most of the currently known examples of the Pd-catalyzed alkynyl–alkenyl coupling involve the use of Cu, Zn, and Sn. In some cases, Mg has also been shown to be satisfactory and competitive. In many less-demanding cases, these reactions appear to give roughly comparable results, and once again, some other factors, such as cost, ease of operation, and toxicity, may prove to be decisive factors in the final selection. This generalization may be supported by the results reported over the past two decades shown in Table 8 and Schemes 18–20. Other more delicate and demanding cases will be discussed in section III.

Despite the very favorable results obtained with both alkenyl chlorides and iodides shown in Scheme 14,[133] the Sonogashira alkynylation has been shown to be very sensitive to various factors. For example, under the conditions of the original procedure for the Sonogashira coupling,[5] the reaction of 1-heptyne with (*E*)-1-iodo-1-hexene and (*Z*)-1-bromo-1-hexene gave the desired products only in 30% and 32% yields, respectively. The former yield was improved to 50%

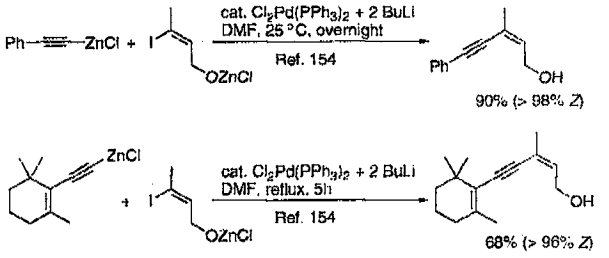
Scheme 18



Scheme 19

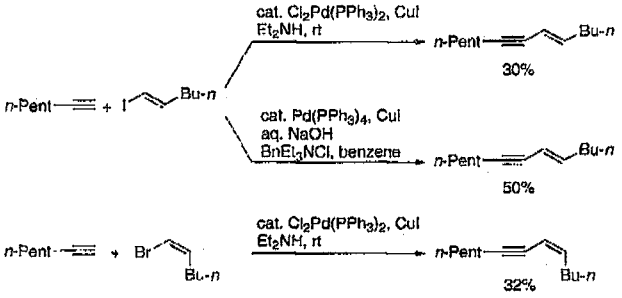


Scheme 20



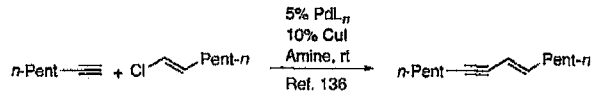
through the use of 10% aqueous NaOH in place of Et$_2$NH and BnEt$_3$NCl as a phase transfer catalyst[155] (Scheme 21).

Scheme 21

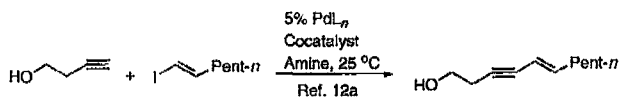


The strongly condition-dependent and unpredictable nature of the alkynyl−alkenyl coupling by the Sonogashira reaction may be further gleaned from the results shown in Scheme 22. Fortunately, one or more satisfactory sets of conditions have been observed in each case.

Scheme 22



Pd Complex	Amine	Product Yield, %
$Pd(PPh_3)_4$	piperidine	11
$Pd(PPh_3)_4$	*n*-$PrNH_2$	62
$Cl_2Pd(PPh_3)_2$	piperidine	93
$Cl_2Pd(PhCN)_2$	piperidine	93

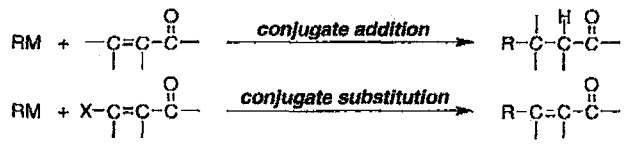


Pd Complex	Cocatalyst	Amine	Product Yield, %
$Pd(PPh_3)_4$	none	*i*-Pr_2NH	3
$Pd(PPh_3)_4$	10% CuI	*i*-Pr_2NH	81
$Pd(PPh_3)_4$	none	piperidine	93
$Pd(PPh_3)_4$	10% CuI	piperidine	90

2. Conjugate Substitution with β-Halo-α,β-unsaturated Carbonyl and Related Derivatives

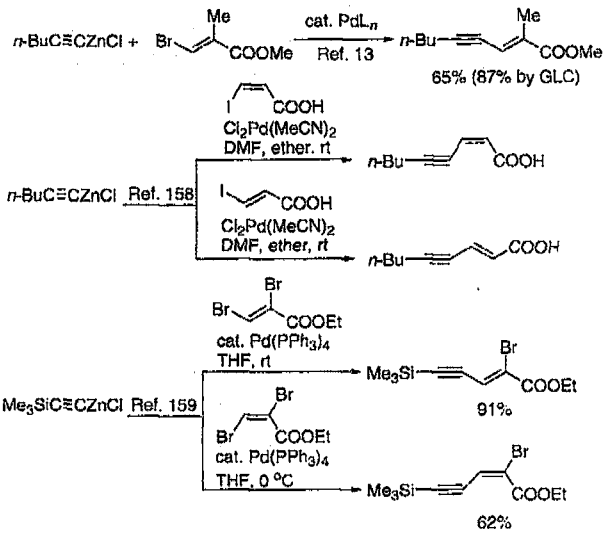
The Pd-catalyzed cross-coupling of α- and β-halo-α,β-unsaturated carbonyl and related derivatives commands special attention. It has been clearly demonstrated that, whereas that of α-halo-substituted derivatives is sluggish and often problematical,[156] the corresponding reaction of β-halo derivatives is generally facile and very favorable. Since the latter process is the substitution analogue of conjugate addition, it has conveniently been termed "conjugate substitution".[157] (Scheme 23).

Scheme 23



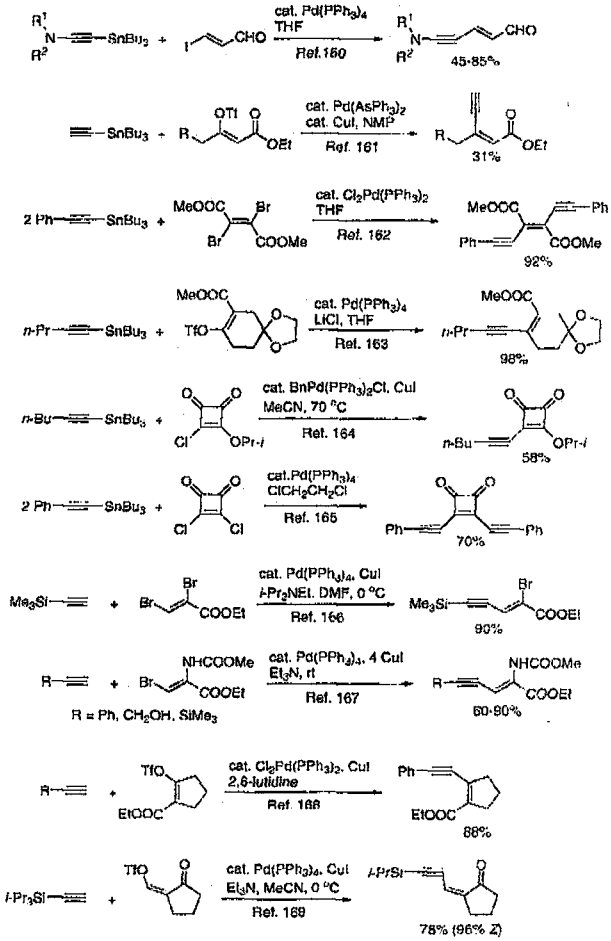
The reaction shown at the top of Scheme 24[13] most probably was the first example of the Pd-catalyzed

Scheme 24



alkynylation via conjugate substitution. Since then, a large number of examples of the Pd-catalyzed conjugate substitution have been reported, as shown in Schemes 24 and 25. The results shown in Scheme

Scheme 25



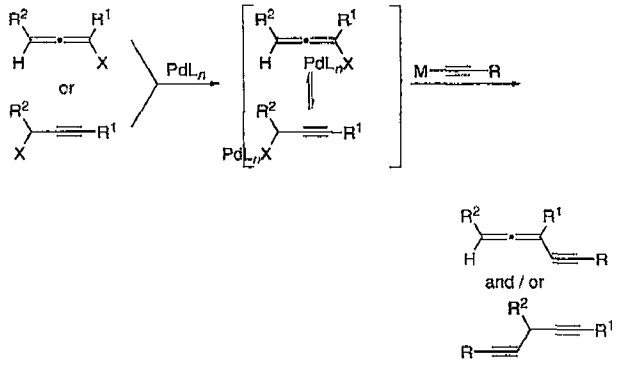
25 indicate that Sn and Cu have served as satisfactory metal countercations in addition to Zn. Unlike β-alkynylation, the more sluggish and demanding

Pd-catalyzed α-alkynylation of α,β-unsaturated carbonyl compounds is of more recent origin, and it will be discussed in section III.B.4.

3. Allenyl and Propargyl Electrophiles

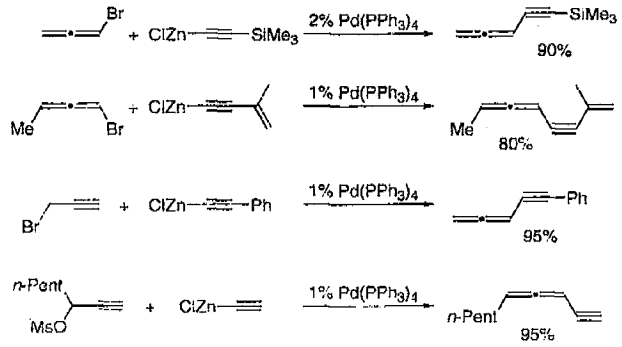
Allenyl and propargyl electrophiles also deserve special attention. When they are converted to organopalladium derivatives, they can be engaged in allenyl−propargyl equilibria that can lead to the formation of conjugated allenynes and/or 1,4-diynes upon alkynylation (Scheme 26). In reality, however, the reaction has produced exclusively or nearly exclusively allenynes, thereby providing an excellent route to allenynes.[170−175]

Scheme 26



Some representative results are summarized in Scheme 27. A systematic counteraction screening has

Scheme 27

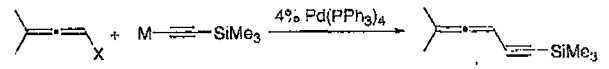


indicated that Zn and Cu are the two most satisfactory metals, even though Ag and Mg have also been shown to be satisfactory in some cases.[171−175] Another point of note is that propargyl derivatives are significantly more reactive than allenyl derivatives. Thus, not only propargyl bromides (and presumably chlorides) but also acetates, mesylates, and even phosphates are satisfactory (Scheme 28). Some related reactions of alkynylalanes and alkynyl epoxides[145] are also known (Scheme 29).

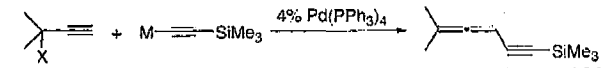
D. Acyl Halides and Related Electrophiles

As a class of compounds represented by C_{sp^2}−X, acyl halides also readily participate in the Pd-catalyzed alkynylation. Since alkynylmagnesium derivatives are highly reactive toward ketones, Mg may not be a suitable counteraction. On the other hand,

Scheme 28

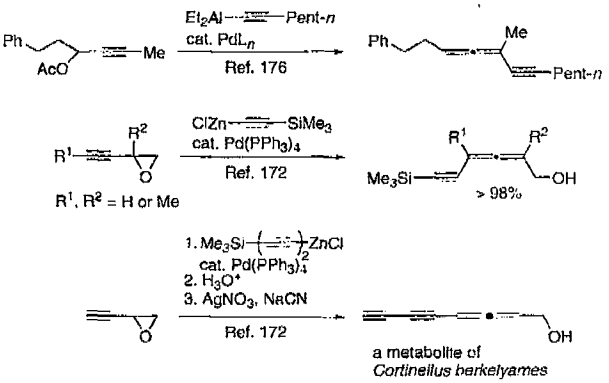


X	Product yield (%) M = ZnCl	M = (CuLi)$_{1/2}$	M = Cu	M = MgCl	M = Ag	M = Li
Br	100	100	33	80	23	3
OAc	7	-	4	34	-	0



X	Product yield (%) M = ZnCl	M = Cu	M = MgCl	M = Ag	M = Li
Br	98	-	70	98	0
OAc	98	98	75	86	0
OSO_2Me	98	98	90	< 5	-
$OPO(OEt)_2$	98	4	98	80	20

Scheme 29



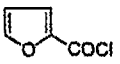
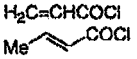
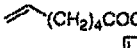
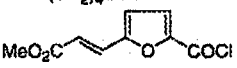
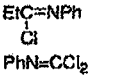
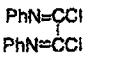
the Sonogashira reaction[7] and those involving Zn[177] and Sn[178] have been successfully applied to alkynylation of acyl halides. Collectively, these reactions represent one of the best methods for the synthesis of ketones from acyl halides. Some of the seminal and/or representative examples are shown in Table 9. In less demanding cases, such as those shown in Table 9, all three major protocols appear to be comparably satisfactory. Also shown in Table 9 are some results obtained with less frequently used metals, such as Al[185] and In.[47]

Acylation of an alkynylzinc chloride by the Negishi alkynylation has been applied to the synthesis of *modhephene*,[186] as shown in Scheme 30.

E. Pd-Catalyzed Alkynyl−Alkynyl Coupling

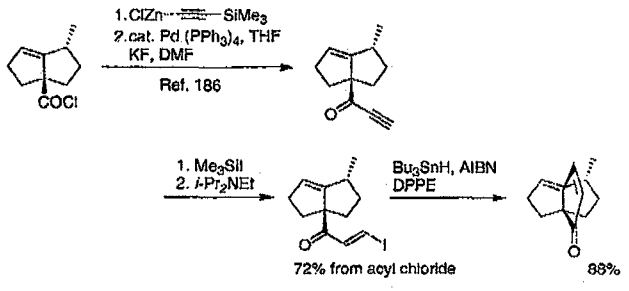
Currently, the most widely used method for alkynyl−alkynyl coupling is the Cadiot−Chodkiewicz reaction of terminal alkynes with 1-haloalkynes in the presence of a Cu catalyst without the use of a Pd complex.[58] In view of the facile oxidative addition of Pd to 1-haloalkynes, the Pd-catalyzed reaction of terminal alkynes or alkynylmetals with 1-haloalkynes might be expected to proceed readily to provide a satisfactory alternative to the Cadiot−Chodkiewicz

Table 9. Pd-Catalyzed Alkynylation of Acyl Halides

$R^1C{\equiv}CH$ or $R^1C{\equiv}CM$	R^1COCl	Reaction Conditions: Procedure[a]	Others	Yield of Product, %[b]	Ref.
Sonogashira Alkynylation					
n-BuC≡CH	*i*-PrCOCl	Cu-Ib	Et_3N, 50 °C, 3 h	61	7
PhC≡CH	*t*-BuCOCl	Cu-Ib	Et_3N, rt, 15 h	79	7
PhC≡CH		Cu-Ib	Et_3N, benzene, rt, 15 h	80	7
PhC≡CH	PhCH=CHCOCl	Cu-Ib	Et_3N, benzene, rt, 15 h	75	7
PhC≡CH	$Me_2NCOCOCl$	Cu-Xb	Et_3N, Et_3P, 90 °C, 6 h	92	7
Negishi Coupling with RC≡CZnX					
n-PentC≡CZnCl	MeCOCl	Zn-II	THF, 25 °C	81 (97)	177
n-PentC≡CZnCl	MeCOCl	Zn-II	THF, 25 °C	73 (97)	177
PhC≡CZnCl	$H_2C{=}CHCOCl$	Zn-II	THF, 10 °C, 10 min	56	179
n-PentC≡CZnCl		Zn-II	THF, 25 °C	92	177
n-HexC≡CZnCl	ClCOOMe	Zn-II	THF, 25 °C	72	177
PhC≡CZnCl	*t*-BuCOCl	Zn-II	THF, 25 °C	78	179
Alkynylation with RC≡CSnBu$_3$					
$PhC{\equiv}CSnBu_3$	*i*-PrCOCl	Sn-I	$(CH_2Cl)_2$, 84 °C	69	178
$PhC{\equiv}CSnBu_3$	PhCOCl	Sn-I	$(CH_2Cl)_2$, 84 °C	94	178
$Me_3SiC{\equiv}CSnBu_3$	*i*-PrCOCl	Sn-I	$(CH_2Cl)_2$, 84 °C	71	178
$Me_3SiC{\equiv}CSnBu_3$	PhCOCl	Sn-I	$(CH_2Cl)_2$, 84 °C	64	178
$Me_3SiC{\equiv}CSnBu_3$		Sn-I	$(CH_2Cl)_2$	44	180
$n\text{-}BuC{\equiv}CSnBu_3$		Sn-VI	PhCN, PPh_3, CH_2Cl_2	60	181
$PhC{\equiv}CSnBu_3$		Sn-I	PhEt, 70 °C, 5 h	69	182
$n\text{-}BuC{\equiv}CSnBu_3$	$PhN{=}CCl_2$	Sn-I	PhH, 70 °C	70	183
$PhC{\equiv}CSnBu_3$		Sn-I	PhMe, 50 °C, 5 h	50	184
Alkynylation with RC≡CAlX$_2$					
$n\text{-}BuC{\equiv}CAlEt_2$	PhCOCl	Al-II	THF, 25 °C	67	185
$n\text{-}BuC{\equiv}CAlEt_2$	PhCH=CHCOCl	Al-II	THF, 25 °C	74	185
$PhC{\equiv}CAlEt_2$	*n*-HeptCOCl	Al-II	THF, 25 °C	61	185
$Me_3SiC{\equiv}CAlEt_2$	$H_2C{=}CH(CH_2)_8COCl$	Al-II	THF, 25 °C	51	185
Alkynylation with (RC≡C)$_3$In					
$1/3\,(PhC{\equiv}C)_3In$	PhCOCl	In-II	THF, reflux, 1 h	94	47
$1/3\,(PhC{\equiv}C)_3In$	$Me_2C{=}CHCOCl$	In-II	THF, reflux, 2 h	90	47
$1/3\,(Me_3SiC{\equiv}C)_3In$	$Me_2C{=}CHCOCl$	In-II	THF, reflux, 3 h	90	47

[a] See Table 2 for procedure symbols. [b] Isolated yields. The numbers in parentheses are GLC or NMR yields.

Scheme 30

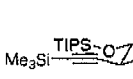
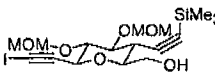
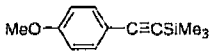
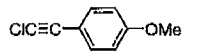


reaction. Some preliminary results obtained in the authors' laboratories in the 1970s indicated that the Pd-catalyzed coupling reaction of alkynylmetals, including those containing Zn, with 1-bromo- or 1-iodoalkynes proceeded readily and almost quantitatively in some cases but that it led to nearly statistical mixtures of the desired cross-coupled two homo-coupled products[187] (eq 2). Although there have

$$n\text{-PentC}{\equiv}\text{CZnCl} + \text{XC}{\equiv}\text{CBu-}n \xrightarrow[\text{X = I or Br}]{\text{cat. PdL}_n} \underset{\sim 50\%}{n\text{-PentC}{\equiv}\text{C-C}{\equiv}\text{CBu-}n} + \underset{\sim 25\%}{n\text{-PentC}{\equiv}\text{C-H}} + \underset{\sim 25\%}{n\text{-BuC}{\equiv}\text{C-H}} \quad (2)$$

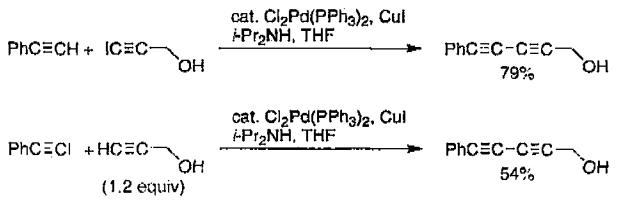
been some reports on preferential formation of unsymmetrical conjugated diynes[188-194] (Table 10), it is not clear if the favorable results are due to favorable substrates or due to favorable procedures. Thus, for example, the use of $PhC{\equiv}CH$ and $IC{\equiv}CCH_2OH$ led to the formation of $PhC{\equiv}CC{\equiv}CCH_2OH$ in 79% yield, but the reaction of $PhC{\equiv}CI$ with $HC{\equiv}CCH_2OH$ gave the same diyne only in 54% yield[188] (Scheme 31). Further systematic investigation would be needed to fully clarify this point. In the meantime, a strictly

Table 10. Pd-Catalyzed Alkynyl–Alkynyl Coupling

$R^1C{\equiv}CH$ or $R^1C{\equiv}CM$	$XC{\equiv}CR^2$	Reaction Conditions: Procedure[a]	Reaction Conditions: Others	Yield of Product, %[b]	Ref.
n-HeptC≡CH	IC≡CCH$_2$OH	Cu-Ia (*i*-Pr$_2$NH)	THF	73	188
n-OctC≡CH	BrC≡CPent-*n*	Cu-Ia	pyrrolidine, 20 °C	61	192
PhC≡CH	BrC≡CPent-*n*	Cu-Ia	pyrrolidine, 20 °C	66	192
HO(H$_2$C)$_2$C≡CH	BrC≡CPent-*n*	Cu-Ia	pyrrolidine, 20 °C	91	192
Me$_2$NH$_2$CC≡CH	BrC≡CPent-*n*	Cu-Ia	pyrrolidine, 20 °C	82	192
n-PentCH(OH)C≡CH	IC≡CCEt$_2$NH$_2$	Cu-X[c] (NEt$_3$)	MeCN/H$_2$O	65	191
		Cu-IIb	Et$_3$N	64	190
	ClC≡CPh	Si-I (CuCl)	DMF	80	193
PhC≡CSiMe$_3$		Si-I (CuCl)	DMF	62	193
EtOOCC≡CZnBr	IC≡CHex-*n*	Zn-II	THF, 23 °C	86	194

[a] See Table 2 for procedure symbols. [b] Isolated yields.

Scheme 31

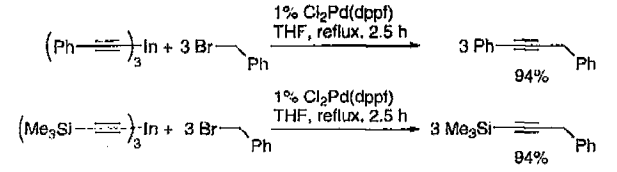


pair-selective and satisfactory procedure for the synthesis of conjugated diynes via β-haloenynes has been developed,[59,60] as discussed in section III.B.5.

F. Allyl and Benzyl Electrophiles

As discussed in section II.C, propargyl electrophiles, which can serve as synthetic equivalents to allenyl electrophiles, are generally favorable reagents for the Pd-catalyzed synthesis of allenynes. Although very little is known, a very recent report on the reaction of tris(alkynyl)indiums with benzyl bromide catalyzed by $Cl_2Pd(dppf)$[47] shown in Scheme 32 is noteworthy.

Scheme 32



III. Comparison of Various Protocols in More Demanding Cases of the Pd-Catalyzed Alkynylation

A. Background

The experimental results described in the preceding sections indicate that the Pd-catalyzed alkynylation can satisfactorily be achieved in many cases either by the Sonogashira and related Heck-type reactions or by the Negishi alkynylation with alkynylzincs and related reactions involving several other metals, including Mg and Sn. More recently, however, an increasing number of difficulties associated with these reactions, especially the most widely used Sonogashira reaction, have also been reported, as discussed in section III.B. In many cases of difficulties encountered in the Sonogashira and related reactions, the alkynylzinc protocol and other related reactions of alkynylmetals have been shown to provide satisfactory solutions. Although less frequently encountered, the opposite may also be true in some cases. Listed below are some of the frequently encountered difficulties in the Sonogashira reaction:

1. alkyne homodimerization,
2. difficulties in the direct synthesis of terminal alkynes from ethyne due to predominant 1,2-disubstitution,
3. failure to produce the desired alkynes in practically useful yields in cases where the starting alkynes are substituted with electron-withdrawing groups, such as carbonyl-containing groups and CF_3,
4. failure to produce the desired alkynes in practically useful yields observed with various organic electrophiles, such as ICH=CHBr, and
5. limitations associated with sterically demanding organic electrophiles.
6. Although it may not be considered as a difficulty, Pd-catalyzed alkynylation with 1-halo-1-alkynes is not an alternative available to the Sonogashira reaction except in the alkynyl–alkynyl coupling.

These and some other noteworthy topics, such as α-alkynylation of α-halo-α,β-unsaturated carbonyl derivatives, are discussed in this section with emphasis on differences among various Pd-catalyzed alkynylation protocols.

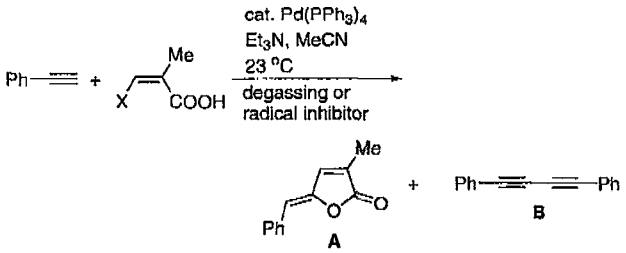
B. Critical Comparisons between the Sonogashira Reaction and the Pd-Catalyzed Alkynylation with Alkynylzincs and Related Alkynylmetals

1. Alkyne Dimerization

Alkyne homodimerization is a frequent and often serious side reaction in the Sonogashira alkynylation. Although mechanistic details are not clear, minimization of alkyne dimerization through degassing and/or addition of radical inhibitors points to radical

processes in such cases. Some representative results are shown in Scheme 33.[110]

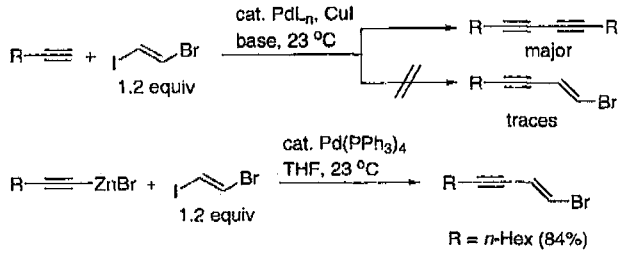
Scheme 33



X	Modification	Yield, % A	Yield, % B	X	Modification	Yield, % A	Yield, % B
I	none	5	50	Br	none	50	34
I	degassing	78	16	Br	degassing	74	20
I	Galvinoxyl	66	23	Br	BHT	77	13

In some other cases, such as that shown in Scheme 34, however, little effects of added radical inhibitors

Scheme 34



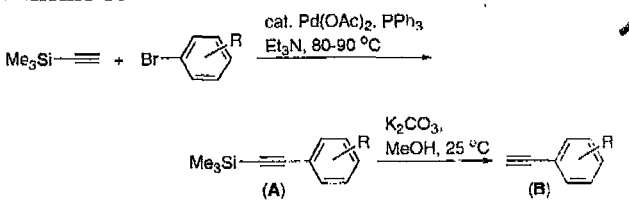
have been observed.[194,195] It is therefore conceivable that alkyne dimerization in such cases may arise via nonradical processes. In any event, the corresponding reaction of alkynylzincs provides the desired enynes in excellent yields (Scheme 34).[194] Regardless of the precise mechanistic details, the Sonogashira reaction does appear to be much more prone to alkyne homodimerization than the alkynylzinc reaction.

2. Direct Synthesis of Terminal Alkynes from Ethyne or Ethynylmetals

The Sonogashira reaction of ethyne itself with organic electrophiles was reported to produce predominantly 1,2-disubstituted alkynes even in cases where the molar ratio of the organic electrophile to ethyne is ≤ 1,[5] and this has been confirmed by others.[32] Consequently, the synthesis of terminal alkynes by the Sonogashira reaction has required (a) preparation of monoprotected ethynes, such as $Me_3SiC{\equiv}CH$ and $HOCMe_2C{\equiv}CH$, (b) their Sonogashira coupling,[8] and (c) deprotection.[196-198] Deprotection of the Me_3Si group can be achieved by various methods, including treatment with methanolic K_2CO_3 at room temperature, whereas removal of the hydroxyalkyl groups usually requires stronger bases, such as KOH, and higher temperatures. These three-step procedures are at best circuitous, often leading to modest overall yields of the desired terminal alkynes, as indicated by the results shown in Scheme 35.[196]

In marked contrast with the Sonogashira reaction, it has been known since 1977 that the Pd-catalyzed

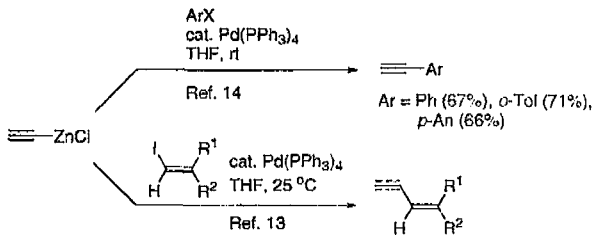
Scheme 35



R	Yield, % (A)	(B)	Overall
o-CHO	75	80	60
m-CHO	80	84	67
p-CHO	99	100	99
m-CO_2Me	70	71	50
p-CO_2Me	69	73	50

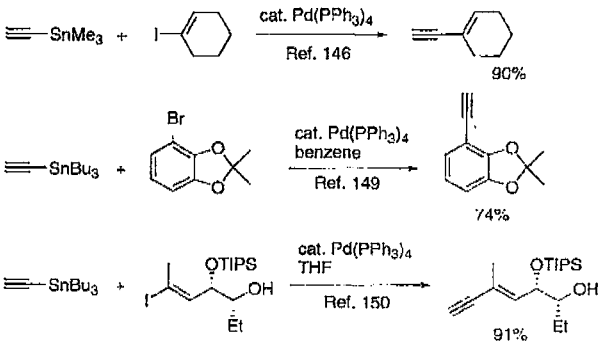
cross-coupling with ethynylzinc chlorides and bromides produces selectively terminal alkynes in high yields (Scheme 36).[13-17] The use of ethynyltin derivatives was also reported later[146,149,150] (Scheme 37).

Scheme 36



R^1	R^2	Yield, %
n-Bu	H	83
H	*n*-Bu	76
Et	*n*-Bu	70

Scheme 37

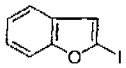
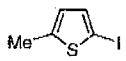
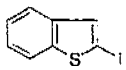


Recent comparative studies using commercially available $HC{\equiv}CMgBr$ and $HC{\equiv}CNa$ as the starting alkynyl reagents[32,109] have indicated that not only $HC{\equiv}CZnX$ (X=Br or Cl) and $HC{\equiv}CSnR_3$ (R=Me or *n*-Bn) but also commercially available $HC{\equiv}CMgBr$ are all comparably satisfactory in less demanding cases, as shown in Table 11.[32,109] On the other hand, the use of ethynylmetals containing Li, Na, or BBu_3M, where M is Li or Na, do not produce the desired terminal alkynes.[32] In view of successful results observed with various alkynylborates,[15,24-27,33] some side reactions unique to ethynyl(trialkyl)borates, such as 1,2-migration, may be suspected for the ethynyl(trialkyl)borate reaction.

27
1924
930

Table 11. Pd-Catalyzed Ethynylation of Organic Electrophiles with Ethynylmetals Containing Zn, Mg, and Sn

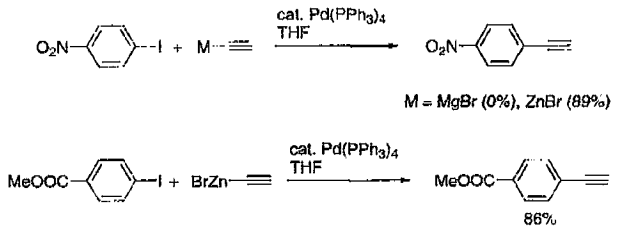
RX + M—≡ —(cat. Pd(PPh$_3$)$_4$, THF or THF/DMF)→ R—≡

Organic Electrophile	Yield of R—≡, [a] % ZnBr	MgBr	SnBu$_3$	Ref.
Aryl Electrophiles				
PhI	95-98	96	96	32
p-MeC$_6$H$_4$I	[b]	92 (86)	[b]	32
p-MeOC$_6$H$_4$I	95	95	[b]	32
p-FC$_6$H$_4$I	94	97 (72)	[b]	32
Heteroaryl Electrophiles				
	76	[b]	[b]	109
	92	[b]	[b]	109
	78 (72)	[b]	[b]	109
	85 (71)	[b]	[b]	109
	87 (80)	35[c]	[b]	109
	92 (71)	[b]	[b]	109
Alkenyl Electrophiles				
(*E*)-*n*-HexCH=CHI	96	95	95	32
(*E*)-*n*-PrCH=C(I)Pr-*n*	98	98	[b]	32
(*E*)-*n*-Hex(Me)C=CHI	94	94	[b]	32
(*E*)-*n*-Pr(Me)C=C(I)Pr-*n*	85	82	[b]	32

[a] By GLC or NMR. The numbers in parentheses are isolated yields. [b] Not reported. [c] The 1,2-disubstituted alkyne product was produced in 24% yield.

Upon further examination, however, some notable differences among Zn, Mg, and Sn have become apparent. First, it is well-known that organomagnesium reagents, including HC≡CMgBr are very reactive toward various carbonyl, nitro, and other electrophilic functional groups and hence mostly incompatible with these functional groups. Perhaps less well-known is the ability of organozincs to tolerate many such electrophilic functional groups[32] (Scheme 38).

Scheme 38



Even in the absence of electrophilic heteroatom functionalities, steric and other electronic effects can play some significant roles, leading to clear discrimination of various metal countercations. As in the Sonogashira reaction, 1,2-disubstitution of ethyne can be a serious side reaction even in the reactions of ethynylmetals. This must arise via metal−hydrogen exchange, and the extent to which this takes place may be expected to be a function of various factors, including alkynyl−metal bond polarity or ionicity and relative rates of the desired alkynylation and metal−hydrogen exchange (Scheme 39).[32] Steric retardation in the reaction of ethynylmetals containing Mg and Sn relative to that of HC≡CZnBr is also clearly seen in the ethynylation of iodomesitylene.[32]

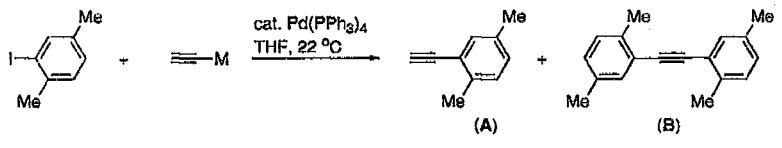
Aside from toxicity and other practical issues, it may be stated that the ethynylzinc reaction generally leads to the most satisfactory results. Even so, however, it is not without some difficulties. Thus, for example, in the Pd-catalyzed reaction of HC≡CZnBr with some bromo derivatives of six-membered *N*-containing heteroarenes, the extents of disubstitution were considerable, although significantly less than those observed with HC≡CMgBr. The use of 2-iodopyridine in place of 2-bromopyridine improved the product yield from 21% to 70%. Alternatively, substitution of HC≡CZnBr with BrZnOC(Me$_2$)C≡CZnBr did lead to a high cross-coupling yield of 83%[109] (Scheme 40).

The direct terminal alkyne synthesis involving mostly Zn but also Mg in some cases has been applied to the synthesis of natural products, as shown in Scheme 41. Since HC≡CZnBr is usually generated from HC≡CMgBr or its equivalents, it is advisable to see if HC≡CMgBr or its equivalents might be a satisfactory reagent for the desired alkynylation before their conversion into HC≡CZnBr or other second-generation ethynylmetals. It should be noted that the Sonogashira−Lu cascade cross-coupling−lactonization protocol[199] discussed later in detail has been used in the construction of the butenolide moieties shown in Scheme 41.

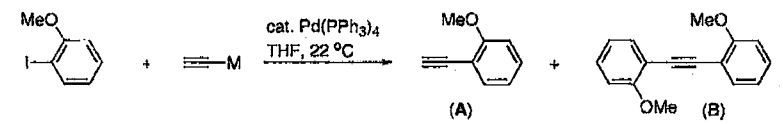
In most of the synthetic tasks, terminal alkynes are not the ultimate target compounds, and they are to be further converted to some ultimate targets as in the cases shown in Scheme 41. In this context, the synthesis of terminally protected alkynes followed by their conversion to 1,2-disubstituted alkynes can, in principle, be a viable alternative to the route via terminal alkynes, and the use of HC≡CSiMe$_3$ is potentially attractive. The required Me$_3$Si-protected alkynes can be satisfactorily prepared by either the Sonogashira reaction[8,196] or via Me$_3$SiC≡CM containing Zn,[48] Sn,[35] B,[24,25] In,[46,47] and others.

More critical is the conversion of the silyl-protected alkynes into 1,2-disubstituted alkynes. One obvious option is to carry out desilylation with K_2CO_3 or another suitable reagent and use terminal alkynes for further substitution, but this would not be competitive in most cases with the two-stage disubstitution of ethyne via terminal alkynes that can, in principle, be achieved in one pot. Nonetheless, this would provide a point of reference with which to compare the relative merits of other protocols. As presented earlier, various protocols for Pd-catalyzed alkynylation with alkynylsilanes have been devel-

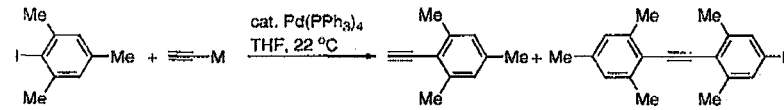
Scheme 39



M	Time, h	Yield, % (A)	(B)	SM
ZnBr	3	92	4	0
MgBr	48	60	24	14
$SnBu_3$	24	73	6	15



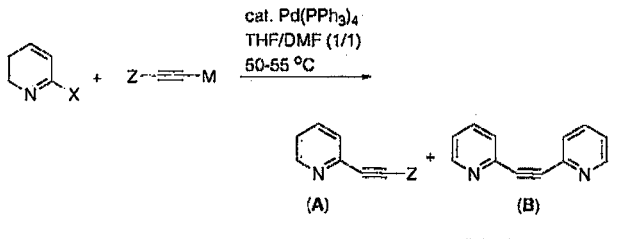
M	Time, h	Yield, % (A)	(B)	SM
ZnBr	2	77	trace	NA
MgBr	20	51	36	NA



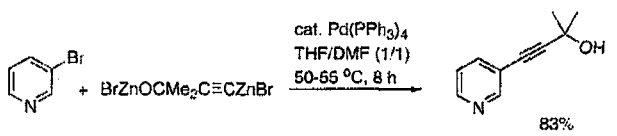
M	Time, h	Yield, % (A)	(B)	SM
ZnBr	18	74	10	trace
MgBr	48	24	12	66
$SnBu_3$	72	36	8	52

SM = Starting material, *i.e.*, aryl halide.
NA = Data not available.

Scheme 40



Z	X	M	Time, h	Yield, % (A)	(B)
H	Br	MgBr	24	<2	65
H	Br	ZnBr	24	21	44
H	I	ZnBr	5	70	<2
$BrZnOCMe_2$	Br	ZnBr	6	83	–

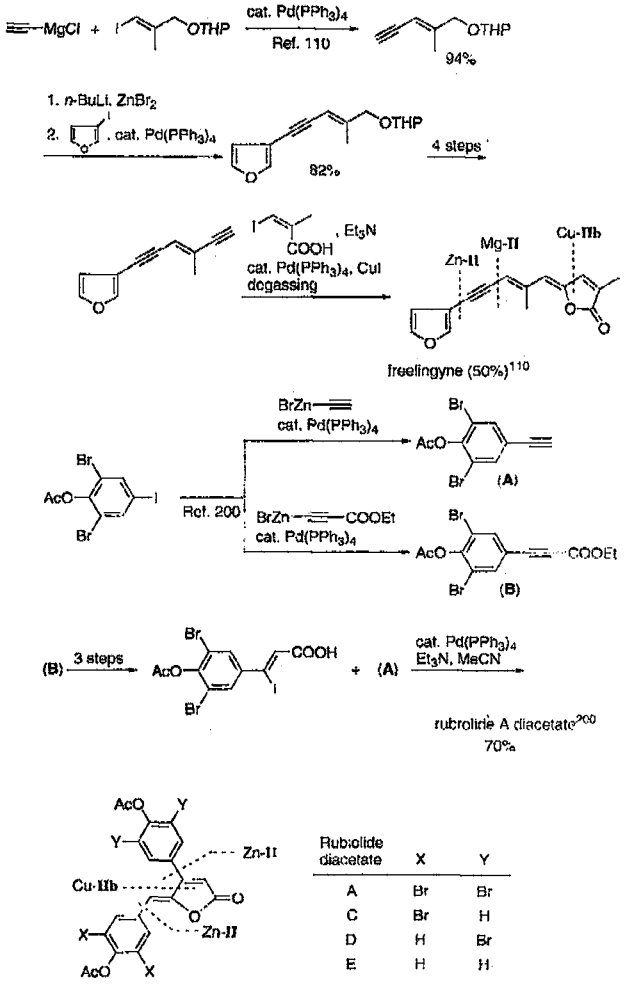


oped. Some representative ones involve the use of TASF (Scheme 18),[35,36] CuCl as a cocatalyst in conjunction with aryl triflates,[37] and TBAF in conjunction with AgI (Scheme 16).[56] While these reactions are interesting, they do involve the use of relatively expensive chemicals, and their practical synthetic values must be judiciously weighed against (a) the direct disubstitution route via terminal alkynes and (b) the conventional desilylation with inexpensive reagents followed by alkynylation using optimal cross-coupling procedures. At present, it may be stated that the successive disubstitution protocol via terminal alkynes, preferably carried out in one pot, does appear to be the method of choice at least in most cases.

3. Use of Alkynes and Alkynylmetals Containing Electron-Withdrawing Groups

As is well-known, electron-withdrawing groups that are directly bonded to either alkenyl or alkynyl π-bonds can exert significant effects on the π-bond reactivity through π-bond polarization, as shown in

Scheme 41



Rubrolide diacetate	X	Y
A	Br	Br
C	Br	H
D	H	Br
E	H	H

Scheme 42. For the sake of simplicity and clarity, the ester (COOR) group is shown as a representative electron-withdrawing group. General effects of placing a halogen or a related substituent in the α- or β-position of the alkenyl group and of placing a metal (or hydrogen) in the β-position of the alkynyl group on the Pd-catalyzed cross-coupling, for example, may

Table 12. Pd-Catalyzed Cross-Coupling of Electron Deficient Alkynes with Aryl, Alkenyl, and Alkynyl Electrophiles

Alkyne	Organic Electrophile	Product Yield,[a] % Negishi (M = ZnBr) Procedure Zn-II[b]	Sonogashira (M = H) Procedure Cu-Ia[c]	Sonogashira (M = H) Modified Cond.
Aryl Electrophiles[204]				
MeOOC—≡—M	IPh	95(99)	<1	98[d]
MeOOC—≡—M	IC_6H_4Br-*m*	91(94)	<1	33[d]
MeOOC—≡—M	IC_6H_3(Me-2)(OMe-4)	87(89)	<1	3[d]
n-PentOC—≡—M	IPh	95(98)	<1	[e]
c-HexOC—≡—M	IPh	82(85)	<1	65[f]
PhOC—≡—M	IPh	94(95)	<1	70[f]
Alkenyl Electrophiles[194]				
EtOOC—≡—M	(*E*)-ICH=CHHex-*n*	87	<1	45[d]
EtOOC—≡—M	(*E*)-ICH=C(Me)Hex-*n*	84	<1	23[d]
EtOOC—≡—M	TfO—	86	[e]	[e]
EtOOC—≡—M	TfO— Me	83	[e]	[e]
EtOOC—≡—M	Br— —Hex-*n*	88	<1	27[g]
EtOOC—≡—M	Cl— —Hex-*n*	<1	<1	<1[g]
Alkynyl Electrophiles[194]				
EtOOC—≡—M	I—≡—Hex-*n*	86	[e]	42[d]

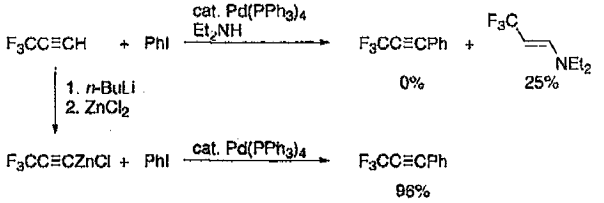
[a] Isolated yields. The numbers in parentheses are GLC yields. [b] Zn-II = 3 mol % Pd $(PPh_3)_4$, 23 °C. [c] Cu-Ia = 5 mol % $Cl_2Pd(PPh_3)_4$, 10 mol % CuI, Et_2NH. [d] K_2CO_3 used as a base (ref 202a). [e] Not performed. [f] Diphenyliodonium salts used in place of PhI. K_2CO_3 used as a base (ref 71). [g] Cs_2CO_3 used as a base (ref 202b).

Scheme 42

be predicted as indicated in Scheme 42. As amply demonstrated in section II.C.2, β-halo-α,β-unsaturated carbonyl and related derivatives serve as generally favorable electrophilic cross-coupling partners in the Pd-catalyzed cross-coupling. By the same token, propynoic esters and related alkyne derivatives containing β-electron-withdrawing substituents as well as their β-halo derivatives may be generally favorable electrophiles but unfavorable nucleophiles.

Alkynes substituted with electron-withdrawing groups have indeed been generally poor nucleophiles in the Sonogashira alkynylation. To make the matter worse, these alkynes can serve as good electrophiles and readily undergo Michael-type additions as unwanted side reactions, e.g., Scheme 43, thereby accentuating the difficulty in their use as nucleophiles. In principle, this difficulty may be overcome or alleviated by generating more nucleophilic alkynylmetals, as demonstrated by the sharply contrasting results shown in Scheme 43.[87]

Scheme 43



Despite a number of attempts to overcome difficulties encountered in the use of propyonic acids and other related derivative in the Sonogashira reaction,[201-203] there do not appear to be generally satisfactory solutions except for the use of the corresponding β-metal-substituted derivatives. Among various metals, Zn offers a combination of (a) high intrinsic reactivity, (b) compatibility with various carbonyl and related functional groups including esters, amides, ketones, and nitriles, and (c) low toxicity. It thus appears to be the metal countercation of choice, although Sn has also been used in some cases. Some representative results obtained with Zn along with contrasting results observed in the corresponding Sonogashira reaction are shown in Table 12.[194,204]

Table 13. Comparison of Zn and Sn in the Pd-Catalyzed Arylation of MC≡CCOOEt

$$ArI + MC{\equiv}CCOOEt \xrightarrow[\text{Ref. 95}]{\text{cat. } Cl_2Pd(PPh_3)_2} ArC{\equiv}CCOOEt$$

Ar	M	Additional Reagent	Solvent	Product Yield,[a] % M = ZnCl	M = $SnBu_3$
Ph	ZnCl	none	THF	56	–
Ph	$SnBu_3$	Et_4NCl	THF	–	48
Ph	$SnBu_3$	Et_4NCl	DMF	–	94
p-Tol	ZnCl	none	THF	67	–
p-Tol	$SnBu_3$	Et_4NCl	DMF	–	23
p-$MeOC_6H_4$	ZnCl	none	THF	54	–
p-$MeOC_6H_4$	$SnBu_3$	Et_4NCl	DMF	–	0
p-$O_2NC_6H_4$	ZnCl	none	THF	61	–
p-$O_2NC_6H_4$	$SnBu_3$	Et_4NCl	DMF	–	27
p-$O_2NC_6H_4$	$SnBu_3$	Et_4NCl	benzene	–	47

[a] Isolated yield.

In some cases, $Bu_3SnC{\equiv}CCOOR$, where R is Me or Et, has also been used in place of Zn derivatives. The results of a comparative study[95] summarized in Table 13 indicate that the yields of 3-arylpropyonate esters observed with Zn were higher than those observed with Sn in all cases except for a single and somewhat puzzling case of PhI observed with DMF as a solvent. The same solvent, which has been shown to be superior to THF in many organozinc cross-coupling reactions, was not used for the alkynylzinc reaction. In the same study, an indirect route involving the Sonogashira alkynylation of $HC{\equiv}CC(OEt)_3$ was also reported,[95] but it does not appear to be a superior alternative to the alkynylzinc reaction.

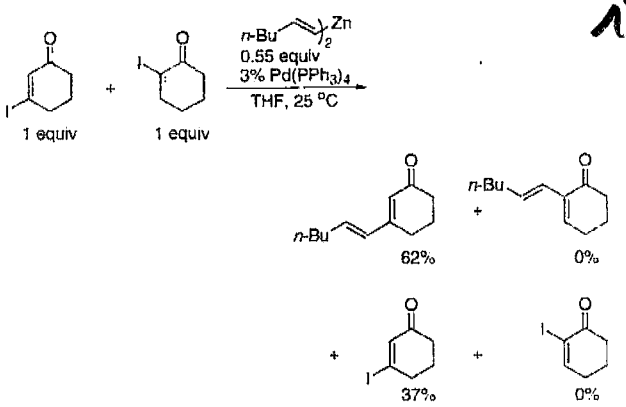
In summary, the Sonogashira reaction including various modifications of alkynes containing various electron-withdrawing groups generally leads to low product yields. On the other hand, the corresponding reactions of alkynylzincs are generally satisfactory. Although the corresponding alkynyltins can provide the same products, their reactions are significantly inferior to those of alkynylzincs in most cases. Preliminary results obtained in the authors' laboratories also indicate that the use of Mg, B, Al, and In does appear problematical,[194] thereby making Zn the countercation of choice.

4. α-Alkynylation of α-Halo-α,β-unsaturated Carbonyl Compounds

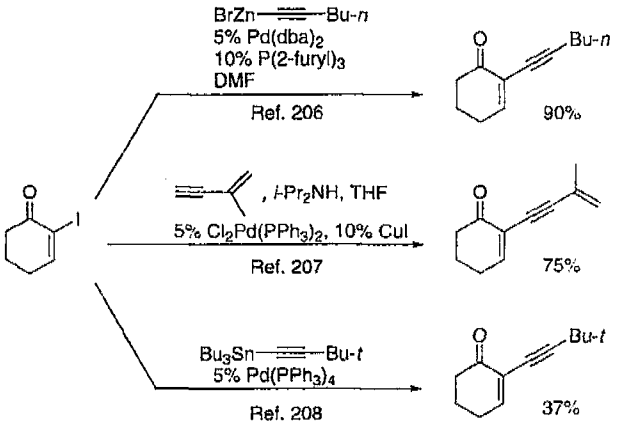
As discussed in sections II.C and III.B.3, α-halo-α,β-unsaturated carbonyl derivatives are generally unfavorable electrophiles. An explicit comparison of 2- and 3-iodo-2-cyclohexenones in the Pd-catalyzed reaction with $(n\text{-BuCH=CH})_2Zn$ reported in 1991[156] clearly demonstrated their highly contrasting behavior, including the instability of 2-iodo-2-cyclohexenone under the Pd-catalyzed cross-coupling conditions (Scheme 44). It was also demonstrated in the same study that the use of Zn as a countercation, either PPh_3 or P(2-furyl)$_3$ as a ligand, and DMF as a solvent would lead to the most favorable results in α-alkenylation. Some other metals, such as Al, Sn, and Zr, were shown to be inferior.[156]

This seminal investigation of α-substitution of α-haloenones by Pd-catalyzed cross-coupling[156] triggered extensive investigations in the 1990s[205] and led to the development of the first highly satisfactory method for α-alkynylation of α,β-unsaturated ketones[205-208] (Scheme 45) and esters[209] (Scheme 46).

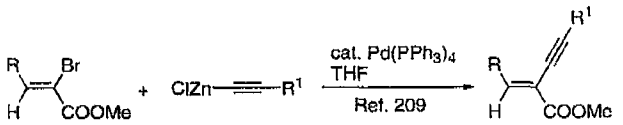
Scheme 44



Scheme 45



Scheme 46



R	R^1	Yield, %
n-Bu	*n*-Hex	62
i-Bu	Ph	71
3,5-$Cl_2C_6H_3$	4-MeC_6H_4	84

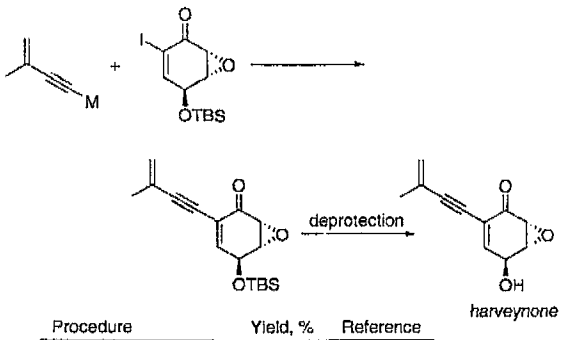
In this context, it should be pointed out that various Pd-catalyzed alkynylation of halogen-substituted heteroarenes, quinones, and related compounds may have been developed earlier. The aromatic and hence robust nature of heteroarene derivatives makes their alkynylation substantially more favorable. Invariably, α-haloquinones are at the same time β-haloquinones due to the presence of two carbonyl groups, which must render them considerably more favorable electrophiles. For these reasons, their reactions, which have indeed been generally very favorable must be distinguished from those cases that are discussed in this section.

On the basis of the generalization presented in Scheme 42, one might predict that α-metal-substi-

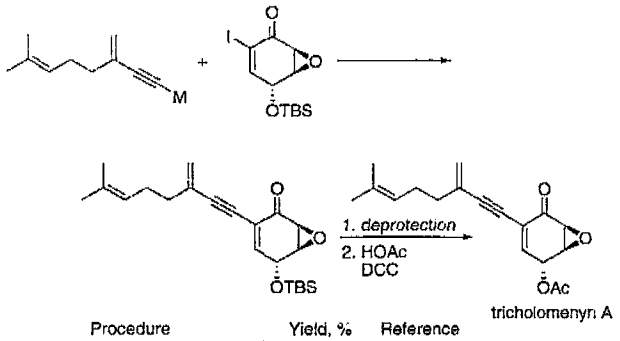
tuted α,β-unsaturated carbonyl derivatives would readily undergo Pd-catalyzed α-alkynylation. Although there does not appear to be any report on this reaction, α-stanno-[204,210-213] and α-zinco-α,β-unsaturated carbonyl derivatives[214,215] have indeed been shown to undergo Pd-catalyzed α-arylation and α-alkenylation.[205] The corresponding α-alkynylation appears to be feasible.

The synthetic usefulness of the Pd-catalyzed α-alkynylation of α,β-unsaturated carbonyl compounds has been eloquently demonstrated in the synthesis of harveynone and tricholomenyn A[206,207,216,217] (Scheme 47).

Scheme 47



Procedure	Yield, %	Reference
M = H cat. $Cl_2Pd(PPh_3)_2$ cat. CuI, i-Pr_2NH	52	207
M = Zn cat. $Pd(dba)_2$, P(2-furyl)$_3$ DMF	73	206



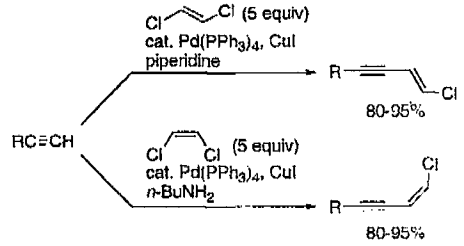
Procedure	Yield, %	Reference
M = H cat. $Cl_2Pd(PPh_3)_2$ cat. CuI, i-Pr_2NH	54	207
M = Zn cat. $Pd(dba)_2$, P(2-furyl)$_3$ DMF	80	206

5. Alkynylation of 1,2-Dihaloethylenes

There are six different 1,2-dihaloethylenes containing Cl, Br, and/or I, each of which can exist as the *E* and *Z* isomers. Of these, (*E*)- and (*Z*)-1,2-dichloroethylenes are the only two that are commercially available as isomerically pure compounds. 1,2-Dibromoethylene is also commercially available but only as a mixture of the *E* and *Z* isomers (typically *E*/*Z* = 2/1). The others are also known, and (*E*)-ICH=CHCl and (*E*)-ICH=CHBr have been shown to be of considerable synthetic utility, as discussed below. On the other hand, the Pd-catalyzed alkynylation of their *Z* isomers as well as of BrCH=CHCl and ICH=CHI remains largely unexplored.

The Pd-catalyzed alkynylation of 5 equiv of commercially available (*E*)- or (*Z*)-1,2-dichloroethylene under the Sonogashira conditions was shown to produce the corresponding chloroenynes in 80−95% yields as early as 1981[218] (Scheme 48). Under the conditions used, the extents of dialkynylation must be insignificant.

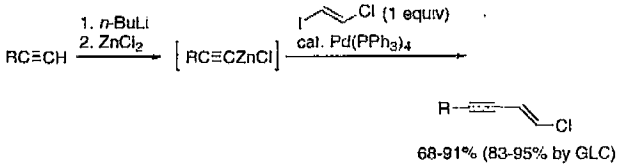
Scheme 48



R = *n*-Pent, CH_2OTHP, CH_2OAc, CH_2SMe, etc.

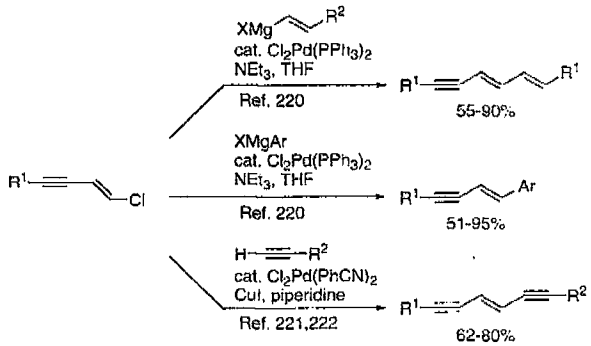
As satisfactory as the results shown in Scheme 48 are, the need for the use of 5 equiv of dichloroethylenes is at best somewhat inconvenient. It would, for example, preclude in situ generation of chloroenynes and their use as intermediates in the same pot without the removal of the excess of dichloroethylene. In 1984, the Pd-catalyzed reaction of alkynylzincs with (E)-ICH=CHCl, readily preparable in 83% yield from acetylene and ICl,[219] was reported as a cleaner and selective alternative permitting direct use of the chloroenyne products in the same pot[59] (Scheme 49).

Scheme 49



(*E*)-Chloroenynes prepared above can be further substituted with alkenyl, aryl, and alkynyl groups by the Pd-catalyzed cross-coupling[220-222] (Scheme 50).

Scheme 50



Another notable use of chloroenynes is their conversion to terminal and internal 1,3-diynes, as shown in Scheme 51 and Table 14.[59,60,195] The same overall conversion of terminal alkynes into unsymmetrically

Scheme 51

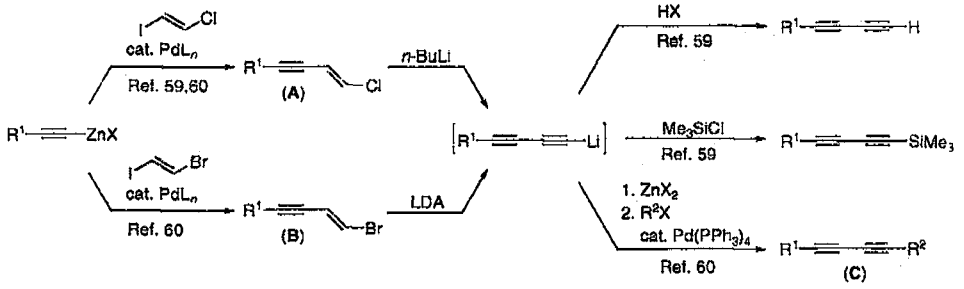


Table 14. Conversion of Terminal Alkynes into Unsymmetrical 1,3-Diynes via Double Pd-Catalyzed Alkynylation

R^1 of $R^1C\equiv CH$	X of	Yield,% of (A) or (B)	R^2 of R^2I	Base	Yield, %, of (C) Based on (A) or (B)	Yield, %, of (C) Based on $R^1C\equiv CH$
Ph	Cl	91	o-EtOOCC$_6$H$_4$	n-BuLi	85	77
p-MeC$_6$H$_4$	Cl	90	p-MeOC$_6$H$_4$	n-BuLi	74	67
p-MeC$_6$H$_4$	Cl	90	p-FC$_6$H$_4$	n-BuLi	88	79
p-FC$_6$H$_4$	Cl	81	p-MeC$_6$H$_4$	n-BuLi	81	66
p-CF$_3$C$_6$H$_4$	Cl	84	p-NO$_2$C$_6$H$_4$	n-BuLi	87	73
n-Hex	Br	74	Ph	LDA	90	67
n-Hex	Br	74	HOOC(Me)C=CH-	LDA	88	65

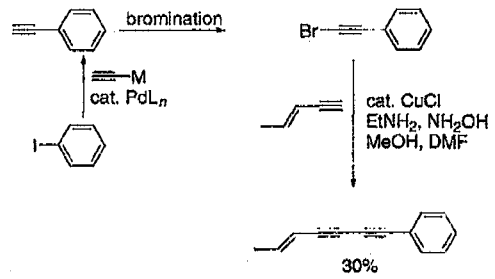
disubstituted conjugated diynes can also be achieved by the preparation of bromoenynes followed by their conversion to conjugated diynes.[60]

The high-yielding and strictly pair-selective nature of the new protocol in comparison with the Cadiot–Chodkiewicz reaction may be seen in comparative data shown in Scheme 52.[60] Both methods require three synthetic operations starting from (*E*)-3-penten-1-yne, iodobenzene, and acetylene, but the Pd-catalyzed double cross-coupling method is not only completely pair-selective but also considerably higher-yielding. Similar differences have been observed also in several other comparative experiments.[60]

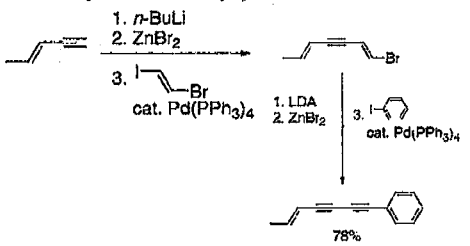
The corresponding reactions of (*Z*)-ClCH=CHCl have yielded similar results, as those shown in Schemes 49 and 50.[223] Particularly noteworthy is the use of (*Z*)-ClCH=CHCl in the synthesis of complex natural products containing a (*Z*)-enediyne moiety, such as calicheamicin γ_1^I, esperamicin A_1, and dynemicin A[224–233] (Scheme 53). This approach to the synthesis of enediynes should be compared with an alternative approach involving the use of iodoalkynes

Scheme 52

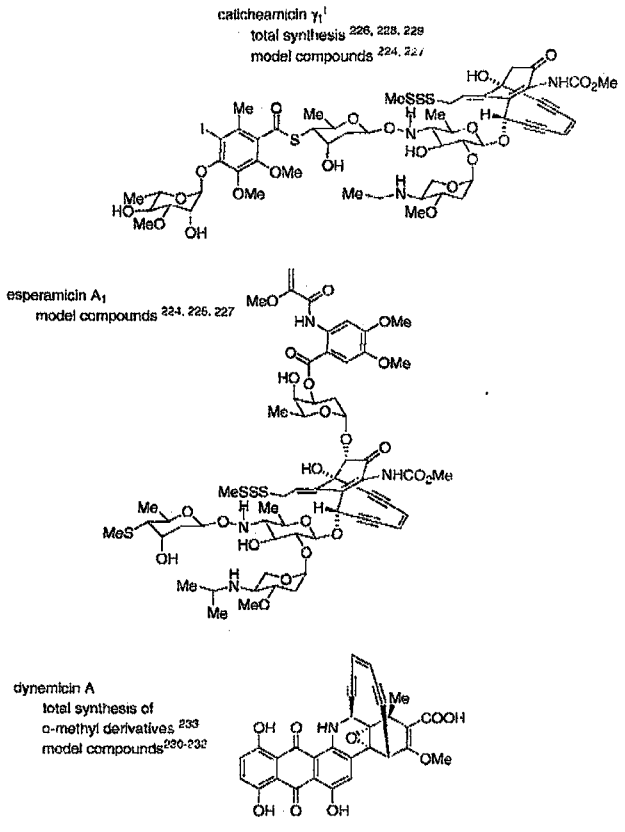
Cadiot-Chodkewicz Protocol



Pd-Catalzyed Double Alkynylation Protocol



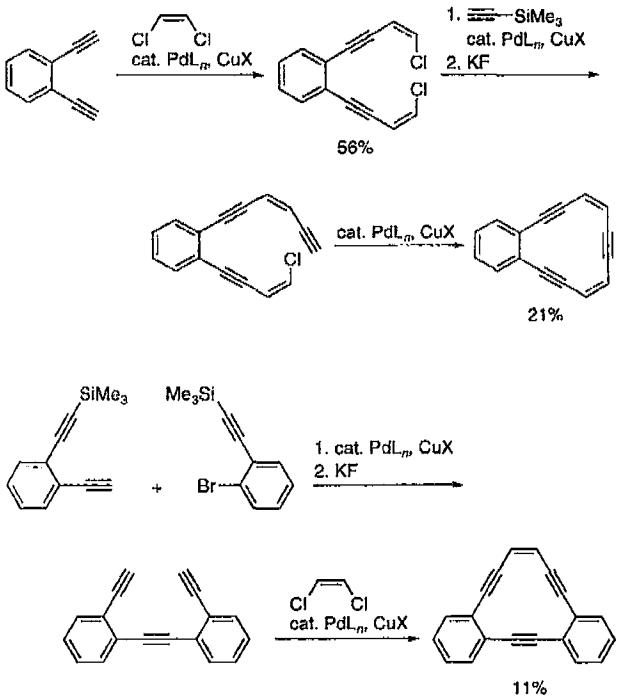
Scheme 53



and (*Z*)-$Me_3SnCH{=}CHSnMe_3$[234-236] discussed later in section III.B.8.

Also interesting is the synthesis of 12-membered trienetriynes, as shown in Scheme 54.[237]

Scheme 54

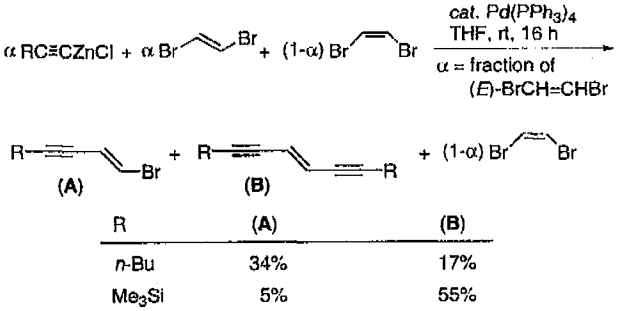


Although the results obtained with (*E*)- and (*Z*)-ClCH=CHCl and (*E*)-ICH=CHCl described above are generally favorable, the scope of Pd-catalyzed cross-coupling reactions of chloroenynes is nevertheless limited due to the intrinsically low reactivity of the C−Cl bonds in Pd-catalyzed cross-coupling. It is therefore desirable to generate bromoenynes by Pd-catalyzed alkynylation of BrCH=CHBr or ICH=CHBr.

The Pd-catalyzed reaction of a commercially available mixture of (*E*)- and (*Z*)-1,2-dibromoethylenes, typically a 2:1 mixture of the *E* and *Z* isomers, with alkynylzinc chloride such that the molar ratio of the alkynylzinc chloride to (*E*)-1,2-dibromoethylene is 1:1 gives a mixture of the desired bromoenyne and 3-ene-1,5-diyne, both of which are >99% *E*. So, the reaction takes place nearly exclusively with (*E*)-1,2-dibromoethylene. Thus, the reaction is highly stereoselective, but it generally produces the desired bromoenynes in low yields largely due to the formation of 1,2-dialkynylated products, as shown in Scheme 55.[238]

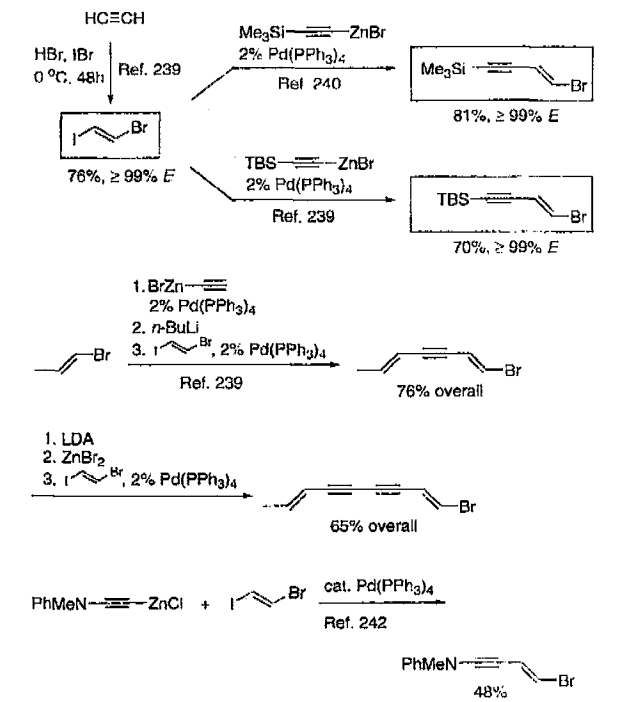
In contrast with 1,2-dibromoethylene, (*E*)-1-bromo-2-iodoethylene can selectively be monosubstituted to give the desired (*E*)-bromoenynes in high yields[60,239,240] (Scheme 56). Particularly noteworthy are the reactions of $Me_3SiC{\equiv}CZnX$ and $TBSC{\equiv}CZnX$, where X = Br or Cl, producing the corresponding (*E*)-bromoenynes in 81% and 70% yields, respectively. The former case should be compared with the corresponding reaction in Scheme 55 producing the same product only in 5% yield. Also important is the development of a vastly improved method for the preparation of ≥99% (*E*)-ICH=CHBr in 76% yield by

Scheme 55



R	(A)	(B)
n-Bu	34%	17%
Me_3Si	5%	55%

Scheme 56



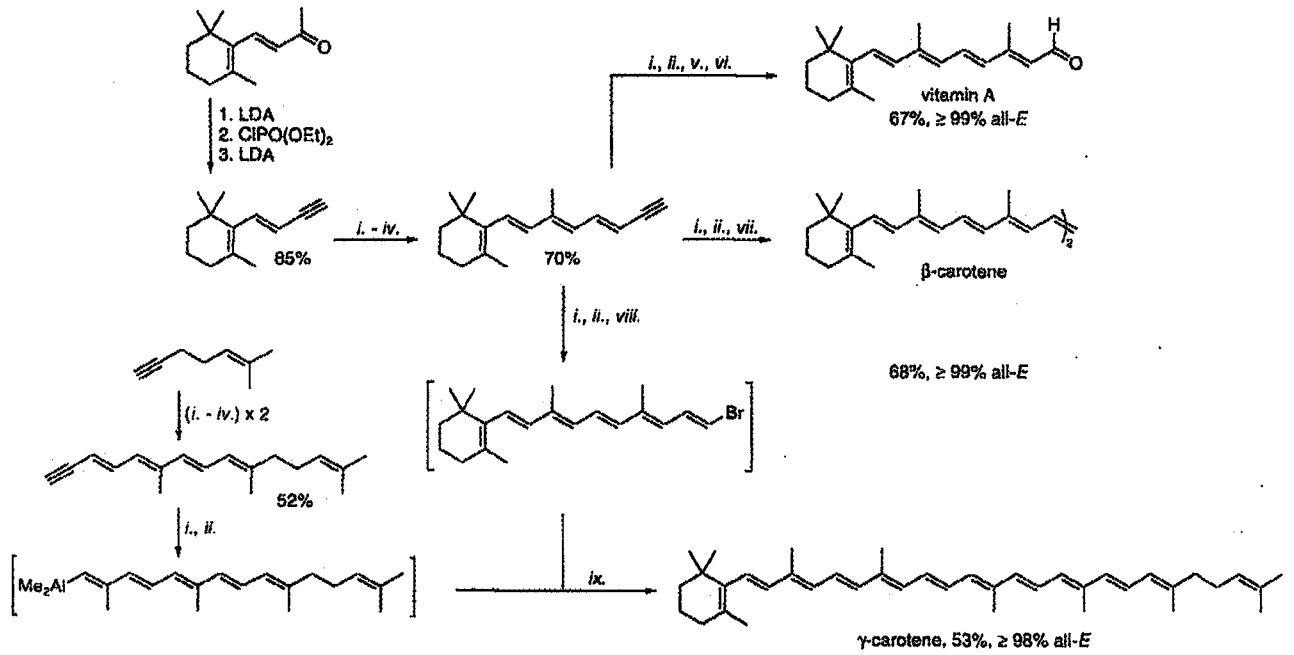
the reaction of acetylene with commercially available IBr and HBr.[60,239,240] Its previous synthesis using a mixture of I_2 and Br_2 produced ICH=CHBr only in 45% yield.[241]

Both (*E*)-$Me_3SiC{\equiv}CCH{=}CHBr$ and (*E*)-$TBSC{\equiv}CCH{=}CHBr$ have proved to be very useful C_4 synthons in the synthesis of carotenoids, retinoids[240] (Scheme 57), conjugated oligoenes that can serve as intermediates for a number of oligoene macrolide antibiotics,[243] such as amphotericin B (Scheme 58), and many other complex natural products, such as xerulin[239] (Scheme 59).

More recent studies directed toward the synthesis of some other natural products have not only yielded the following favorable results obtained by the Pd-catalyzed alkynylation of (*E*)-ICH=CHBr but also revealed that these compounds cannot be prepared by the Sonogashira reaction (Scheme 60).[194]

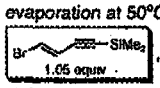
Furthermore, some of the results shown in Scheme 60 led to a suspicion that the difficulty encountered in the Sonogashira reaction might stem, in part, from the use of (*E*)-ICH=CHBr despite many favorable results obtained with 1,2-dichloroethylenes[218] (Scheme 48). As indicated earlier in Scheme 34, (*E*)-ICH=CHBr may not be readily used in the Sonogashira

Scheme 57



i. Me_3Al (2 equiv), Cp_2ZrCl_2, $(CH_2Cl)_2$, 23 °C, 4 h.

ii. evaporation at 50°C and < 0.5 mmHg.

iii.  , $ZnCl_2$, THF, 2.5 mol% $Pd_2(dba)_3$, 10 mol% P(2-furyl)$_3$, DMF, 23 °C, 8 h.

iv. K_2CO_3, MeOH, 23 °C, 3 h.

v. THF, *n*-BuLi, 23 °C, 0.5 h.

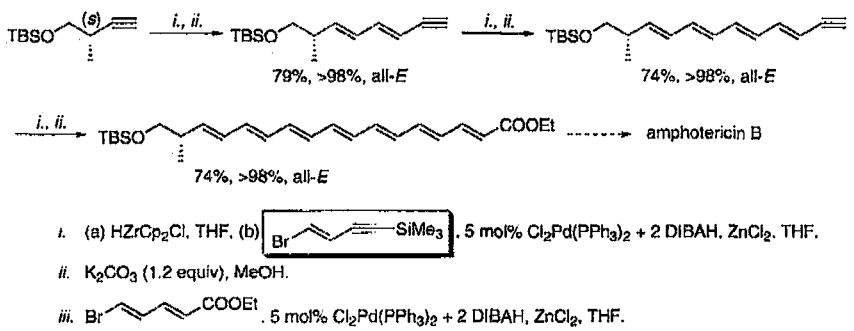
vi. $(CHO)_n$ (3 equiv), 23 °C, 5 h.

vii.  (0.5 equiv), $ZnCl_2$, THF, 2.5 mol% $Pd_2(dba)_3$,10 mol%P(2-furyl)$_3$, DMF, 23 °C, 8 h.

viii.  (1.05 equiv), $ZnBr_2$, THF, 5 mol% $Pd(PPh_3)_4$, DMF, 23 °C, 2 h.

ix. $ZnCl_2$, THF, 2.5 mol% Pd(dba)$_3$,10 mol% P(2-furyl)$_3$, DMF, 23 °C, 6 h.

Scheme 58



i. (a) $HZrCp_2Cl$, THF, (b) , 5 mol% $Cl_2Pd(PPh_3)_2$ + 2 DIBAH, $ZnCl_2$, THF.

ii. K_2CO_3 (1.2 equiv), MeOH.

iii. , 5 mol% $Cl_2Pd(PPh_3)_2$ + 2 DIBAH, $ZnCl_2$, THF.

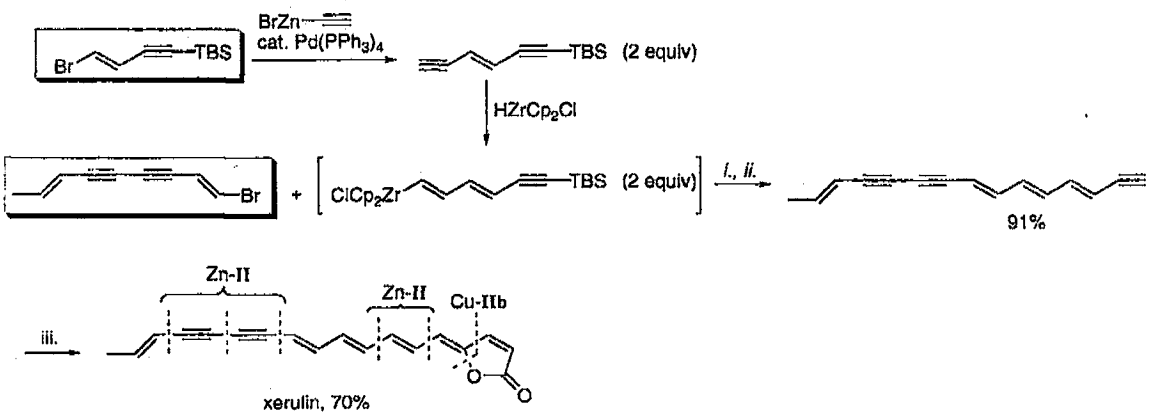
reaction due to extensive alkyne dimerization that cannot be alleviated by degassing and/or addition of radical inhibitors.

Very little is currently known about the use of BrCH=CHCl and ICH=CHI. However, BrCH=CHCl does not appear to offer any readily expected advantage over either ClCH=CHCl or ICH=CHCl. Judging from the results obtained with 1,2-dibromoethylenes (Scheme 55), competitive disubstitution is likely to be a serious side reaction with ICH=CHI. The current scope of the Pd-catalyzed cross-coupling with various 1,2-dihaloethylenes may be summarized as shown in Table 15.

6. Alkynylation of Sterically Demanding Organic Electrophiles

It has already been discussed in section III.B.2 that aryl halides in which one or both of the ortho positions are substituted generally suffer from complications in steric origin and that alkynylmetals containing Zn can cope with steric problems better than those containing Mg or Sn. A recent report on the synthesis of hexaalkynylbenzenes[244] (Scheme 61) suggests that the Negishi protocol is also superior to the Sonogashira reaction in coping with problems stemming from steric hindrance.

Scheme 59

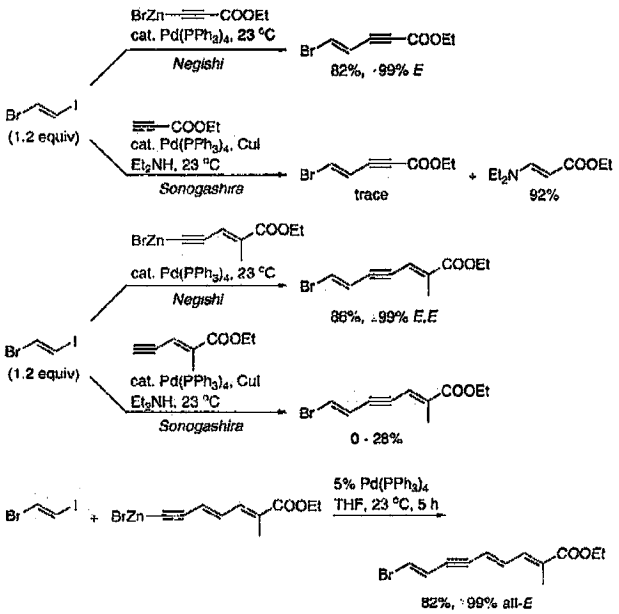


i. $ZnCl_2$, 5 mol% $Cl_2Pd(PPh_3)_2$ + 2 DIBAH.

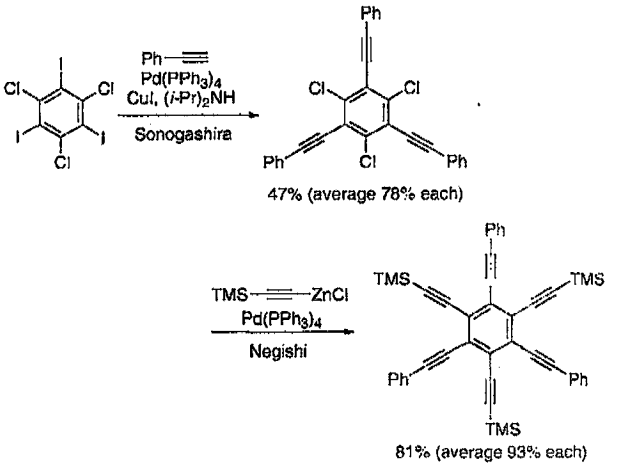
ii. Bu_4NF

iii. , 5 mol% CuI, NEt_3 (4 equiv), 1 mol% BHT, degassing.

Scheme 60



Scheme 61



7. Cascade Processes Involving Pd-Catalyzed Alkynylation

Cascade processes in this review may be defined as those chemical processes involving a series of two or more consecutive steps occurring under one set of reaction conditions. Those cascade processes that are considered in this section include one or more Pd-catalyzed alkynylation steps. The other steps may or may not be Pd-catalyzed. One aspect of critical importance in such cascade processes is the correct queuing of all of the steps, which would require an appropriate rate, neither too fast nor too slow, for each step.

a. Catalytic Carbopalladation–Alkynylation Cascade Processes. Trapping of "living" alkenylpalladium derivatives generated via carbopalladation of alkynes with organometals is a potentially useful synthetic operation. Although some results observed with organometals containing B and Zn were published in the late 1980s,[245-248] critical factors remained to be clarified. A systematic screening of metal counteractions summarized in Scheme 62[249] indicated, for the first time, that the desired carbopalladation–alkynylation cascade process is disfavored by fast Pd-catalyzed alkynylation reactions involving Zn or Cu but favored by slow alkynylation reactions involving Sn and B. It was also clearly shown that "premature" alkynylation before cyclic carbopalladation was the origin of difficulties with Zn and Cu.

The cyclic carbopalladation–alkynylation cascade process involving alkynylations has since been applied to the formation of the A ring of neocarzinostatin chromophore, as shown in Scheme 63.[250-252]

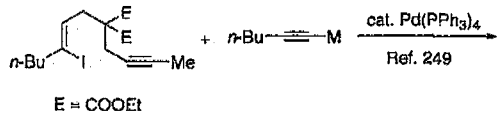
b. Catalytic Alkynylation–Lactonization Cascade Processes. The Pd-catalyzed alkynylation of (*Z*)-β-haloacrylic acids containing I or Br under the Sonogashira coupling conditions does not produce the expected cross-coupling products to any detectable extent. It instead produces (*Z*)-γ-alkylidenebutenolides,[199] thereby providing an unprecedentedly efficient and attractive route to (*Z*)-γ-alkylidenebutenolides. The use of at least 4 equiv of PPh_3 relative to Pd and MeCN as a solvent was shown to be desirable

36 138 139

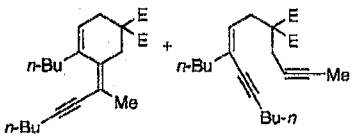
Table 15. Current Scope of the Pd-Catalyzed Alkynylation with 1,2-Dihaloethylenes

1,2-dihaloethylene	commercial availability or method of synthesis	scope and limitations
(*E*)-ClCH=CHCl and (*Z*)-ClCH=CHCl	• both isomers commercially available	• selective monosubstitution with an excess (5-fold) of the reagent generally satisfactory • widely used • second substitution of Cl by cross-coupling potentially problematic
BrCH=CHCl	• not commercially available • preparable by treatment of $Br_2C=CCl_2$ with Zn	• little or nothing known about its cross-coupling
ICH=CHCl	• not commercially available • the *E* isomer preparable by treatment of HC≡CH with ICl (83% yield)	• monosubstitution potentially more selective and favorable than with ClCH=CHCl • wide application expected • same limitation in the second cross-coupling as observed with ClCH=CHCl
BrCH=CHBr	• commercially available as an *E* and *Z* mixture	• selective monosubstitution problematic and hence of limited synthetic usefulness
ICH=CHBr	• commercially available (*E* isomer) • the *E* isomer preparable by treatment of HC≡CH with IBr and HBr (76% yield)	• selective monosubstitution with RC≡CZnX • wide synthetic scope and considerable utility expected
ICH=CHI	• not commercially available • the *E* isomer preparable by treatment of HC≡CH with I_2 and Al_2O_3 (33% yield)	• little known about its cross-coupling

Scheme 62

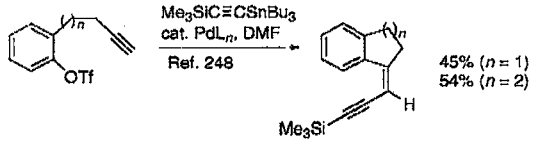


E = COOEt



n-Bu—≡—M	Conditions	Yield, % (A)	Yield, % (B)
$(n\text{-Bu}{-}{\equiv}{-})_2$Zn	THF, 25 °C	8	75
n-Bu—≡—H	CuI (5 mol%) *n*-$BuNH_2$ (5 equiv) benzene, 25 °C	16	49
n-Bu—≡—BBu_3Li	THF, 25 °C	45	[a]
n-Bu—≡—$SnMe_3$	THF-HMPA, reflux	73	<5

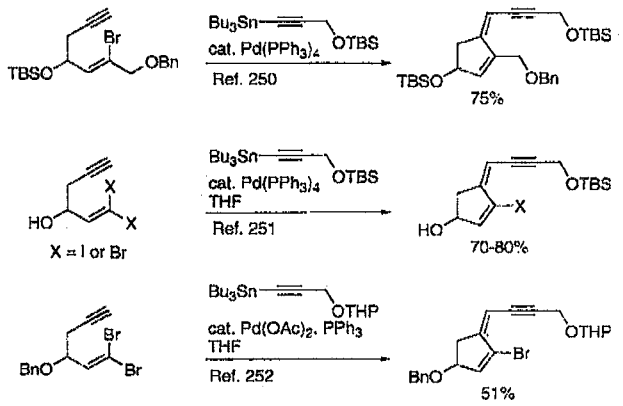
[a] Not determined.



for high yields of (*Z*)-γ-alkylidenebutenolides.[200] As already discussed in sections III.B.1 and III.B.2, this cascade process has been applied to the synthesis of a number of natural products containing (*Z*)-γ-alkylidenebutenolides.[109,110,200,239,253,254]

In sharp contrast with the cascade process mentioned above, the Negishi alkynylation of zinc salts of (*Z*)-haloacrylic acids with alkynylzinc derivatives

Scheme 63

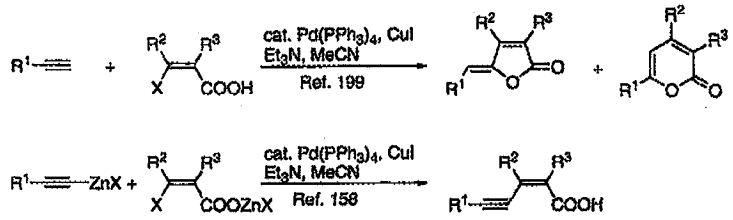


produces the expected cross coupling products in excellent yields (Scheme 64).[158,255] Thus, in cases where 2-en-4-ynoic acids are desired, the Negishi protocol may be used, even though the use of esters in place of free carboxylic acids has been shown to permit cross-coupling without lactonization[256] under either the Sonogashira or the Negishi coupling conditions.

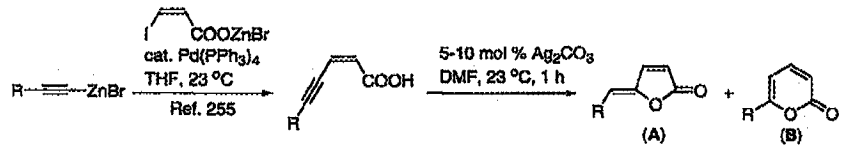
Although very attractive, the Sonogashira–Lu alkynylation–lactonization cascade process has also been shown to be complicated by various side reactions. Alkyne homodimerization as a side reaction was already discussed in section III.B.1. Another widely observed side reaction is formation of six-membered 2*H*-pyran-2-ones. With relatively unhindered alkyl groups as R^1, the ratio of 5*H*-furan-2-ones to 2*H*-pyran-2-ones tend to be only 2–4,[255] as shown in Scheme 64.

On the other hand, 2-en-4-ynoic acids preparable by the Pd-catalyzed alkynylation with alkynylzinc derivatives typically in over 90% yields can selectively be converted to 5*H*-furan-2-ones in excellent

Scheme 64

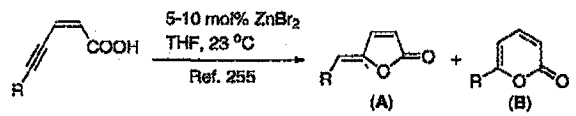


R	(A) + (B), %	(A) : (B)
n-Hex	77	64 : 34
i-Pr	75	80 : 20
c-Hex	65	80 : 20
t-Bu	76	97 : 3



R	(A) + (B), %[a]	(A) : (B)
n-Hex	90	96 : 4
i-Pr	93	95 : 4
c-Hex	88	97 : 3
t-Bu	86	98 : 2

[a] Based on R—≡



R	(A) + (B), %[a]	(A) : (B)
n-Hex	90	6 : 94
i-Pr	92	4 : 96
c-Hex	86	4 : 96
t-Bu	86	34 : 66

[a] Based on R—≡

yields by using Ag_2CO_3[257] as a catalyst[255] (Scheme 64). Furthermore, it has also been demonstrated recently that 2-en-4-ynoic acids can selectively be converted to 2*H*-pyran-2-ones in the presence of a catalytic amount of $ZnBr_2$ without any transition metal catalyst[255] (Scheme 64). It should be noted that, under the Sonogashira reaction conditions, 2*H*-pyran-2-ones have been obtained only as minor products.

In summary, the preparation of 2-en-4-ynoic acids by the Negishi coupling permits their selective and high-yield conversion to either (*Z*)-5-alkylidene-5*H*-furan-2-ones (**A**) or 5-alkyl-2*H*-pyran-2-ones (**B**).

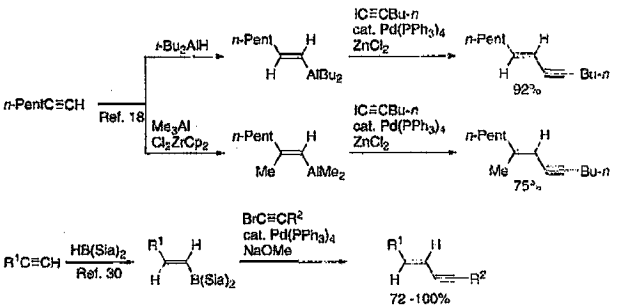
8. Pd-Catalyzed Alkynylation with 1-Halo-1-alkynes

The use of 1-halo-1-alkynes in the Pd-catalyzed alkynylation was reported first by Negishi in 1978[18] by using alkenylalanes as nucleophilic reagents. This was soon followed by the development of the corresponding reaction of alkenylboron derivatives[30] (Scheme 65). It should be clearly noted that this option is not available to the Sonogashira reaction-based methodology. As might be expected, aryl- and alkenylzinc derivatives also participate readily in this reaction (Scheme 66). More recently, related reactions of organotin compounds have also been developed, as shown in Scheme 67.

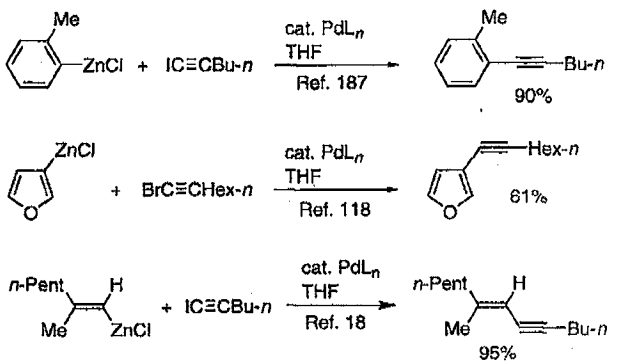
9. Recent Modifications of the Sonogashira and Negishi Alkynylation Protocols

One of the commonly perceived advantages of the Sonogashira and other Heck-type alkynylation pro-

Scheme 65



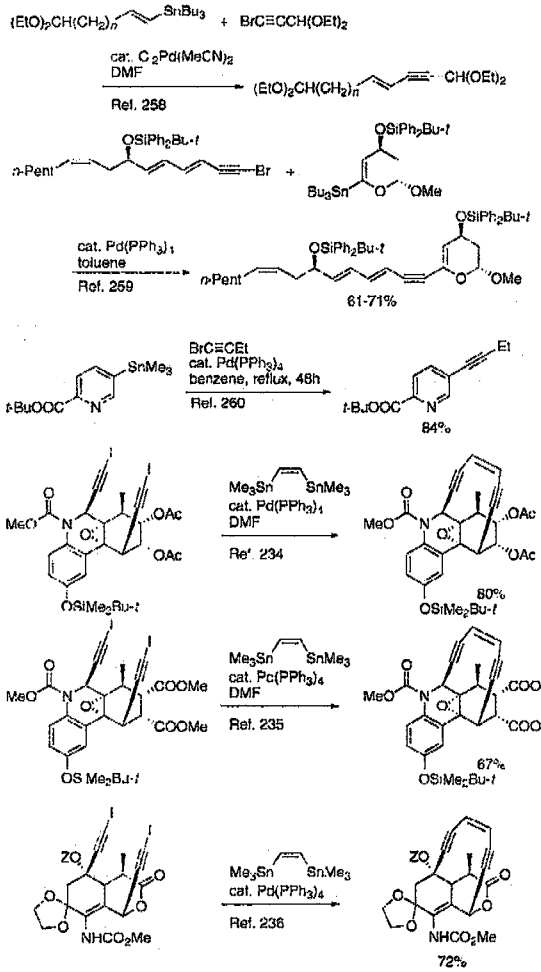
Scheme 66



tocols over the Negishi and other related alkynylation reactions involving the stoichiometric quantities of alkynylmetals is the direct use of terminal alkynes without stoichiometric metalation. In the Sonogash-

38

Scheme 67

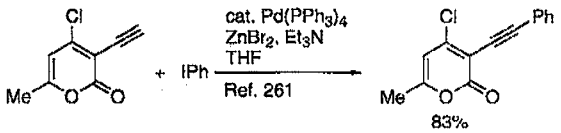


ira reaction, a catalytic amount of CuI or CuCl is used. What is often overlooked is that the Sonogashira and related protocols do require an amine or an alternate base in the stoichiometric quantity. Frequently encountered Michael-type addition reactions arising from the use of amines and other bases should also be recalled. Another widely perceived advantage of the Sonogashira protocol is its compatibility with water and other protonated solvents as well as air. With respect to air, however, difficulties associated with alkyne dimerization, which appears to be a radical process at least in some cases, must be kept in mind, e.g., Schemes 33 and 34, as the use of degassing and/or radical inhibitors might more than offset the advantage mentioned above.

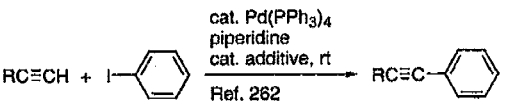
Despite all of these, selection of protocols and reagents is seldom made on scientifically sound and fully rational grounds. For example, general toxicity associated with Sn has long been known. And yet, Sn has been clearly one of the most widely used metals until recently. As discussed earlier, Sn does offer special chemical advantages in some cases (Schemes 62, 63, and 67). In the other cases, however, its use will have to be minimized in the future. Continuous changes and efforts to improve and optimize various protocols are being made and will be made in the future. Along with alkynylmetals containing Li, Na, K, Mg, Si, Sn, and so on, those containing Zn, B, and In should also become commercially available.

Along a more scientific and chemical vein, some efforts to use directly terminal alkynes along with stoichiometric or substoichiometric amounts of Zn salts and one or more equivalents of a base, such as Et_3N, have recently been reported (Schemes 68–71).

Scheme 68

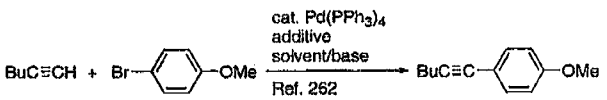


Scheme 69



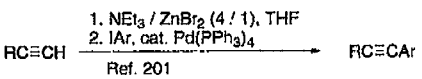
R	Additive	Yield, %
Ph	cat. $ZnCl_2$, I_2	80-94
Ph	cat. $ZnCl_2$, NaI	94
Ph	cat. $ZnCl_2$, NaN_3	100
Bu	cat. $ZnCl_2$, NaI	94
Me_3Si	cat. $ZnCl_2$, NaI	100
$HC{\equiv}C(CH_2)_4$	cat. $ZnCl_2$, NaI	100
$HOCH_2$	cat. $ZnCl_2$, NaI	100

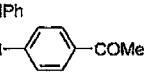
Scheme 70



Additive	Solvent / Base	Yield, %
cat. $ZnCl_2$, NaI	piperidine	86
cat. $ZnCl_2$, NaI	Et_3N, DMSO, DBU	88
cat. Zn dust, NaI	Et_3N, DMSO, DBU	100

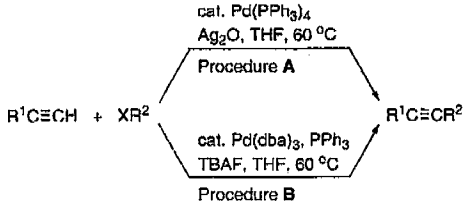
Scheme 71



RC≡CH	IAr	Yield, %
n-HexC≡CH	IPh	95
$Me_3SiC{\equiv}CH$	IPh	97
n-HexC≡CH		95
n-HexC≡CH	IC_6H_4OMe-*p*	87
n-HexC≡CH	$IC_6H_4NO_2$-*p*	89
MeOOCC≡CH	IPh	75

Two other Pd-catalyzed alkynylation protocols reported recently involve the stoichiometric use of Ag_2O and TBAF[39] (Scheme 72). Since the reagents and catalysts used in the two protocols are different, comparison between the two cannot be made in a reliable manner. Even so, the two appear to be of comparable merits, but their advantages over the

Scheme 72



R^1	XR^2	Yield, % A	Yield, % B
n-Hex	IPh	90	59
$HOMe_2C$-	IPh	73	64
t-Bu	IC_6H_4Ac-*p*	87	-
Ph	IPh	60	75
Ph	(*E*)-BrCH=CHPh	79	-
Ph	IC_6H_4OMe-*p*	-	83
Ph	IC_6H_4CN-*p*	-	86
Me_3Si	IPh	79	-

widely used methods, such as the Sonogashira reaction, remain to be demonstrated.

IV. Other Topics

A. Recent Methodological Development. Search for Superior Phosphines and Other Ligands

As one examines the general equation of the Pd-catalyzed alkynylation with either terminal alkynes or alkynylmetals (Scheme 1), it is noticeable that most of the changeable parameters in the equation have been widely varied not only for delineation of the scope and limitations of this synthetic methodology but also for optimization of reaction conditions. In competitive situations, factors permitting selection of optimal parameters among various available alternatives have been reasonably well delineated. As one thumbs through this article, one should also be struck by the fact that the great majority of Pd catalysts used for alkynylation are Pd−PPh_3 complexes, represented by $Pd(PPh_3)_4$ and $Cl_2Pd(PPh_3)_2$. Since PPh_3 is currently one of the least expensive phosphines or even the least expensive, its use is very reasonable as long as it leads to highly satisfactory results.

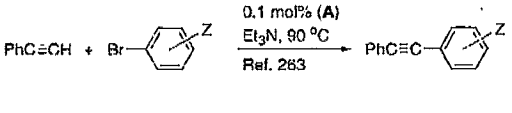
Looking into the future, however, one should note that there still is considerable room for improvement. Thus, the leaving groups in organic electrophiles have been mostly I, with Br and OTf accounting for most of a relatively small number of the remaining cases. In fact, Cl has been used in some cases, but the current scope of the Pd-catalyzed alkynylation of organic chlorides is still rather limited. In this respect, (i) optimization of ligands and Pd complexes, (ii) screening and development of superior additives including cocatalysts, and (iii) screening and development of solvents and other reaction parameters are highly desirable. Other more technological developments, such as immobilization of Pd catalysts, cocatalysts, and other additives, should also be made.

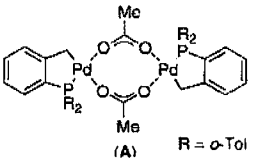
Closely related are the issues of catalyst turnover rate (TOR) and turnover number (TON). At present, product yield is used as a criterion for comparison. In fact, the turnover numbers determined in a limited number of cases have rarely exceeded 1000. It is desirable to attain TONs exceeding 10^4 or 10^5.

With these goals in mind, substitution, of PPh_3 with other phosphines, such as TFP and dppf, has been made but only in a limited number of cases. In some other cases, nonphosphine ligands, such as MeCN and PhCN, have also been used in place of PPh_3. Nonetheless, systematic and more intensive search for superior phosphines and other ligands may have been made only within the past several years.

In a recent investigation of the Heck alkynylation shown in Scheme 73,[263] the use of a palladacycle(A) was found to lead to TONs ranging from 800 to 8000.

Scheme 73



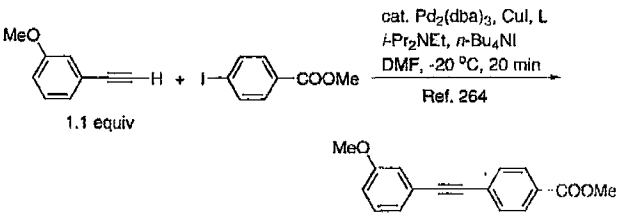


(A) R = *o*-Tol

Z	Time, h	Yield, %	TON
p-Ac	5	99	990
p-Ac	24	80	8000
p-Cl	16	90	900
p-Bu	24	80	800

In a favorable case of Pd-catalyzed alkynylation by the Sonogashira reaction shown in Scheme 74,[264]

Scheme 74



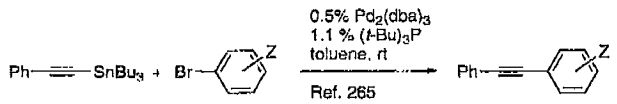
L (20 mol %)	Yield, %
PPh_3	32
$(p\text{-Tol})_3P$	39
$(o\text{-Tol})_3P$	52
$(Mesityl)_3P$	100

optimization of phosphine ligands was conducted at −20 °C. The results indicate that a sterically hindered phosphine, i.e., tris(mesityl)phosphine, produces a catalytically more active Pd complex for the reaction. Interestingly, Ph_3PO, PhOH, and 2,6-$(t\text{-Bu})_2C_6H_3OH$ are nearly as effective as $(mesityl)_3P$.

It has recently been demonstrated that $(t\text{-Bu})_3P$ is effective in the Pd-catalyzed cross-coupling reactions of organic bromides and chlorides.[265] The results summarized in Scheme 75 indicate that the improved procedure reported in this study can very satisfactorily handle sterically hindered and/or electronically deactivated aryl bromides.

It does appear that sterically hindered phosphines, such as $(mesityl)_3P$ and $(t\text{-Bu})_3P$, might prove to be useful in further improving the Pd-catalyzed alkynylation, but many more persuasive developments and examples will be needed to fully justify the use of structurally more elaborate and/or expensive phosphines.

Scheme 75

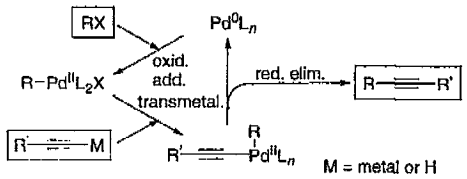


Z	Yield, %
p-Ac	97
o-Me	97
2,4-$(MeO)_2$	83
2,6-Me_2	95

B. Mechanistic Aspects of the Pd-Catalyzed Alkynylation

The standard three-step catalytic cycle consisting of (i) oxidative addition of a Pd(0) complex with an organic electrophile, (ii) transmetalation to generate diorganopalladium derivatives, and (iii) their reductive elimination to produce the desired alkynes with concomitant regeneration of the Pd(0) complex (Scheme 76) has been proposed already in the 1970s

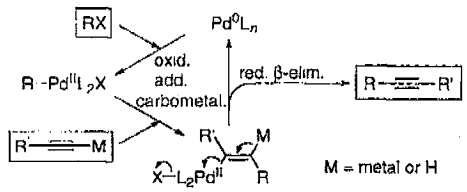
Scheme 76



for both the Sonogashira reaction[5] and the Negishi alkynylation with alkynylzincs and related alkynylmetals.[15,16] Although this mechanism has never been rigorously established, it has been repeatedly cited and profitably used as a basis for various discussions and predictions. A generally accepted notion of nucleophilic characteristics of Pd(0) complexes and electrophilic nature of Pd(II) complexes has also served as a useful guiding principle.

An alternative catalytic cycle consisting of (i) the same oxidative addition as in Scheme 76, (ii) carbopalladation, and (iii) reductive β-dehydropalladation was also proposed by Negishi in 1978[15,16] (Scheme 77). Indeed, carbopalladation of alkynes is a widely

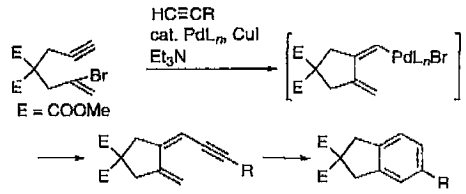
Scheme 77



observed process[266] which is known to occur with both terminal and internal alkynes and expected to be a fundamentally favorable process with election-rich metalated alkynes, provided that it can favorably compete with potentially competitive transmetalation involving the C–M σ bond. Furthermore, β-metalloorganopalladium derivatives thus formed is expected to undergo facile reductive β-elimination to produce the desired alkyne with concomitant regeneration of Pd(0) complex. Thus, this mechanism is highly plausible, but it has not attracted much attention. Nor has it been ruled out.

Since the final alkyne product does not retain any structural features of pertinent organopalladium intermediates permitting discrimination of the two different mechanisms shown in Schemes 76 and 77, it would be desirable to trap any organopalladium intermediates that are unique to one or the other mechanism. Torii reported in 1991[267] a cascade cyclization reaction of a bromoenyne under the conditions of the Sonogashira reaction shown in Scheme 78 and interpreted the results by a mechanism

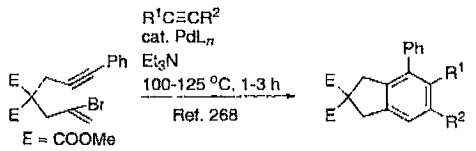
Scheme 78



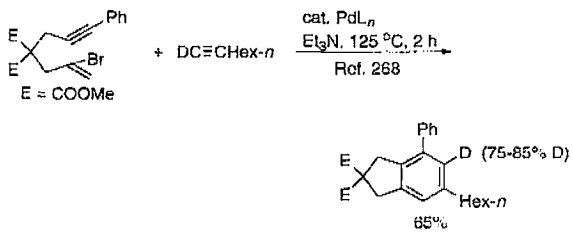
consisting of (i) oxidative addition, (ii) cyclic carbopalladation, (iii) cross-coupling, and (iv) either Pd-catalyzed or uncatalyzed electrocyclic process to produce a benzene derivative. However, no firm experimental evidence was presented. Nor was the process of the dienyne formation specified and clarified. Only terminal alkynes were used as the second alkyne reagent.

Two years later Negishi[268] reported a related Pd-catalyzed cyclization of bromoenynes without the use of a Cu(I) salt. Not only terminal monoalkynes but also internal alkynes, including alkynylsilanes, were used, and all produced the expected arenes in comparable yields ranging from 62% to 83% (Scheme 79).

Scheme 79



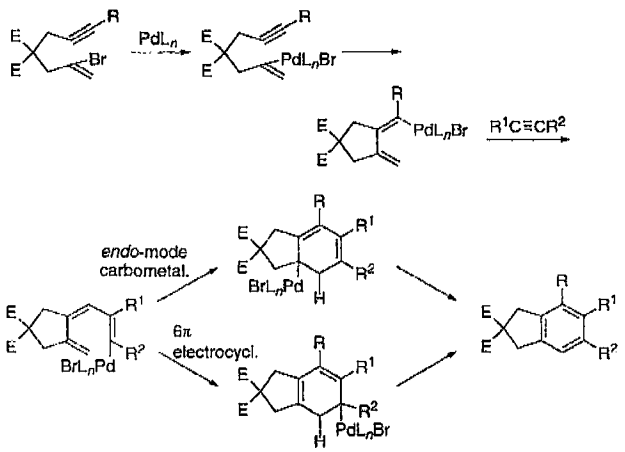
$R^1C{\equiv}CR^2$	Yield, %	Regioselectivity, %
HC≡CHex-*n*	67	≥ 93
HC≡CPh	73	≥ 92
n-HexC≡CSiMe_3	63	≥ 98
PhC≡CSiMe_3	62	≥ 98
n-PrC≡CPr-*n*	83	–
PhC≡CPh	62	–



In cases where internal alkynes are used as the second alkyne, the mechanism via the formation of dienynes shown in Scheme 78 cannot be operative.

To accommodate all of the results in a unified manner, Scheme 80 was proposed. Although not

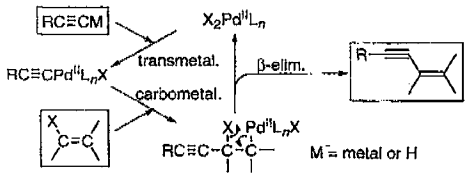
Scheme 80



supported firmly by experimental evidence, this mechanism appears to be imminently plausible for the reactions of internal alkynes. Apropos of the present mechanistic discussion, if this mechanism should prove to be operative in the cases of terminal alkynes as well, it would amount to a long-sought trapping of the intermediate formed via carbopalladation shown in Scheme 77. This point remains to be fully clarified. However, the use of DC≡CHex-*n* led to a 75−85% D incorporation in the position predicted by the mechanism shown in Scheme 80. Thus, the experimental results are consistent with the carbopalladation mechanism shown in Scheme 77. Since the fate of D based on the mechanism shown in Scheme 76 is not clear, this mechanism cannot yet be ruled out.

In both of the mechanisms shown in Schemes 76 and 77, oxidative addition of a Pd(0) complex with an organic electrophile is considered to be a critical step triggering the desired catalytic cycle. There can, however, be some other mechanistic schemes for Pd-catalyzed alkynylation that may not require the oxidative addition of a Pd(0) complex to an organic electrophile. One such mechanism for alkynylation of alkenyl halides, for example, is shown in Scheme 81. It is not clear to the authors if the mechanism

Scheme 81



shown in Scheme 81 can be ruled out on the basis of currently available experimental data. Inasmuch as such a mechanism goes counter to the currently prevailing mechanistic notion, however, it would be desirable to settle issues such as this as they arise.

The two alternative mechanisms indicated in Schemes 77 and 81 pose two fundamental questions about two steps, i.e., transmetalation and oxidative addition, in the widely accepted mechanism represented by Scheme 76. There can be many minor ramifications associated with each of these three fundamentally discrete mechanisms. Some ramifications may be of fundamental and general significance. Such aspects should be pursued and clarified. Most of the others may be of specific nature and applicable mainly to those specific cases investigated. In reality, relatively little is currently known beyond speculations based on starting material—product relationships.

V. Conclusions

1. The Heck-type alkynylation with terminal alkynes, especially the Sonogashira protocol, and the Pd-catalyzed alkynylation with alkynylmetals, especially the Negishi protocol with alkynylzincs, have emerged as two of the most general and reliable methods for the synthesis of alkynes over the past quarter of a century by supplanting the Cu-promoted Castro−Stephens reaction. In less demanding cases, all or most of the currently known protocols of Pd-catalyzed alkynylation including Heck alkynylation, Sonogashira reaction, as well as alkynylation with alkynyl metals containing Mg, Zn, B, Al, In, Si, and Sn may prove to be highly satisfactory.

In cases where the starting alkynes are most readily available in the form of free terminal alkynes either from commercial sources or otherwise, the Heck alkynylation without the use of a Cu cocatalyst would be the least involved and hence operationally simplest. It should therefore be considered first. In reality, however, it may prove to be desirable in many cases to use the Sonogashira protocol by adding a Cu(I) salt. On the other hand, in cases where the starting alkynes are generated via alkynylmetals containing alkali metals, such as Li and Na, or Mg, alkynylation with alkynylmetals directly generated in situ as mentioned above would be simpler than the Heck and Sonogashira protocols and should therefore be considered first. Alkynylmetals containing alkali metals must generally be converted to second-generation alkynylmetals via in situ transmetalation, and alkynylzincs appear to be the currently best option to be considered first. In cases where alkynylmagnesium derivatives are the most readily available precursors, however, they should be tested before converting them into alkynylzincs or other alkynylmetals.

Although alkynyltins have also been widely used, they are generally less satisfactory than alkynylzincs. Furthermore, their toxicity is a serious concern. They do, however, offer some unique advantages as discussed in section III. So, their use must be reserved for such special cases and executed with ample attention paid to their toxicity.

Although alkynylmetals containing B, Al, In, and Si have also been used, especially over the past several years, their scopes and limitations, especially their merits and demerits relative to the Sonogashira reaction and the Negishi alkynylation with alkynylzincs, must be further delineated. At present, relatively little is known about their clear-cut advantages over the widely used protocols mentioned above.

2. As detailed in section II and summarized in Table 1, the Pd-catalyzed alkynylation of class C_{sp^2}—X electrophiles, i.e., aryl, heteroaryl, alkenyl, allenyl (propargyl), and acyl electrophiles, has proved to be generally satisfactory. A wide variety of organic compounds including natural products[269] and compounds of material chemical interest have been conveniently and satisfactorily synthesized.

Although alkynyl electrophiles also readily participate in Pd-catalyzed alkynyl—alkynyl coupling, formation of unwanted alkyne homodimers has been a frequently encountered problem, and its general solution does not appear to have been devised. In fact, this is also a frequent problem associated with the Cu-catalyzed Cadiot—Chodkiewicz reaction. On the other hand, an alternate method involving the intermediacy of 1-halo-1-alken-3-ynes (section III.B.5) is not only general but also strictly cross-selective and offers a superior alternative in many cases.

Allyl and benzyl electrophiles are known to readily participate in the Pd-catalyzed cross-coupling. Curiously, however, little is known about their Pd-catalyzed alkynylation. Judging from a recent successful report on successful alkynylation of benzyl halides,[47] further investigation may prove to be fruitful. The well-known difficulty in the oxidative addition of alkyl electrophiles lacking β,γ-unsaturation appears to generally disfavor their use in Pd-catalyzed alkynylation.

3. Although widely applicable, the Sonogashira reaction has also been shown either to fail altogether or to be problematic in many demanding cases of alkynylation, as amply demonstrated in sections III.B.1 (Schemes 33 and 34), III.B.2 (p. 50), III.B.3 (Scheme 43 and Table 12), III.B.5 (Scheme 60), and III.B.6 (Scheme 61). In many such cases, the organozinc protocol has been shown to be significantly superior and a satisfactory alternative. Besides being operationally somewhat simpler in many cases, the Sonogashira reaction may also prove to be chemically superior to the alkynylzinc protocols in some cases, such as polymerization via Pd-catalyzed alkynylation. Clearly, further delineation of merits and demerits among various alternatives, especially the Sonogashira reaction and the Negishi alkynylation, is desirable.

4. Some of the important pending issues include (i) substantial improvement in the catalytic turnover numbers (TON) and rates (TOR), (ii) other technological improvements, such as immobilization of catalysts, and (iii) structural and mechanistic investigation. For example, it is desirable to attain TONs exceeding 10^4—10^5 through development of (a) new and superior ligands and Pd-catalysts, (b) superior cocatalysts, other additives, and solvents, as well as (c) various advanced technological devices.

VI. Acknowledgments

The authors are deeply indebted to their co-workers for invaluable contributions in the area of Pd-catalyzed alkynylation, especially those made by Dr. A. O. King, M. Kotora, and C. Xu. The names of the other co-workers are shown in their papers cited herein. These studies have been mainly supported by the National Institutes of Health, the National Science Foundation, and Purdue University, including the H. C. Brown Distinguished Professorship Fund (E.N.) and a Purdue Research Foundation Graduate Research Fellowship (L.A.).

VII. References

(1) Brandsma, L.; Heus-Kloos, Y. A.; Van Der Heiden, R.; Verkruijsse, H. D. *Preparative Acetylenic Chemistry*, 2nd ed.; Elsevier: New York, 1988.
(2) Brandsma, L.; Vasilevsky, S. F.; Verkruijsse, H. D. *Application of Transition Metal Catalysts in Organic Synthesis*; Springer-Verlag: New York, 1998.
(3) Castro, C. E.; Stephens, R. D. *J. Org. Chem.* **1963**, *28*, 2163.
(4) Dieck, H. A.; Heck, F. R. *J. Organomet. Chem.* **1975**, *93*, 259.
(5) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
(6) Sonogashira, K.; Yatake, T.; Tohda, Y.; Takahashi, S.; Hagihara, N. *J. Chem. Soc., Chem. Commun.* **1977**, 291.
(7) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777.
(8) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, 627.
(9) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998, pp 203—229.
(10) Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; pp 493—529.
(11) Institute for Scientific Information. *Science Citation Index Expanded (Web of Science)*; Institute for Scientific Information: Philadelphia, 1977.
(12) See for example: (a) Alami, M.; Ferri, F.; Linstrumelle, G. *Tetrahedron Lett.* **1993**, *34*, 6403. (b) Xu, C.; Negishi, E. *Tetrahedron Lett.* **1999**, *40*, 431. (c) Liao, B.; Negishi, E. *Heterocycles* **2000**, *52*, 1241.
(13) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683.
(14) King, A. O.; Negishi, E.; Villani, F. J., Jr.; Silveira, A., Jr. *J. Org. Chem.* **1978**, *43*, 358.
(15) Negishi, E. In *Aspects of Mechanism and Organometallic Chemistry*; Brewster, J. H., Ed.; Plenum Press: New York, 1978; pp 285—317. See also ref 16.
(16) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.
(17) Negishi, E.; Xu, C. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; pp 531—549.
(18) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254.
(19) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253.
(20) Negishi, E.; Akiyoshi, K.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1987**, 477.
(21) Dang, H. P.; Linstrumelle, G. *Tetrahedron Lett.* **1978**, 191.
(22) Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1980**, *21*, 2531.
(23) Sato, M.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1609.
(24) Soderquist, J. A.; Matos, K.; Rane, A.; Ramos, J. *Tetrahedron Lett.* **1995**, *36*, 2401.
(25) Soderquist, J. A.; Rane, A. M.; Matos, K.; Ramos, J. *Tetrahedron Lett.* **1995**, *36*, 6847.
(26) Fürstner, A.; Seidel, G. *Tetrahedron* **1995**, *51*, 11165.
(27) Fürstner, A.; Nikolakis, K. *Liebigs Ann. Chem.* **1996**, 2107.
(28) (a) Kashin, A. N.; Bumagina, I. G.; Bumagin, N. A.; Beletskaya, I. P.; Reutov, O. A. *Izv. Akad. Nauk SSSR. Ser. Khim.* **1980**, 479, (b) Bumagin, N. A.; Bumagina, I. G.; Beletskaya, I. P. *Dokl. Akad. Nauk SSSR* **1983**, *272*, 1384.
(29) (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. (b) For studies by Farina on effective cocatalysts for the Stille reaction, see Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C. J.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.
(30) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, 3437.
(31) (a) Castanet, A. S.; Colobert, F.; Schlama, T. *Org. Lett.* **2000**, *2*, 3559 (b) Oh, C. H.; Jung, S. H. *Tetrahedron Lett.* **2000**, *41*, 8513.
(32) Negishi, E.; Kotora, M.; Xu, C. *J. Org. Chem.* **1997**, *62*, 8957.
(33) Hiyama, T.; Shirakawa, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; pp 285—309.
(34) Latimer, W. *Oxidation Potentials*, 2nd Ed., Prentice-Hall: Englewood Cliffs, NJ, 1961.
(35) Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918.
(36) Hatanaka, Y.; Matsui, K.; Hiyama, T. *Tetrahedron Lett.* **1989**, *30*, 2403.

(37) Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Chem. Lett.* **1997**, 1233.
(38) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.-I.; Mori, A.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 1780.
(39) Mori, A.; Kawashima, J.; Shimada, T.; Suguro, M.; Hirabayashi, K.; Nishihara, Y. *Org. Lett.* **2000**, *2*, 2935.
(40) Mori, A.; Kondo, T.; Kato, T.; Nishihara, Y. *Chem. Lett.* **2001**, 286.
(41) Marshall, J. A.; Chobanian, H. R.; Yanik, M. M. *Org. Lett.* **2001**, *3*, 4107.
(42) Chang, S.; Yang, S. H.; Lee, P. H. *Tetrahedron Lett.* **2001**, *42*, 4833.
(43) Bertus, P.; Pale, P. *Tetrahedron Lett.* **1996**, *37*, 2019.
(44) Bertus, P.; Pale, P. *Tetrahedron Lett.* **1997**, *38*, 8193.
(45) Bertus, P.; Pale, P. *J. Organomet. Chem.* **1998**, *567*, 173.
(46) Perez, I.; Perez Sestelo, J.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267.
(47) Perez, I.; Perez Sestelo, J.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155.
(48) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393.
(49) Mishima, M.; Ariga, T.; Tsuno, Y.; Ikenaga, K.; Kikukawa, K. *Chem. Lett.* **1992**, 489.
(50) Kosugi, M.; Tanji, T.; Tanaka, Y.; Yoshida, A.; Fugami, K.; Kameyama, K.; Migita, T. *J. Organomet. Chem.* **1996**, *508*, 255.
(51) Yamada, J.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1302.
(52) Kang, S. K.; Ryu, H. C.; Choi, S. C. *Chem. Commun.* **1998**, 1317.
(53) Kang, S. K.; Ryu, H. C.; Son, H. J. *Synlett* **1998**, 771.
(54) Barton, D. H. R.; Ozbalik, N.; Ramesh, M. *Tetrahedron* **1988**, *44*, 5661.
(55) Dillinger, S.; Bertus, P.; Pale, P. *Org. Lett.* **2001**, *3*, 1661.
(56) Halbes, U.; Bertus, P.; Pale, P. *Tetrahedron Lett.* **2001**, *42*, 8641.
(57) Riguet, E.; Alami, M.; Cahiez, G. *J. Organomet. Chem.* **2001**, *624*, 376.
(58) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, 1969; pp 597–647.
(59) Negishi, E.; Okukado, N.; Lovich, S. F.; Luo, F. T. *J. Org. Chem.* **1984**, *49*, 2629.
(60) Negishi, E.; Hata, M.; Xu, C. *Org. Lett.* **2000**, *2*, 3687.
(61) Matsushita, H.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 2882.
(62) Negishi, E.; Matsushita, H.; Okukado, N. *Tetrahedron Lett.* **1981**, *22*, 2715.
(63) Negishi, E.; Chatterjee, S.; Matsushita, H. *Tetrahedron Lett.* **1981**, *22*, 3737.
(64) (a) Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385. (b) Tsuji, J. *Pure Appl. Chem.* **1982**, *54*, 197.
(65) Tamura, M.; Kochi, J. *Synthesis* **1971**, 303.
(66) Danheiser, R. L.; Gee, S. K. *J. Org. Chem.* **1984**, *49*, 1672.
(67) Negishi, E.; Zhang, Y.; Cederbaum, F. E.; Webb, M. B. *J. Org. Chem.* **1986**, *51*, 4080.
(68) Negishi, E.; Baba, S. *J. Am. Chem. Soc.* **1975**, *97*, 7385.
(69) Hinkle, R. J.; Poulter, G. T.; Stang, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 11626.
(70) Ryan, J. H.; Stang, P. J. *J. Org. Chem.* **1996**, *61*, 6162.
(71) Radhakrishnan, U.; Stang, P. J. *Org. Lett.* **2001**, *3*, 859.
(72) Pschirer, N. G.; Bunz, U. H. F. *Tetrahedron Lett.* **1999**, *40*, 2481.
(73) Kropp, P. J.; Crawford, S. D. *J. Org. Chem.* **1994**, *59*, 3102.
(74) Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63*, 8551.
(75) Bumagin, N. A.; Ponomarev, A. B.; Beletskaya, I. P. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1984**, *33*, 1433.
(76) Singh, R.; Just, G. *J. Org. Chem.* **1989**, *54*, 4453.
(77) Casalnuovo, A. L.; Calabrese, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 4324.
(78) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729.
(79) Negishi, E.; Takahashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 3402.
(80) Tsukayama, M.; Kikuchi, M.; Kawamura, Y. *Heterocycles* **1994**, *38*, 1487.
(81) Nandi, B.; Kundu, N. G. *Org. Lett.* **2000**, *2*, 235.
(82) Hay, L. A.; Koenig, T. M.; Ginah, F. O.; D., C. J.; Mitchell, D. *J. Org. Chem.* **1998**, *63*, 5050.
(83) D'Auria, M. *Synth. Commun.* **1992**, *22*, 2393.
(84) Powell, N. A.; Rychnovsky, S. D. *Tetrahedron Lett.* **1996**, *37*, 7901.
(85) Negishi, E.; Takahashi, T.; Akiyoshi, K. *J. Organomet. Chem.* **1987**, *334*, 181.
(86) Klusener, P. A. A.; Hanekap, J. C.; Brandsma, L.; Schleyer, P. *J. Org. Chem.* **1990**, *55*, 1311.
(87) Yoneda, N.; Matsuoka, S.; Miyaura, N.; Fukuhara, T.; Suzuki, A. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2124.
(88) Chen, Q.; He, Y. *Tetrahedron Lett.* **1987**, *28*, 2387.
(89) Löffler, A.; Himbert, G. *Synthesis* **1992**, 495.
(90) Tietze, L. F.; Görlitzer, J. *Synthesis* **1997**, 877.
(91) Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856.
(92) Bumagin, N. A.; Bumagina, I. G.; Beletskaya, I. P. *Dokl. Chem. (Engl. Transl.)* **1984**, *274*, 39.
(93) Shirakawa, E.; Yoshida, H.; Takaya, H. *Tetrahedron Lett.* **1997**, *38*, 3759.
(94) Kashin, A. N.; Bumagina, I. G.; Bumagin, N. A.; Beletskaya, I. P. *J. Org. Chem. USSR (Engl. Transl.)* **1981**, *17*, 18.
(95) Sakamoto, T.; Shiga, F.; Yasuhara, A.; Uchiyama, D.; Kondo, Y.; Yamanaka, H. *Synthesis* **1992**, 746.
(96) Miyawaki, K.; Ueno, F.; Ueda, I. *Heterocycles* **2001**, *54*, 887.
(97) Sakamoto, T.; Yasuhara, A.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1994**, *42*, 2032.
(98) Wiegelmann, J. E. C.; Bunz, U. H. F.; Schuel, P. *Organometallics* **1994**, *13*, 4649.
(99) Bunz, U. H. F.; Enkelmann, V. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1653.
(100) Lo Sterzo, C.; Stille, J. K. *Organometallics* **1990**, *9*, 687.
(101) Bunz, U. H. F.; Enkelmann, V.; Rader, J. *Organometallics* **1993**, *12*, 4745.
(102) Wright, M. E. *J. Organomet. Chem.* **1989**, *376*, 353.
(103) For a recent review with over 130 references including 16 pertinent reviews, see: Bunz, U. H. F. *Chem. Rev.* **2000**, *100*, 1605.
(104) (a) Giesa, R.; Schultz, R. C. *Makromol. Chem.* **1990**, *191*, 857. (b) Nishihara, Y.; Ando, J.; Kato, T.; Mori, A.; Hiyama, T. *Macromolecules* **2000**, *33*, 2779.
(105) Bochmann, M.; Kelly, K. *J. Chem. Soc., Chem. Commun.* **1989**, 532.
(106) (a) Huang, S.; Tour, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 4908. (b) Tour, J. M. *Acc. Chem. Res.* **2000**, *33*, 791.
(107) Rossi, R.; Carpita, A.; Lezzi, A. *Tetrahedron* **1984**, *40*, 2773.
(108) (a) Ye, X.-S.; Wong, H. N. C. *J. Chem. Soc., Chem. Commun.* **1996**, 339. (b) Ye, X.-S.; Wong, H. N. C. *J. Org. Chem.* **1997**, *62*, 1940.
(109) Negishi, E.; Xu, C.; Tan, Z.; Kotora, M. *Heterocycles* **1997**, *46*, 209.
(110) Liu, F.; Negishi, E. *J. Org. Chem.* **1997**, *62*, 8591.
(111) Karlsson, J. O.; Gronowitz, S.; Frejd, T. *J. Org. Chem.* **1982**, *47*, 374.
(112) Karlsson, J. O.; Svensson, A.; Gronowitz, S. *J. Org. Chem.* **1984**, *49*, 2018.
(113) Edstrom, E. D.; Wei, Y. *J. Org. Chem.* **1994**, *59*, 6902.
(114) Undheim, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; pp 409–492.
(115) Minakawa, N.; Sasabuchi, Y.; Kiyosue, A.; Kojima, N.; Matsuda, A. *Chem. Pharm. Bull.* **1996**, *44*, 288.
(116) Taylor, E. C.; Patel, H. H. *Tetrahedron* **1992**, *48*, 8089.
(117) Sakamoto, T.; Shiraiwa, M.; Kondo, T.; Yamanaka, H. *Synthesis* **1983**, 312.
(118) Negishi, E.; Luo, F. T.; Frisbee, R.; Matsushita, H. *Heterocycles* **1982**, *18*, 117.
(119) Ducharme, Y.; Wuest, J. D. *J. Org. Chem.* **1988**, *53*, 5787.
(120) Falk-Petersen, M. L.; Undheim, K. *Acta Chem. Scand.* **1998**, *52*, 1327.
(121) Kalgutkar, A. S.; Castagnoli, N. *J. Med. Chem.* **1992**, *35*, 4165.
(122) Crisp, G. T.; Papadopoulos, S. *Aust. J. Chem.* **1999**, *42*, 279.
(123) Draper, T. L.; Bailey, T. R. *J. Org. Chem.* **1995**, *60*, 748.
(124) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1982**, *30*, 2410.
(125) Solberg, J.; Undheim, K. *Acta Chem. Scand., Ser. B* **1986**, *40*, 381.
(126) Robins, M. J.; Barr, P. J. *J. Org. Chem.* **1983**, *48*, 1954.
(127) Vincent, P.; Beaucourt, J.-P.; Pichat, L. *Tetrahedron Lett.* **1981**, *22*, 945.
(128) Adah, S. A.; Nair, V. *Tetrahedron* **1997**, *53*, 6747.
(129) Mangalagiu, I.; Benneche, T.; Undheim, K. *Acta Chem. Scand.* **1996**, *50*, 914.
(130) Akita, Y.; Inoue, A.; Ohta, A. *Chem. Pharm. Bull.* **1986**, *34*, 1447.
(131) See, for example, Negishi, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E. Ed.; Wiley: New York, 2002; Section 1.2, pp 17–35.
(132) For a paper describing the reversal in reactivity order between aryl and alkenyl halides, see: Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
(133) Ratovelomanana, V.; Linstrumelle, G. *Synth. Commun.* **1981**, *11*, 917.
(134) Castedo, L.; Mourino, A.; Sarandeses, L. A. *Tetrahedron Lett.* **1986**, *27*, 1523.
(135) Rudisill, D. E.; Castonguay, L. A.; Stille, J. K. *Tetrahedron Lett.* **1988**, *29*, 1509.
(136) Alami, M.; Linstrumelle, G. *Tetrahedron Lett.* **1991**, *32*, 6109.
(137) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1998**, *63*, 8965.
(138) Nwokogu, G. C. *J. Org. Chem.* **1985**, *50*, 3900.
(139) Bujard, M.; Ferri, F.; Alami, M. *Tetrahedron Lett.* **1998**, *39*, 4243.
(140) Hyuga, S.; Chiba, Y.; Yamashina, N.; Hara, S.; Suzuki, A. *Chem. Lett.* **1987**, 1757.
(141) Andreini, B. P.; Carpita, A.; Rossi, R.; Scamuzzi, B. *Tetrahedron* **1989**, *45*, 5621.
(142) Rossi, R.; Carpita, A.; Lippolis, V. *Synth. Commun.* **1991**, *21*, 333.
(143) Stracker, E.; Zweifel, G. *Tetrahedron Lett.* **1991**, *32*, 3329.

(144) Negishi, E.; Liu, F.; Choueiry, D.; Mohamud, M. M.; Silveira, A., Jr.; Reeves, M. *J. Org. Chem.* **1996**, *61*, 8325.
(145) Tellier, F.; Sauvêtre, R.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 3147. See also Tellier, F.; Sauvêtre, R.; Normant, J. F. *J. Organomet. Chem.* **1987**, *328*, 1.
(146) Stille, J. K.; Simpson, J. H. *J. Am. Chem. Soc.* **1987**, *109*, 2138.
(147) Scott, W. J.; Crisp, G. T.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4630.
(148) Margaretha, P.; Reichow, S.; Agosta, W. C. *J. Chem. Soc., Chem. Commun.* **1992**, 797.
(149) Ley, S. V.; Redgrave, A. J.; Taylor, S. C.; Ahmed, S.; Ribbons, D. W. *Synlett* **1991**, 741.
(150) Le Menez, P.; Faragoas, V.; Bergue, L.; Poisson, J.; Ardisson, J.; Lallemand, J. Y.; Pancrazi, A. *J. Org. Chem.* **1995**, *60*, 3592.
(151) Baldwin, J. E.; Bamford, S. J.; Fryer, A. M.; Rudolph, M. P. W.; Wood, M. E. *Tetrahedron* **1997**, *53*, 5233.
(152) Siesel, D. A.; Staley, S. W. *Tetrahedron Lett.* **1993**, *34*, 3679.
(153) Chattani, N.; Amishiro, N.; Murai, S. *J. Am. Chem. Soc.* **1991**, *113*, 7778.
(154) Negishi, E.; Ay, M.; Gulevich, Y. V.; Noda, Y. *Tetrahedron Lett.* **1993**, *34*, 1437.
(155) Rossi, R.; Carpita, A.; Quirici, M. G.; Gaudenzi, M. L. *Tetrahedron* **1982**, *38*, 631.
(156) Negishi, E.; Owczarczyk, Z. R.; Swanson, D. R. *Tetrahedron Lett.* **1991**, *32*, 4453.
(157) Negishi, E.; Dumond, Y. R. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; pp 767−789.
(158) Arbabi, A.; Farain, J.-L.; Cintrat, J.-C.; Duchêne, A. *Synthesis* **1996**, 82.
(159) Bellina, F.; Carpita, A.; De Santis, M.; Rossi, R. *Tetrahedron Lett.* **1994**, *35*, 6913.
(160) Berger, D.; Bartlome, A.; Neuenschwander, M. *Helv. Chim. Acta* **1996**, *79*, 179.
(161) Gibbs, R. A.; Krishnan, U.; Dolence, J. M.; Poulter, C. D. *J. Org. Chem.* **1995**, *60*, 7821.
(162) Boldi, A. M.; Anthony, J.; Knobler, C. B.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1240.
(163) Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Synlett* **1995**, 871.
(164) Liebeskind, L. S.; Wang, J. *Tetrahedron Lett.* **1990**, *31*, 4293.
(165) Rubin, Y.; Knobler, C. B.; Diederich, F. *J. Am. Chem. Soc.* **1990**, *112*, 1607.
(166) Myers, A. G.; Alauddin, M. M.; Fuhry, M. A. M.; Dragovich, P. S.; Finney, N. S.; Harrington, P. M. *Tetrahedron Lett.* **1989**, *30*, 6997.
(167) Miossec, B.; Danion-Bougot, R.; Danion, D. *Synthesis* **1994**, 1171.
(168) Nakatani, K.; Isoe, S.; Maekawa, S.; Saito, I. *Tetrahedron Lett.* **1994**, *35*, 605.
(169) Dai, W.-M.; Wu, J. *Tetrahedron* **1997**, *53*, 9107.
(170) Jeffery-Luong, T.; Linstrumelle, G. *Tetrahedron Lett.* **1980**, *21*, 5019.
(171) Ruitenberg, K.; Kleijn, H.; Elsevier: C. J.; Meijer, J.; Vermeer, P. *Tetrahedron Lett.* **1981**, *22*, 1451.
(172) Kleijn, H.; Meijer, J.; Overbeek, G. C.; Kermeer, P. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 97.
(173) Ruitenberg, K.; Kleijn, H.; Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1982**, *101*, 405.
(174) Kleijn, H.; Westmijze, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 378.
(175) Elsevier: C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. *J. Org. Chem.* **1986**, *48*, 1103.
(176) Keinan, E.; Bosch, E. *J. Org. Chem.* **1986**, *51*, 4006.
(177) Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F. T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181.
(178) Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549.
(179) Verkruijsse, H. D.; Heus-Kloos, Y. A.; Brandsma, L. *J. Organomet. Chem.* **1988**, *338*, 289.
(180) Akroyd, J.; Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1985**, *68*, 338.
(181) Crisp, G. T.; O'Donoghue, A. I. *Synth. Commun.* **1989**, 1745.
(182) Kobayashi, T.; Sakakura, T.; Tanaka, M. *Tetrahedron Lett.* **1985**, *26*, 3463.
(183) (a) Ito, Y.; Inouye, M.; Murakami, M. *Tetrahedron Lett.* **1988**, *29*, 5379. (b) Ito, Y.; Inouye, M.; Murakami, M. *Chem. Lett.* **1989**, 1261.
(184) Faust, R.; Göbelt, B. *Tetrahedron Lett.* **1997**, *38*, 8017.
(185) Wakamatsu, T.; Okuda, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2425.
(186) Jasperse, C. P.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 5601.
(187) King, A. O. Ph.D. Dissertation. Syracuse University, Rochester, NY, 1979.
(188) Wityak, J.; Chan, J. B. *Synth. Commun.* **1991**, *21*, 977.
(189) Hoye, T. R.; Hanson, P. R. *Tetrahedron Lett.* **1993**, *34*, 5043.
(190) Alzeer, J.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 177.
(191) Amatore, C.; Blart, E.; Genêt, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.* **1995**, *60*, 6829.
(192) Alami, M.; Ferri, F. *Tetrahedron Lett.* **1996**, *37*, 2763.
(193) Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Tetrahedron Lett.* **1998**, *39*, 4075.
(194) Negishi, E.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett.* In press.
(195) For a recent comparative study of the Pd-catalyzed Sonogashira and Negishi alkynylation of 1,1-dihaloalkenes, see: Qian, M.; Negishi, E. *Org. Process Res. Dev.* In press.
(196) Austin, W. B.; Bilow, N.; Kelleghan, W. J.; Lau, K. S. Y. *J. Org. Chem.* **1981**, *46*, 2280.
(197) Havens, S. H.; Hergenrother, P. M. *J. Org. Chem.* **1985**, *50*, 1763.
(198) Mal'kina, A. G.; Brandsma, L.; Vasilevsky, S. F.; Trofimov, B. A. *Synthesis* **1996**, 589.
(199) Lu, X.; Huang, X.; Ma, S. *Tetrahedron Lett.* **1993**, *34*, 5963.
(200) Kotora, M.; Negishi, E. I. *Synthesis* **1997**, 121.
(201) Yu, K. L.; Chen, S.; Ostrowski, J.; Tramposch, K. M.; Reczek, P. R.; Mansuri, M. M.; Starrett, J. E., Jr. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2859.
(202) (a) Eckert, T.; Ipaktschi, J. *Synth. Commun.* **1998**, *28*, 327. (b) Yang, C.; Nolan, S. P. *Organometallics* **2002**, *21*, 1020.
(203) Barabanov, I. I.; Fedenok, L. G.; Shvartsberg, M. S. *Russ. Chem. Bull.* **1998**, *47*, 2256.
(204) Anastasia, L.; Negishi, E. *Org. Lett.* **2001**, *3*, 3111.
(205) For a review, see Negishi, E. *J. Organomet. Chem.* **1999**, *576*, 179.
(206) Negishi, E.; Tan, Z.; Liou, S.-Y.; Liao, B. *Tetrahedron* **2000**, *56*, 10197.
(207) Miller, M. W.; Johnson, C. R. *J. Org. Chem.* **1997**, *62*, 1582.
(208) Margaretha, P.; Reichow, S.; Agosta, W. C. *J. Org. Chem.* **1994**, *59*, 5393.
(209) Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L.; Vergamini, P. *Tetrahedron* **1998**, *54*, 135.
(210) Negishi, E.; Akiyoshi, K. *Chem. Lett.* **1987**, 1008.
(211) Newhouse, B. J.; Meyers, A. I.; Sirisoma, N. S.; Braun, M. P.; Johnson, C. R. *Synlett* **1993**, 573.
(212) Levin, J. I. *Tetrahedron Lett.* **1993**, *34*, 6211.
(213) Bellina, F.; Carpita, A.; De Santis, M.; Rossi, R. *Tetrahedron* **1994**, *50*, 12029.
(214) Prasad, A. S. B.; Knochel, P. *Tetrahedron* **1997**, *53*, 16711.
(215) Rossi, R.; Bellina, F.; Ciucci, D. *J. Organomet. Chem.* **1997**, *542*, 113.
(216) (a) Kamikubo, T.; Ogasawara, K. *Chem. Commun.* **1996**, 1679. (b) Kamikubo, T.; Ogasawara, K. *Heterocycles* **1998**, *47*, 69.
(217) (a) Graham, A. E.; McKerrecher, D.; Davies, D. H.; Taylor, R. J. K. *Tetrahedron Lett.* **1996**, *37*, 7445. (b) Graham, A. E.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1087.
(218) Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 315.
(219) Van de Walle, H.; Henne, A. *Bull. Cl. Sci., Acad. R. Belg.* **1925**, *11*, 360.
(220) Ramatandrasoa, P.; Brehon, B.; Thivet, A.; Alami, M.; Cahiez, C. *Tetrahedron Lett.* **1997**, *38*, 2447.
(221) Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1984**, *25*, 6001.
(222) Alami, M.; Crousse, B.; Linstrumelle, C. *Tetrahedron Lett.* **1994**, *35*, 3543.
(223) Kende, A. S.; Smith, C. A. *J. Org. Chem.* **1988**, *53*, 2655.
(224) Schreiber, S. L.; Kiessling, L. *J. Am. Chem. Soc.* **1988**, *110*, 631.
(225) Magnus, P.; Carter, P. A. *J. Am. Chem. Soc.* **1988**, *110*, 1626.
(226) Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1377.
(227) Tomioka, K.; Fujita, H.; Koga, K. *Tetrahedron Lett.* **1989**, *30*, 851.
(228) Nicolaou, K. C.; Hummel, C. W.; Pitsinos, E. N.; Nakada, M.; Smith, A. L.; Shibayama, K.; Saimoto, H. *J. Am. Chem. Soc.* **1992**, *114*, 10082.
(229) Nicolaou, K. C.; Hummel, C. W.; Nakada, M.; Shibayama, K.; Pitsinos, E. N.; Saimoto, H.; Mizuno, Y.; Baldenius, K. U.; Smith, A. L. *J. Am. Chem. Soc.* **1993**, *115*, 7625.
(230) Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 7416.
(231) Nicolaou, K. C.; Smith, A. L.; Wendeborn, S. V.; Hwang, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 3106.
(232) Porco, J. A., Schoenen, F. J.; Stout, T. J.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 7410.
(233) Taunton, J.; Wood, J. L.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 10378.
(234) Shair, M. D.; Yoon, T.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 3755.
(235) Takahashi, T.; Sakamoto, Y.; Yamada, H.; Usui, S.; Fukazawa, Y. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1345.
(236) Clive, D. L. J.; Bo, Y.; Tao, Y.; Daigneault, S.; Wu, Y.-J.; Maignan, G. *J. Am. Chem. Soc.* **1996**, *118*, 4904.
(237) Huynh, C.; Linstrumelle, G. *Tetrahedron* **1988**, *44*, 6337.
(238) Carpita, A.; Rossi, R. *Tetrahedron Lett.* **1986**, *27*, 4351.
(239) Negishi, E.; Alimardanov, A.; Xu, C. *Org. Lett.* **2000**, *2*, 65.
(240) Zeng, F.; Negishi, E. *Org. Lett.* **2001**, *3*, 719.
(241) Viehe, H. G.; Franchimont, E. *Chem. Ber.* **1963**, *96*, 3153.
(242) Bartlome, A.; Stampfli, U.; Neuenschvader, M. *Org. Lett.* **2002**, *4*, 703.
(243) Zeng, F.; Negishi, E. *Org. Lett.* **2002**, *4*, 703.
(244) Sonoda, M.; Inaba, A.; Itahashi, K.; Tobe, Y. *Org. Lett.* **2001**, *3*, 2419.

(245) Burns, B.; Grigg, R.; Ratanukul, P.; Sridharan, V.; Stevenson, P.; Skirthalingam, S.; Worakum, T. *Tetrahedron Lett.* **1988**, *29*, 5565.
(246) Burns, B.; Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakum, T. *Tetrahedron Lett.* **1989**, *30*, 1135.
(247) Wang, R.-T.; Chou, F. L.; Luo, F.-T. *J. Org. Chem.* **1990**, *55*, 4846.
(248) Luo, F.-T.; Wang, R.-T. *Tetrahedron Lett.* **1991**, *32*, 7703.
(249) Negishi, E.; Noda, Y.; Lamaty, F.; Vawter, E. J. *Tetrahedron Lett.* **1990**, *31*, 4393.
(250) Nuss, J. M.; Levine, B. H.; Rennels, R. A.; Heravi, M. M. *Tetrahedron Lett.* **1991**, *32*, 5243.
(251) Nuss, J. M.; Rennels, R. A.; Levine, B. H. *J. Am. Chem. Soc.* **1993**, *115*, 6991.
(252) Torii, S.; Okumoto, H.; Todokoro, T.; Nishimura, A.; Rashid, M. A. *Tetrahedron Lett.* **1993**, *34*, 2139.
(253) Lu, X.; Chen, C.; Xia, J.; Guo, G. *Tetrahedron: Asymmetry* **1997**, *8*, 3067.
(254) Mori, H.; Kubo, H.; Hara, H.; Katsumura, S. *Tetrahedron Lett.* **1997**, *38*, 5311.
(255) Anastasia, L.; Xu, C.; Negishi, E. *Tetrahedron Lett.* **2002**, *43*, 5673.
(256) (a) Takeuci, R.; Tanabe, K.; Tanaka, S. *J. Org. Chem.* **2000**, *65*, 1558 (b) Rossi, R.; Bellina, F.; Catanese, A.; Mannina, L.; Valensin, D. *Tetrahedron* **2000**, *56*, 479.
(257) (a) Ogawa, Y.; Maruno, M.; Wakamatsu, T. *Heterocycles* **1995**, *41*, 2587. (b) See ref 163.
(258) Beaudet, I.; Parrain, J.-L.; Quintard, J.-P. *Tetrahedron Lett.* **1992**, *33*, 3647.
(259) Bhatt, R. M.; Chauhan, K.; Wheelan, P.; Murphy, R. C.; Falck, J. R. *J. Am. Chem. Soc.* **1994**, *116*, 5051.
(260) Yamamoto, Y.; Tanaka, T.; Ouchi, H.; Miyakawa, M.; Mori, Y. *Heterocycles* **1995**, *41*, 817.
(261) Azuma, Y.; Sato, A.; Morone, M. *Heterocycles* **1996**, *42*, 789.
(262) Crisp, G. T.; Turner, P. D.; Stephens, K. A. *J. Organomet. Chem.* **1998**, *570*, 219.
(263) Herrmann, W. A.; Böhm, V. P. W.; Reisinger, C.-P. *J. Organomet. Chem.* **1999**, *576*, 23.
(264) Nakamura, K.; Okubo, H.; Yamaguchi, M. *Synlett* **1999**, 549.
(265) Littke, A. F.; Schwartz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343.
(266) Negishi, E.; Copéret, C.; Liou, S.-Y.; Liu, F.; Ma, S. *Chem. Rev.* **1998**, *96*, 365.
(267) Torii, S.; Okumoto, H.; Nishihara, A. *Tetrahedron Lett.* **1991**, *32*, 4167.
(268) Negishi, E.; Ay, M.; Sugihara, T. *Tetrahedron* **1993**, *49*, 5471.
(269) For additional examples of the synthesis of natural products via Pd-catalyzed alkynylation, see Tan, Z.; Negishi, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; pp 863–942.

CR0203771

199 148

Clarke, Modet & Cº
COLOMBIA

ESCOBAR - URIBE ASOCIADOS
Intellectual Property

2942/PCT.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 06-019204- -00007-0000
Fecha: 2008-07-11 09:28:47 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 467 SOLICIPRORROGA Folios: 2

Re: Expediente No. **06.019.204**
Solicitud de Patente a nombre de
Novartis AG.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 No. 86-53, piso 6, obrando como apoderada en este negocio, atentamente solicito a usted se sirva conceder una prórroga de 60 días para dar respuesta al oficio No. 5469 notificado por fijación en lista el 25 de abril de 2008, relacionado con la solicitud de patente que se está tramitando bajo el expediente de la referencia.

Acompaño el recibo Nr. 08-54.042 de 8 de julio de 2008, correspondiente a la tasa de la prórroga del término.

Señor Superintendente,

JIMENA ESCOBAR URIBE
C.C. 39.779.452 de Usaquen
T.P. 68.228
Cod. 5376
EUA/srr.