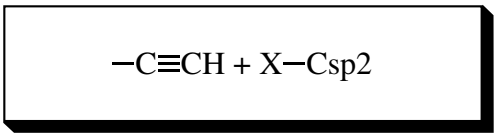

III.2.8 Palladium-Catalyzed Alkynylation

III.2.8.1 Sonogashira Alkyne Synthesis

KENKICHI SONOGASHIRA

A. INTRODUCTION

Conjugated acetylenic compounds are valuable intermediates in organic synthesis for natural products, pharmaceuticals, and organic molecular materials such as molecular wire and molecular architectures on a nanometer scale. These compounds have frequently been synthesized by the use of metal-catalyzed cross-coupling reactions of sp^2-C to sp-C atoms. Two types of transition-metal-mediated cross-coupling reactions of sp^2-C to sp-C atoms are available. These are the cross-couplings of unsaturated organic halides with terminal acetylenes (Sonogashira–Hagihara coupling) and with the alkynylmetal reagents such as Stille coupling for M = Sn, Suzuki coupling for M = B, and Negishi coupling for M = ZnX (**Scheme 1**).

The Pd-catalyzed coupling reactions between sp^2-C halides and terminal acetylenes have been independently reported by three groups in 1975 (**Scheme 1**).[1]–[3] The former two methods[1],[2] have been developed as an extension of the Heck reaction. On the other hand, the latter[3] was discovered as an application of copper-catalyzed alkynylation[4] of Pd complexes into the Stephens–Castro reaction.[5]

These reactions have been used extensively in the synthesis of eneyne-based acetylenic materials. Reaction conditions vary among workers. The general conditions for coupling between aryl or vinyl halides and terminal acetylenes employ a source of Pd(0), the PPh_3 ligand, an alkyl amine as a base, CuI cocatalyst, terminal acetylene, and aryl or vinyl halide at temperatures ranging from 25 °C up to 100 °C.

B. METAL-CATALYZED CROSS-COUPLING REACTIONS BETWEEN ARYL OR VINYL HALIDES WITH TERMINAL ACETYLENES

B.i. Pd-Catalyzed Cross-Coupling Reactions Between Aryl or Vinyl Halides with Terminal Acetylenes

As mentioned earlier, both Dieck and Heck[1] and Cassar[2] developed this procedure as an extension into acetylenes of the Heck Pd-catalyzed arylation of alkenes. As it requires

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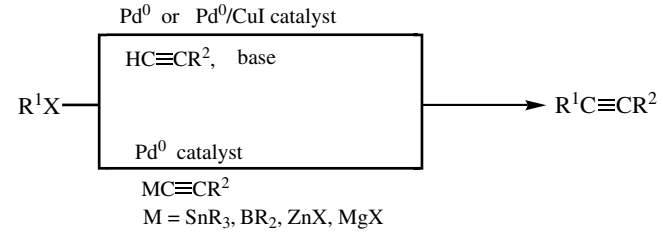
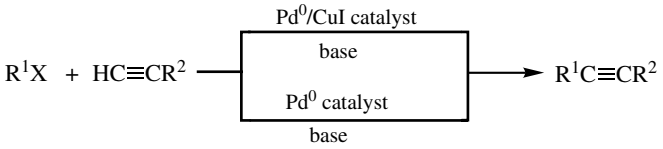
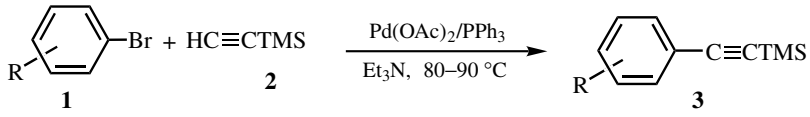


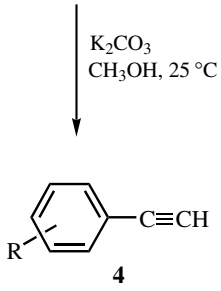


Scheme 1

much more forcing conditions, this procedure is only used in a special case such as reactive halides or triflates (vinyl halides, aryl iodides, and aryl bromide activated by the substituents) or organic halides that can coordinate to Cu^+ by chelation. Thus, ethynylated aromatic compounds can be prepared by Pd-catalyzed cross-coupling of trimethylsilylacetylene with activated aryl bromides as shown in **Scheme 2**.[6]



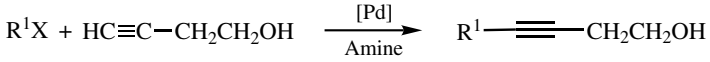
R	Yield(%) 3	4
m-CHO	80	84
p-CHO	99	100
o-CHO	75	80
m-CO_2CH_3	70	71
p-CO_2CH_3	69	73
p-O-(C_6H_4COCOPh-*p*)	88	56



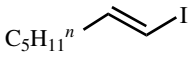
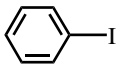
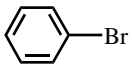
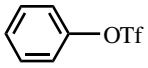
Scheme 2

Linstrumelle and co-workers reported that vinyl and aryl halides or triflates react very rapidly with terminal alkynes, without addition of copper salt, and lead to high yields of eneynes and aryl acetylenes by using $Pd(PPh_3)_4$ as a catalyst. The nature of the amine is critical for the success of the coupling (**Scheme 3**, [Pd]: I). However,

when the reaction is performed in the presence of CuI as a cocatalyst, very short reaction times are observed by using pyrrolidine, piperidine, or diisopropylamine (**Scheme 3**, [Pd]: II).[7]



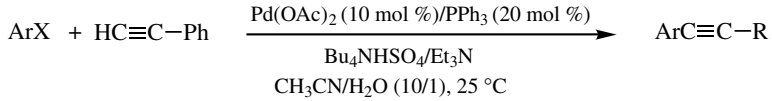
[Pd] ; I = $Pd(PPh_3)_4$ (5 mol %), II = $Pd(PPh_3)_4$ (5 mol %) / CuI (10 mol %)

R^1X	Amine	[Pd]	Temperature °C	Time	Isolated Yield (%)
	$^iPr_2NH$	I	25	72 h	3
	$^iPr_2NH$	II	25	10 min	81
	Pyrrolidine	I	25	15 min	93
	Pyrrolidine	II	25	10 min	90
	Et_2NH	I	25	24 h	0
	Et_2NH	II	25	2 h	92
	$^nBuNH_2$	I	25	25 h	93
	Pyrrolidine	I	25	2.5 h	91
	Pyrrolidine	II	25	10 min	93
	$^nBuNH_2$	I	80	3 h	92
	Pyrrolidine	I	80	2 h	96
	Et_3N	I	25	24 h	71
	Piperidine	I	25	5 min	90
	Pyrrolidine	I	25	5 min	87

Scheme 3

Similarly, in the case of early examples needing higher temperatures, the use of Pd complexes containing water-soluble ligands such as tppts (triphenylphosphinotrisulfonate sodium salt)[8] or $Pd(OAc)_2/PPh_3$ in the presence of a base and a phase transfer reagent (**Scheme 4**)[9] allows the reaction to occur under milder conditions without addition of cuprous iodide in a mixture of acetonitrile and water.

Because copper ion readily reacts with free base porphyrins, sometimes even metalloporphyrins to give copperporphyrins, Pd/Cu-catalyzed coupling reactions cannot be employed in the synthesis of acetylene-linked metalloporphyrins. In this case, triphenylarsine affords faster rates than triphenylphosphine or tri-2-furylphosphine, as

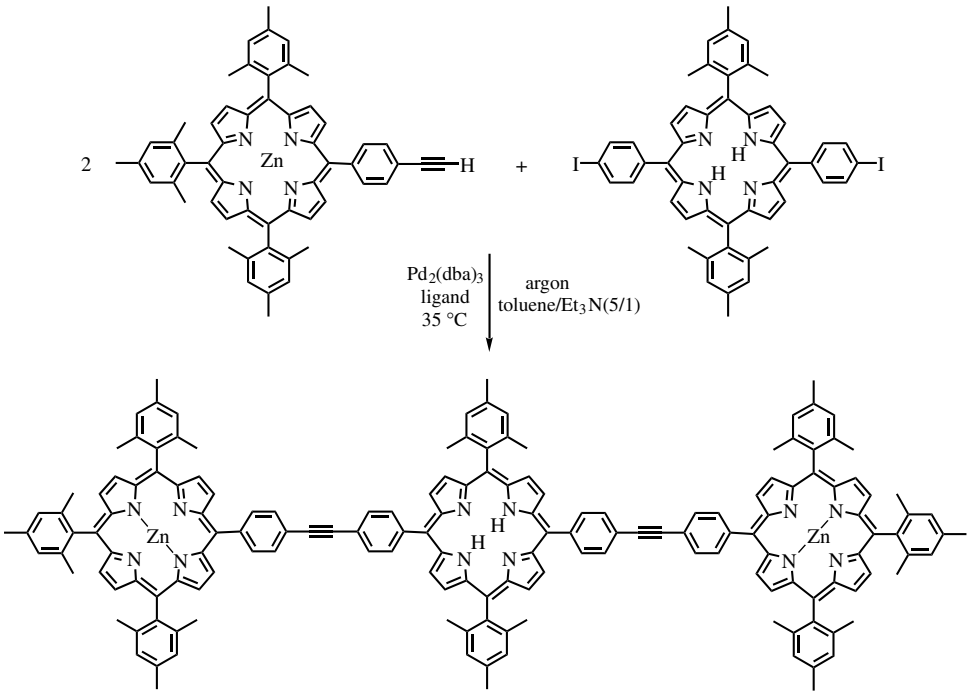


ArX	Time (h)	Yield (%)
C_6H_5I	1.5	89
p-$O_2NC_6H_4Br$	1.25	69

Scheme 4

shown in **Scheme 5**.[10] A wide variety of the acetylene-linked porphyrins have been synthesized by this method.[11]–[14]

Stable free radicals are employed in a variety of studies requiring spin labels, MRI, antioxidants, or magnetic materials. Elongated ethynyl-bridged radicals **7** and **10** based on pyridine- and bipyridine-substituted nitronyl nitroxide (NIT) radicals are also prepared by

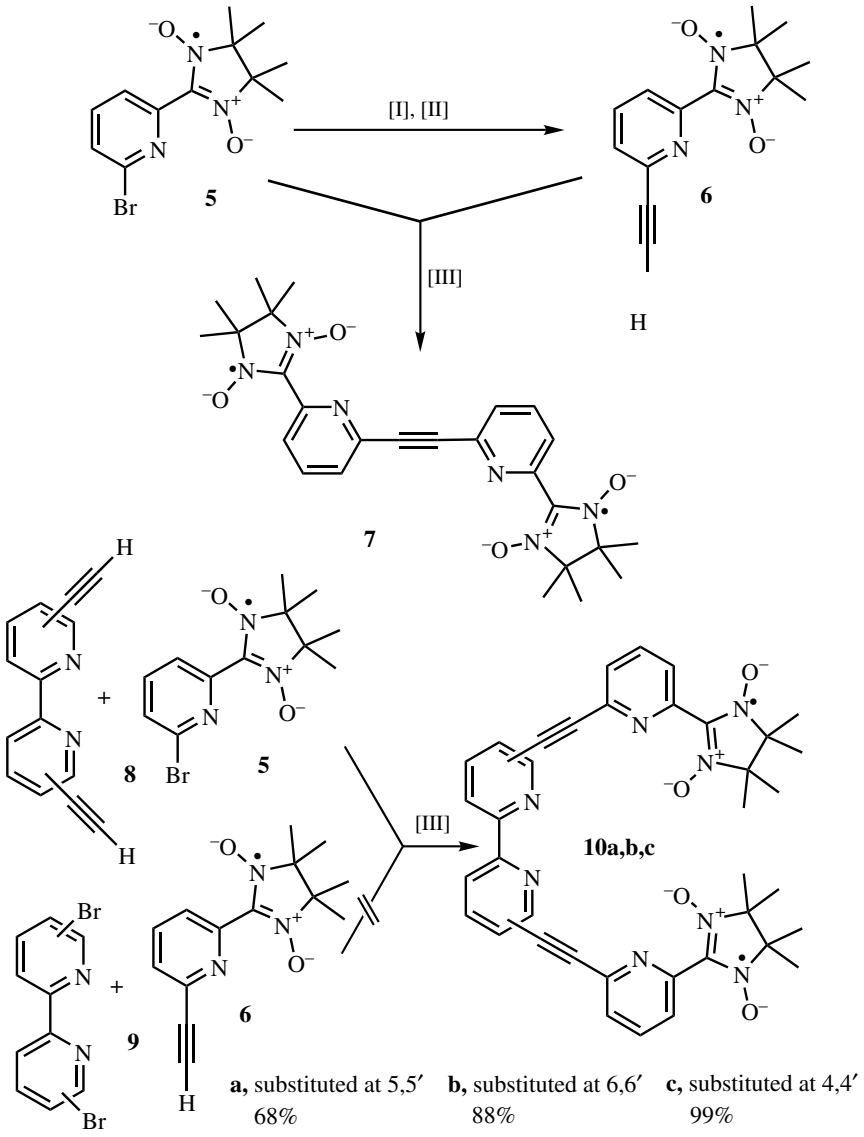


Pd (mol 1%)	Ligand	Ligand/Pd	Time (h)	Yield of Trimer (%)
15	$AsPh_3$	4:1	1	68
15	$AsPh_3$	4:1	2	61
5	$AsPh_3$	2:1	1	1
30	$AsPh_3$	4:1	1	22
15	$P(2\text{-furyl})_3$	4:1	2	7
15	PPh_3	4:1	2	0

Scheme 5

Pd-catalyzed cross-coupling as shown in **Scheme 6**.[15] Double cross-coupling of dibromobipyridine **9** does not proceed because the terminal alkyne function is deactivated by the strong withdrawing effect of NIT radicals.

Starting from benzylaminopolystyrene, the diverse *o*-haloaryl resins **11** are prepared from substituted *o*-haloanilines. Pd-catalyzed cross-coupling under standard conditions with different alkynes affords *o*-alkynylarene resins **12**. Copper is omitted



a, substituted at 5,5′ 68% **b,** substituted at 6,6′ 88% **c,** substituted at 4,4′ 99%

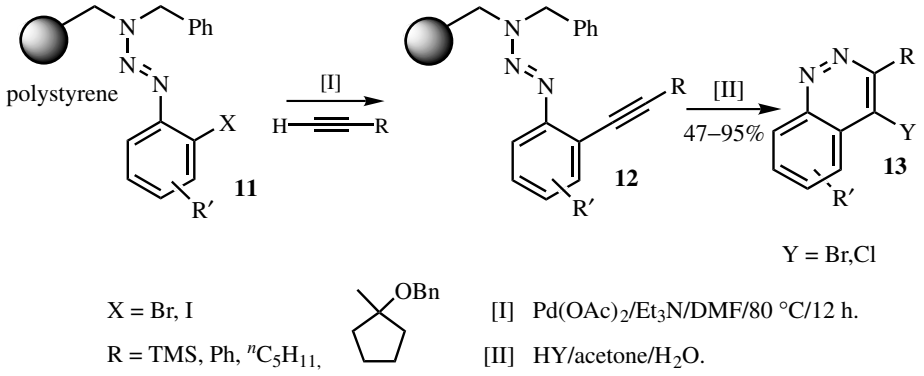
[I] HC≡CTMS/Pd(PPh_3)$_4$ (5 mol %)/C_6H_6/iPr_2NH.

[II] KF/CH_3OH.

[III] Pd(PPh_3)$_4$ (5 mol %)/C_6H_6/^{i}Pr_2NH.

Scheme 6

due to the coordination to the triazene moiety, hence leading to traces of copper in the final product. The Richter cleavage reactions are conducted under acidic conditions to give the quinolines **13** in 47–95% yields and with 60–95% purity without any further purification. The cleavage is successfully conducted in a 2×11 matrix on the Bohdan MiniBlock (**Scheme 7**). The method is applicable to automated synthesis.[16]



Scheme 7

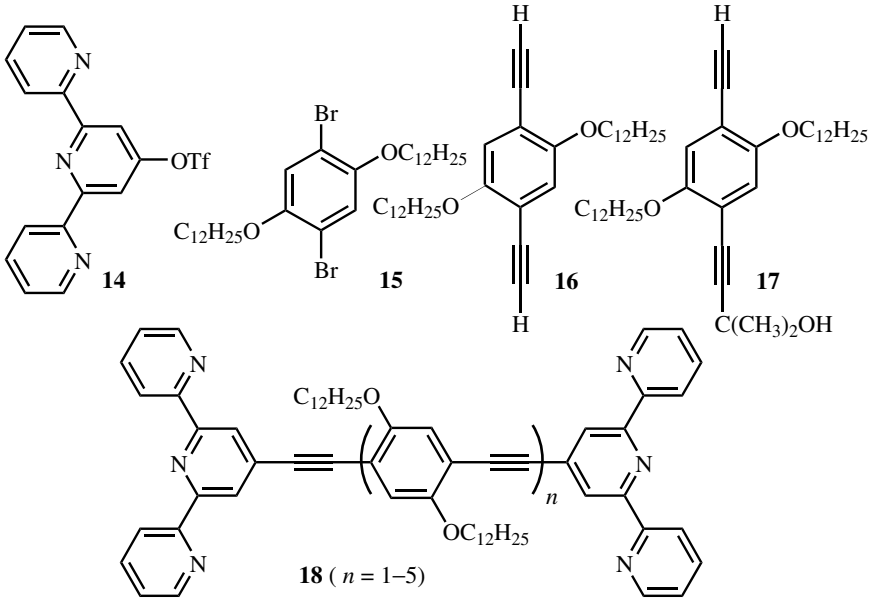
Soluble ditopic terpyridine ligands **18** ($n = 1-5$) bearing an alternate of acetylenic/phenyl modules (one to five) can be synthesized in a stepwise manner by the protocol based on sequential Pd-catalyzed cross-coupling reactions between selected monoterpyridine fragments and either mono-protected arylacetylene **17** or diethynylarene **16** using [Pd(PPh$_3$)$_4$] (6 mol %) as a catalyst and excess ^{i}Pr$_2$NH as a base at 60 °C in yields of 47–84% (**Scheme 8**).[17]

However, a series of alkyne-substituted oligopyridines **19**–**26** (**Scheme 9**) can be synthesized from halogenated precursors **27** at room temperature by Pd/Cu-catalyzed cross-coupling under normal conditions, Cl$_2$Pd(PPh$_3$)$_2$ (3–4 mol %) and CuI (10–14 mol %) in ^{i}Pr$_2$NH, in 60–90% yields. During cross coupling, formation of [Cu(phenRR´)$_2$]$^+$ is observed. Decomposition of the complexes with KCN in water and subsequent sonification is necessary in order to increase the isolated yields from 7% to 60% for **21** and **22**.[18]

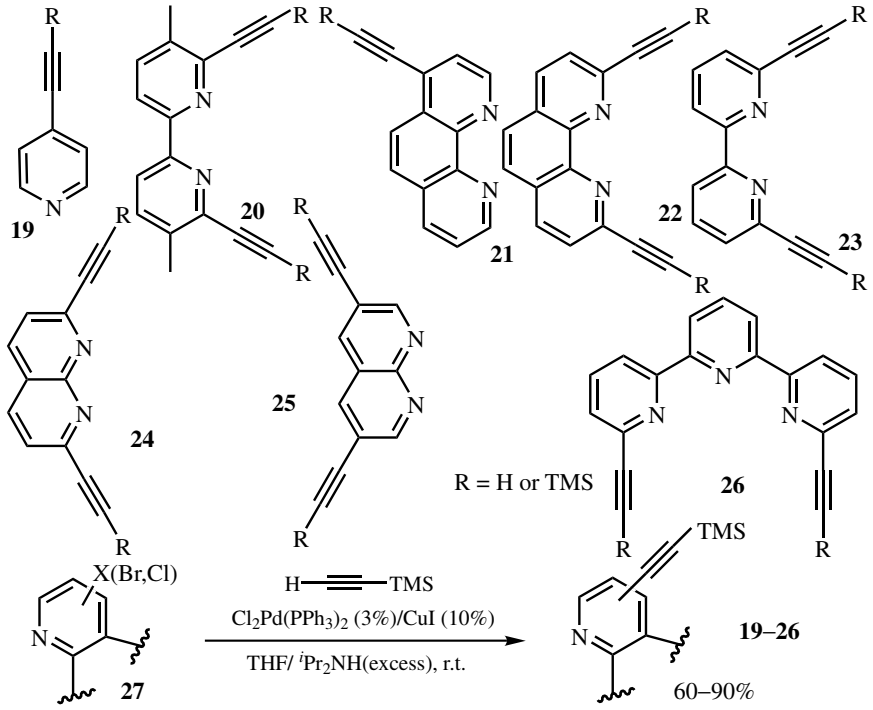
The more forcing conditions required for the Pd-catalyzed coupling reactions in the absence of CuI the more side reactions occur, such as an insertion of acetylenes into the Pd—C bond. In the absence of terminal acetylene, even diphenylacetylene can be inserted into the Pd—C bond. Thus, the Pd-catalyzed reaction of vinylic bromides with diphenylacetylene at 100 °C in the presence of Et$_3$N produces penta- or hexa-substituted fulvenes **28** in low to moderate yields (**Scheme 10**).[19]

B.ii. Cu-Catalyzed Cross-Coupling Reactions of Organic Halides with Terminal Acetylenes

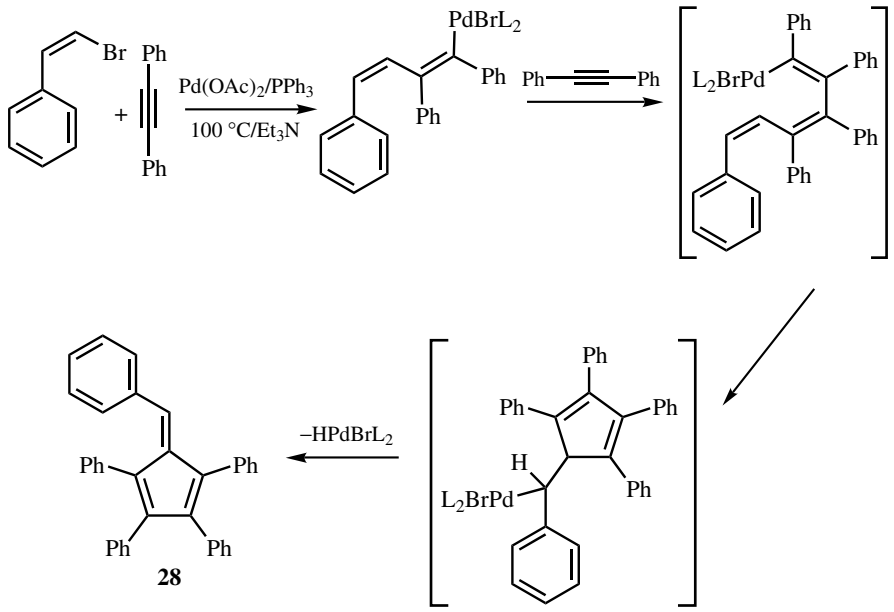
The reaction of aryl halides **29** with alkynylcoppers **30** is known as the Stephens–Castro reaction,[5] which has proved to be particularly important in the synthesis of a wide



Scheme 8

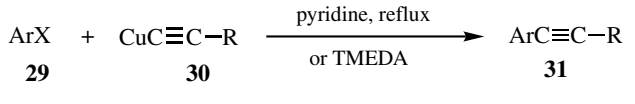


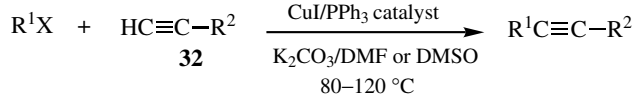
Scheme 9



Scheme 10

range of aromatic and heteroaromatic acetylenes **31** (**Scheme 11**). Vinyl and allenic halides can also be used and several reviews of the reaction have been published.[20],[21] Now, the Castro-type reaction can be applied to terminal acetylenes **32** catalytically without the need for isolation of alkynylcoppers at temperatures of 80–120 °C in the presence of CuI/PPh_3 as a catalyst using K_2CO_3 as a base (**Scheme 11**). Addition of PPh_3 is essential for the reaction to proceed catalytically, indicating initial formation of alkynylcopper species coordinated by PPh_3 followed by reaction with aryl and vinyl halide.[22],[23]





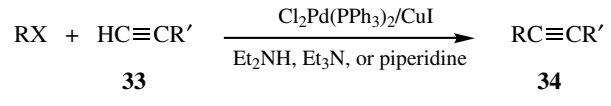
R^1 = aryl, vinyl; X = Br, I

R^2 = Ph, *n*-pentyl

Scheme 11

B.iii. Pd/Cu-Catalyzed Cross-Coupling Reactions of Organic Halides or Triflates with Terminal Acetylenes

A well-established method for the synthesis of internal alkynes **34** is the Pd/Cu-catalyzed coupling of vinyl halides, aryl iodides, bromides, or triflates with terminal acetylenes **33** (**Scheme 12**). Nevertheless, this method suffers not only from the need for large amounts of catalyst (1–5 mol % Pd and 1–10 mol % CuI) but also from the need of higher temperatures for the aryl bromides.



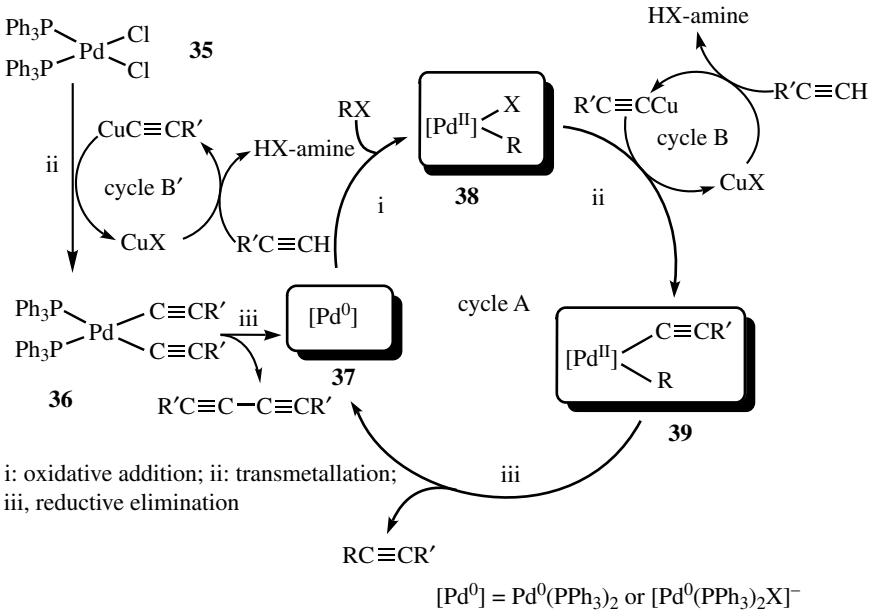
Scheme 12

As shown in the proposed reaction scheme (**Scheme 13**),[3],[24] this protocol is based on the discovery of CuI-catalyzed transmetallation in amine[4] and is constructed by a combination of two catalytic cycles A and B. The reaction certainly follows the normal oxidative addition–reduction elimination process common to Pd-catalyzed C—C bond-forming reactions. The exact mechanism of the reaction, however, is not known. In particular, the structure of the catalytically active species and the role of the copper catalyst remain unclear. The process may be envisaged as involving Pd^0 species [Pd^0] **37**, neutral $Pd^0(PPh_3)_2$,[3] or anionic $[Pd^0(PPh_3)_2X]^-$,[24] generated from the Pd(II) precatalyst **35**, which gives the Pd(II) intermediate **38** by the oxidative addition of the sp^2-C halide. Subsequent reaction with terminal acetylene, possibly via a transient copper acetylide species (cycle B), leads to the alkynylpalladium(II) derivatives **39**, which collapses to give the required coupled products and to regenerate the active Pd species **37**. There is no evidence for acceleration of the reductive elimination step by Cu(I) (step iii, from **39** to **37**), although some destabilization of *cis*-alkenylacetylide **39** via a coordination of Cu(I) to the acetylide ligand is expected.

Aryl halides carrying electron-withdrawing groups *ortho* or *para* to the halide will more readily undergo oxidative addition. The reaction does proceed without the copper cocatalyst but only under more forcing conditions and not with less active substrates, such as aryl bromides or chlorides.

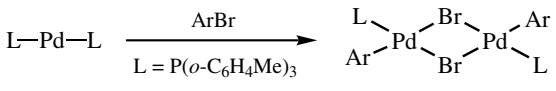
As a palladium source, $Cl_2Pd(PPh_3)_2$ in amines is commonly used, where a catalytically active, coordinatively unsaturated complex **37** is produced by reductive elimination of Pd–acetylide complex **36** generated from $Cl_2Pd(PPh_3)_2$ **35** and a terminal acetylene (**Scheme 13**). In many cases, $Pd(OAc)_2$ or $Cl_2Pd(CH_3CN)_2$, and 2 equiv of a tertiary phosphine, L, and a terminal acetylene, which are reduced *in situ* to the catalytically active complexes **37**, have been used. The consumption of the terminal acetylene to generate the active species causes the unsuitability of this system for polymer synthesis by the cross-coupling methodology. $Pd^0(PPh_3)_4$, which generates active catalytic species **37**, and $Pd^0(PPh_3)_2$ after the endergonic loss of excess triphenylphosphine, is also useful. However, $Pd^0(PPh_3)_2$ is often present at trace levels, with the consequence of low catalytic activity for the active organic halides under milder reaction conditions.

$Pd^0{}_2(dba)_3$ in the presence of phosphine ligands, L, is also a useful Pd^0 source, where dba should easily be removed to afford the active species, PdL_2, in nearly stoichiometric amounts. In contrast with $Pd^0(PPh_3)_4$, $Pd^0{}_2(dba)_3$ is insensitive to oxygen. Accordingly, any special care for its storage and manipulation is not needed. Commercial palladium/carbon (10%) can also be used as a palladium source for the coupling with aryl bromides.[25]



Scheme 13

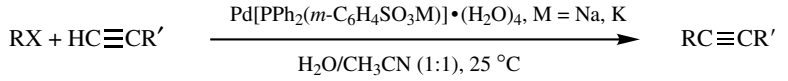
Now, one can predict the mechanism for the cross-coupling to produce eneyne conjugated compounds catalyzed by palladium complexes containing both monodentate and chelating ligands. The catalytic cycles differ in the coordination number of the palladium complexes involved and factors that control the coupling reactions with organic halides. It has been shown that the catalytic cycle for the cross-coupling reaction of alkynes with sp^2-C halides catalyzed by palladium complexes with $P(o\text{-}C_6H_4Me)_3$ ligands exclusively contains monophosphine intermediates, Pd^0L. The active catalyst, Pd^0L_2, is added oxidatively by aryl halides to give dimeric aryl–halide complexes **40** (**Scheme 14**).[26] In contrast, the chemistry catalyzed by palladium complexes with dppf or BINAP ligands involves bisphosphine complexes as a result of ligand chelation and the fact that reductive elimination can occur without ligand dissociation.

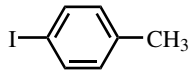


37 **40**

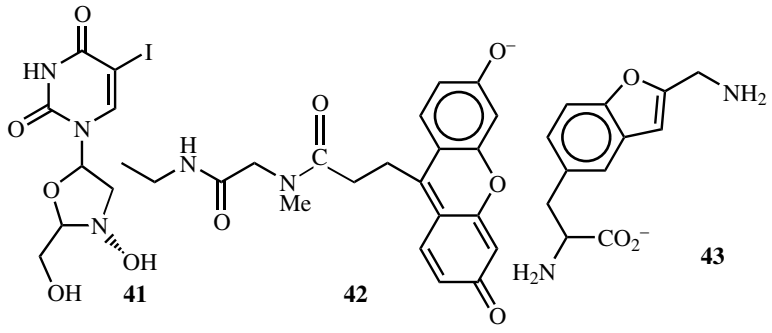
Scheme 14

The advantage of using water-soluble catalysts for a large-scale chemical industry lies in simplifying product isolation and recycling of the catalyst. Casalnuobo and Calabrese reported that, by using the water-soluble Pd(0) catalyst $Pd[PPh_2(m\text{-}C_6H_4SO_3M)]_3$ ($M = Na^+$, K^+), various iodides reacted with terminal alkynes to give the cross-coupling products in high yields in water. Unprotected nucleosides, nucleotides, and amino acids undergo coupling with acetylenes. 3-Iodotyrosine is coupled to propargylamine, leading initially to the expected alkyne, which then cyclized *in situ* to give the benzofuran derivative **43** (**Scheme 15**).[27]



RX	R′	Time (h)	Yield (%)
	Ph	3	100
5-Iodo-2′-deoxyuridine **41**	$CH_2NHCOCF_3$	4	95
5-Iodo-2′-deoxycytidine 5′-monophosphate	CH_2NH_2	3	73
5-Iodo-2′-deoxycytidine 5′-triphosphate	**42**	3	50
3-Iodotyrosine	CH_2NH_2	12	82[a]

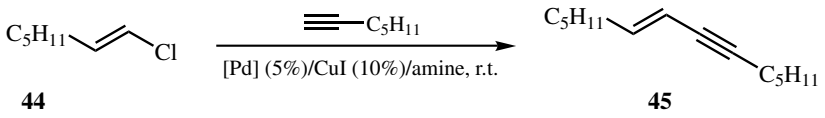
[a]HPLC yield.



Scheme 15

Various conditions have been employed for this reaction, depending on the reactivity of the halide, the alkynes, and the base used. The reactivity order of coupling for organic halides is vinyl iodide ~ vinyl triflate > vinyl bromide > vinyl chloride > aryl iodide >> aryl bromide >> aryl chloride. The coupling of terminal acetylenes with vinyl chlorides **44**, which are inert toward many other catalysts, proceeds efficiently by the "ligandless catalyst" in piperidine. In this case, vinyl iodides, under the same conditions, give lower yields of coupled products **45** than those with vinyl chlorides **44** (**Scheme 16**).[28] For aryl bromides, the coupling can proceed only with bromides activated by substituent at higher temperature, where the additional phosphine is

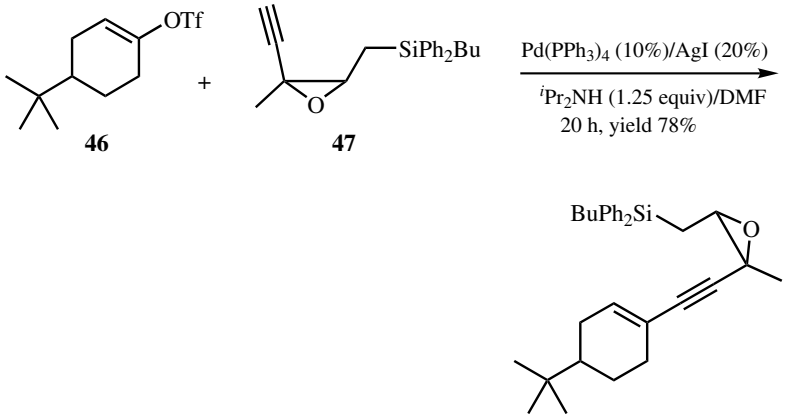
recommended to avoid depositon of metallic palladium.[3] Copper(I) iodide is a particularly effective cocatalyst, allowing the reactions to occur at room temperature. Copper(I) bromide is also useful.[29],[44],[64] For the coupling of ethynyloxiranes **47** with alkenyl triflates **46**, a new set of catalysts, $Pd(PPh_3)_4$ and AgI, gives better results than normal combination of $Pd(PPh_3)_4$/CuI (**Scheme 17**).[30]



44 **45**

[Pd]	Amine	Time (h)	Yield (%)
$Cl_2Pd(PhCN)_2$	Piperidine	0.5	93
$Cl_2Pd(PPh_3)_2$	Piperidine	20	93
$Pd(PPh_3)_4$	Piperidine	16	11
$Pd(PPh_3)_4$	$^{n}PrNH_2$	60	62

Scheme 16



46 **47**

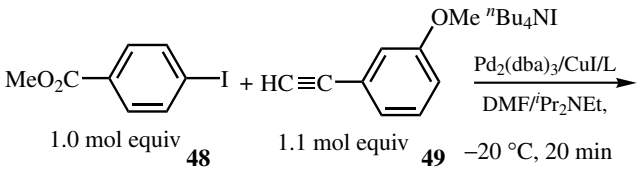
Scheme 17

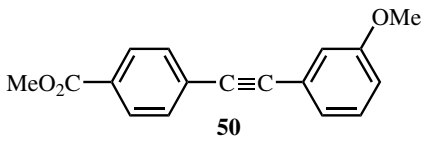
C. RECENT DEVELOPMENT OF Pd-CATALYZED CROSS-COUPLINGS IN ALKYNE SYNTHESIS

In the last decade, there has been tremendous development in Pd-catalyzed coupling systems for Heck-type reactions. Careful choice of substrates and skillful tailoring of reaction conditions open the door to elegant and highly convergent routes to structurally complex molecules. A handicap was the restriction of coupling substrates to aryl and alkenyl bromides and iodides. Consequently, there was great interest in the development

of coupling substrates that are both more economical and preparatively more easily accessible, and reactive even at lower reaction temperature.

Recently, a low-temperature Pd-catalyzed reaction was developed, which coupled equimolar amount of aryl iodide **48** possessing electron-withdrawing groups with aromatic acetylene **49** at −20 °C in quantitative yield. The reaction proceeds in DMF/$^{i}Pr_2NEt$ in the presence of $Pd_2(dba)_3$, CuI, $^{n}Bu_4NI$, and additive for 20 min (**Scheme 18**).[31] While 41% yield of the coupling product is obtained under the nonadditive conditions, no reaction occurs in the absence of $^{n}Bu_4NI$. Thus, the ammonium salt turns out to be essential for the low-temperature coupling reaction. While PPh_3 is not effective, introduction of methyl group at the *ortho*-position improves the yield. The use of a hindered triarylphosphine, tris(2,4,6-trimethylphenyl)phosphine, gives the product **50** in quantitative yields in 20 min. Phosphine oxide and phenols are other good promoters. In these reactions, purification of CuI[32] is critical to obtain reproducible results. The substituent effect of the aryl iodide is substantial. Reactions of aryl iodides lacking the electron-withdrawing group, for example, the reaction with phenyl iodide, *p*-tolyl iodide, or *p*-methoxyphenyl iodide, stops before completion with concomitant formation of palladium black.[31]





50

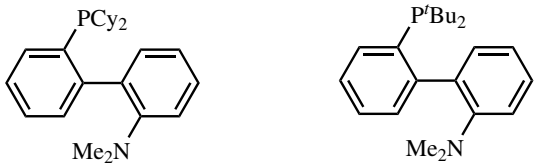
L	mol %	Yield (%)
None		41
None[a]		0
PPh_3	20	32
$(p\text{-Tol})_3P$	20	39
$(o\text{-Tol})_3P$	20	52
$(2,4,6\text{-triMeC}_6H_2)_3P$	20	quant
$(2,4,6\text{-triMeC}_6H_2)_3P$	10	85
$OPPh_3$	20	82
2,6-di^{t}BuC$_6$H$_3$OH[b]	20	92

$^{n}Bu_4NI$	200 mol %
$Pd_2(dba)_3$	2.5 mol %
CuI	20 mol %
L	20 mol %

[a] In the absence of $^{n}Bu_4NI$.
[b] Methyl *m*-iodobenzoate was used.

Scheme 18

One successful approach toward activation of less reactive substrates like aryl chlorides involves the use of aminophosphine ligands. Thus, a mixture of palladium acetate and *o*-(di-*tert*-butylphosphino)biphenyl **51** (**Scheme 19**) catalyzes the room-temperature Suzuki coupling of aryl bromides and aryl chlorides with 0.5–1.0 mol % Pd. Use of *o*-(dicyclohexylphosphino)biphenyl **52** allows Suzuki couplings to be carried out at low catalyst loadings (0.000001–0.02 mol % Pd). The process tolerates a broad range of functional groups and substrate in terms of reaction temperature, turnover number, and steric tolerance, which has been reported to date.[33] However, there is no example for the coupling with terminal acetylenes.



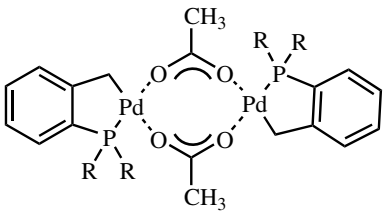
51 **52**

Scheme 19

Another successful approach toward activation of less reactive substrates involves the use of thermally stable palladacycles **53** and **54** as catalyst precursors. For the coupling of activated, electron-poor aryl bromides like 4-bromoacetophenone with phenylacetylene, palladacycle catalyst **53** gives high turnover numbers (TONs) of up to 8000 (mol product/mol Pd) without addition of CuI. Only the reaction in Et_3N as the solvent and base gives satisfactory results. The addition of a cosolvent or cobase slows down the reaction dramatically. This effect is explained by a sensitive association–dissociation equilibrium at active intermediates and the almost quantitative precipitation of Et_3NHBr formed during the reaction (**Scheme 20**).[34] The palladacycle catalysts constitute only a thermally stable reservoir for the active species. For easy to activate aryl iodides, triflates, *in situ* systems are good enough to obtain high yields in the couplings.[34] But if the steric requirements of the substrates dictate higher reaction temperatures or even chlorides for coupling, palladacycle systems should be the catalyst of choice.

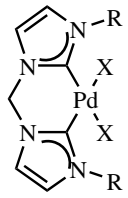
In the last decade, there has been increasing recognition that organic reactions carried out in aqueous media may offer advantages over those occurring in organic solvents.[35] The covalent attachment of nonnatural substructure (reporter groups, physicochemical probes, coenzymes, specificity tags, etc.) to biomolecules requires chemical methods that allow regioselective modification of the multifunctional target without harming its fragile biologically competent three-dimensional structure. Pd-catalyzed cross-coupling in aqueous solution would leave most functions of biomolecules untouched. As a model reaction of biomolecules, the cross-coupling reaction between water-soluble iodoarenes **55** and terminal alkynes **56** in the presence of Pd catalyst prepared from cationic guanidinophosphines is shown in **Scheme 21**. New quantitative cross-couplings were obtained in aqueous solution at 35 °C within minutes even in the presence of a protein.[36]

Pd-catalyzed coupling of 3,5-diiodobenzoic acid **58** with acetylene gas in a basic aqueous medium provides a high molecular weight (~60,000), zigzag phenylethynylene



R = *o*-Tol, Ph, Cy, ^{t}Bu, Mes

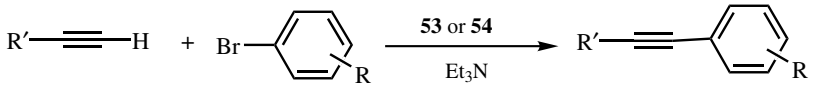
palladacycle **53**



R = CH_3, alkyl, aryl

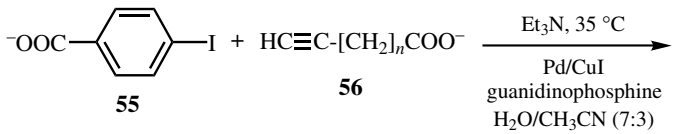
X = I, Br, PF_6, BF_4

palladacycle **54**

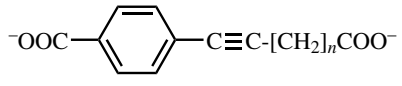


R	R′	Catalyst (mol % Pd)		Temperature (°C)	Reaction Time (h)	Yieid (%)	TON (mol product/mol Pd)
4-$COCH_3$	Ph	**53**	0.1	90	5	99	990
4-$COCH_3$	Ph	**53**	0.1	90	24	80	8000
4-Cl	Ph	**53**	0.1	90	16	90	900
4-$_n$Bu	Ph	**53**	0.1	90	24	80	800
4-$COCH_3$	TMS	**53**	0.1	90	7	0	800
4-$COCH_3$	C_4H_9	**53**	0.1	80	24	0	0
4-$COCH_3$	Ph	**54**	1	90	48	76	76
4-F	Ph	**54**	1	90	48	71	71

Scheme 20



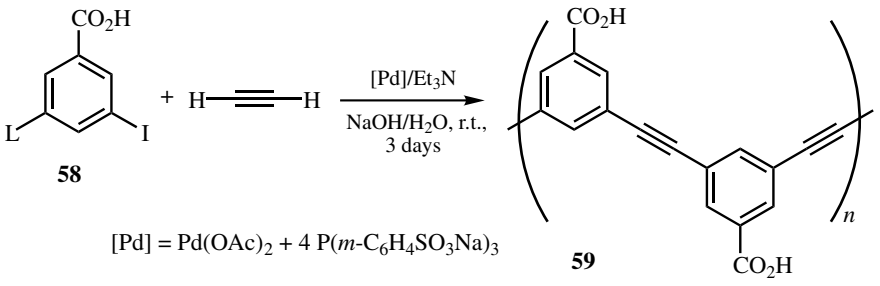
55 **56**



57

Scheme 21

polymer **59**, which is soluble in basic solutions and is reversibly switchable from soluble to hydrogel states in water by changing the pH of the solvent (**Scheme 22**).[37]



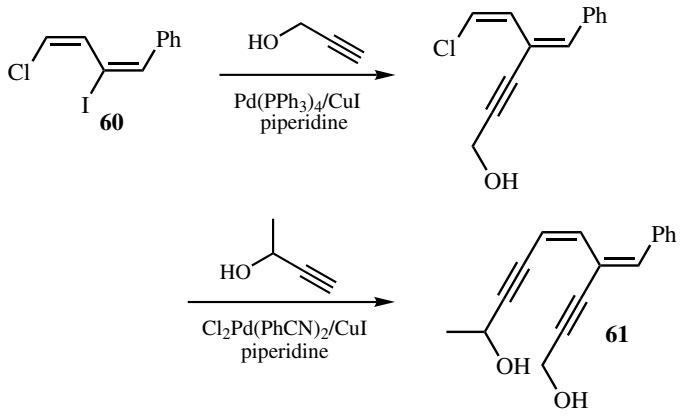
Scheme 22

D. SCOPE OF THE REACTION

D.i. Vinyl Halides and Related Compounds

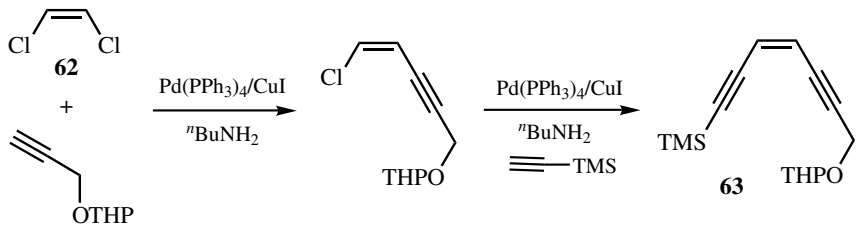
Coupling is commonly applicable to substitution of vinyl iodides, bromides, triflates, and even chlorides under standard conditions and leads to coupled products that are very useful in several areas of natural products. The use of vinyl triflates further extends the scope of coupling as the required triflates are easily prepared from available aldehydes and ketones.

Vinyl halides are generally more reactive than the corresponding aryl halides and reactivity order is I ,OTf . Br . Cl. Sequential coupling of dihalide 60 with 1-alkynes under Pd/Cu catalysis can provide stereodefined (Z,E)-dienediyne 61 in a stepwise manner (**Scheme 23**).[38]



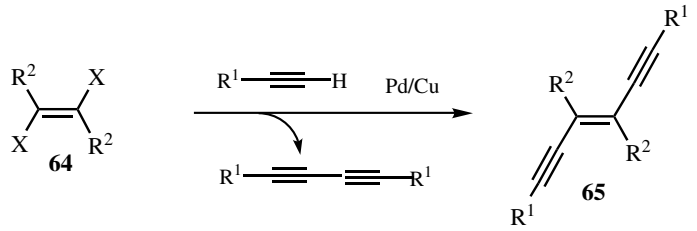
Scheme 23

In general, enediynes are prepared by a Pd/Cu-mediated cross-coupling reaction of vinyl dihalides or analogs with terminal acetylenes under standard conditions in good to excellent yields. In the synthesis of endiyne **63**, acceptable monosubstitution of a vinyl dihalide **62** can be achieved by using a large excess of the dihalides over the alkyne (**Scheme 24**).[39]



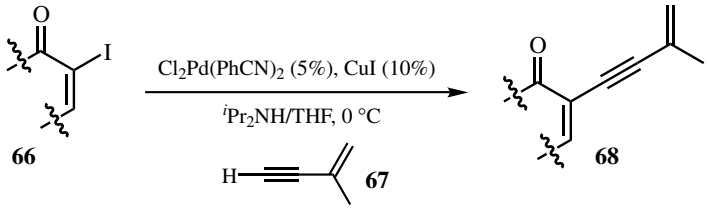
Scheme 24

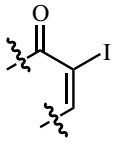
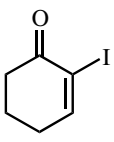
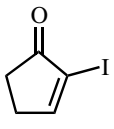
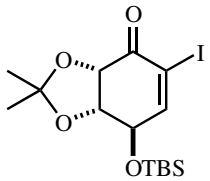
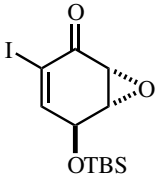
Pd-catalyzed double coupling of a dihalide **64** with a terminal acetylene, while effective in the case of (*Z*)-enediynes, is often problematic with (*E*)-haloalkenes **65** due to competing alkyne oligomerization reactions (**Scheme 25**).[40]



Scheme 25

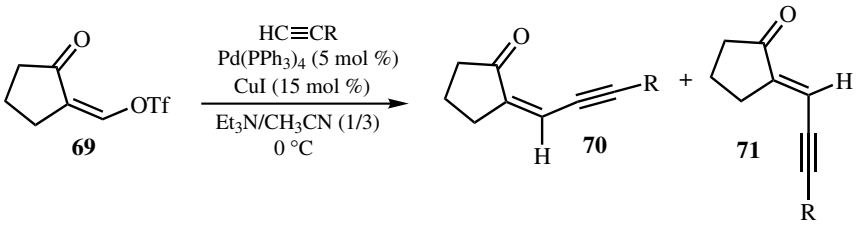
The coupling of a 2-iodo-2-cycloalkenone **66** with a terminal acetylene **67** has been optimized with the presence of $Cl_2Pd(PPh_3)_2$, CuI, and $^iPr_2NH$ in THF at 0°C (**Scheme 26**).[41] The reaction was found to be complete within 25–45 min under these conditions in 52–89% yields. The coupling proceeds faster with $^iPr_2NH$ than with Et_3N.



Product (**68**) (Yield)				
				
	(75%)	(89%)	(75%)	(52%)

Scheme 26

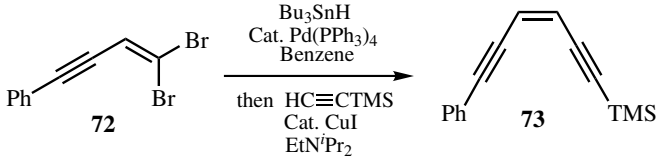
A stereoselective synthesis of (*Z*)-ketoenynes **70** was established by using Pd/Cu-catalyzed cross-coupling of the labile (*Z*)-ketoenol triflate **69** with 1-alkynes under carefully controlled reaction conditions. Isomerization of the coupling products into the more stable (*E*)-ketoeneynes **71** is observed and can be minimized by carrying out the coupling reaction in CH_3CN at 0 °C by limiting the reaction time using Et_3N as the base (**Scheme 27**).[42] The reaction in $^{i}Pr_2NH$/THF (1:3) at room temperature does not give the product **70**.



HC≡CR	Time(min)	**70:71**	Products (%)	
R = $SiEt_3$	15	100:0	**70**	30
R = $Si^{i}Pr_3$	15	96:4	**70**	78
R = $(CH_2)_4OMe$	25	100:0	**70/71**	54:9

Scheme 27

Pd-catalyzed hydogenolysis of 1,1-dibromo-1-alkenes **72** and successive cross-coupling can be carried out either in a stepwise manner or in one-pot under the same Pd catalysis. These two processes should be useful for the synthesis of geometrically pure eneyne with a (*Z*)-alkenyl unit **73** (**Scheme 28**).[43]

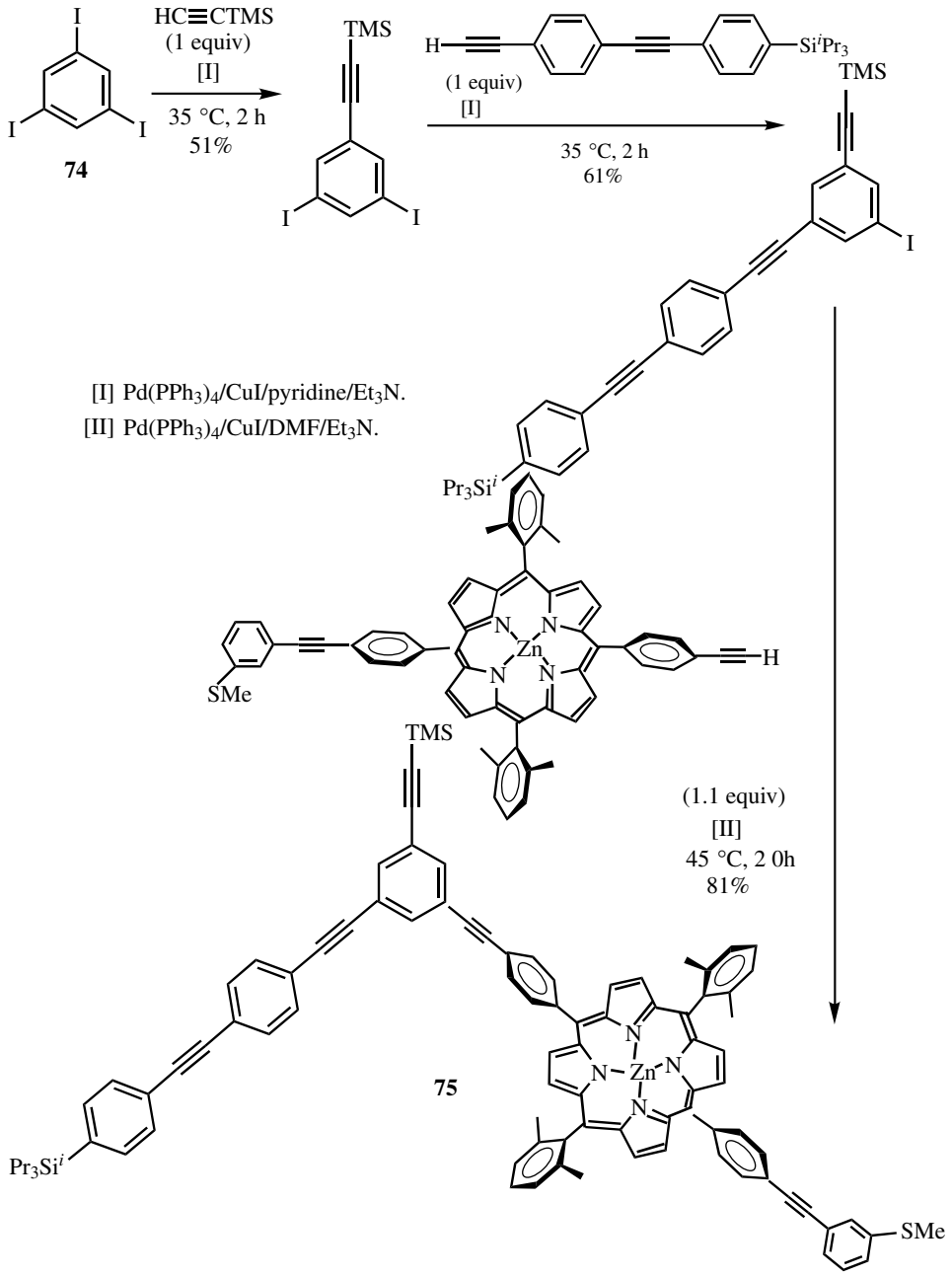


Scheme 28

D.ii. Aryl Iodides

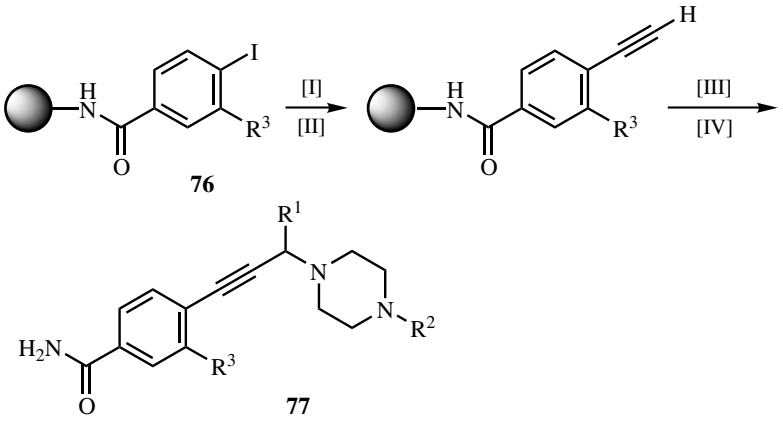
The most commonly used form of the Pd/Cu-catalyzed cross-coupling reaction is that in which an aromatic iodide is coupled with a terminal alkyne. The reaction takes place readily at room temperature and is often complete in a few hours. The reaction of iodides is very reliable and proceeds readily without vigorous purification of substrates and without use of dry or freshly distilled solvents. The presence of a Cu^{+} species is essential for the coupling to proceed at room temperature. CuI is most often used but CuBr has been used successfully.[29],[44],[64] Generally, commercial grade CuI is perfectly adequate in this procedure. The Pd catalyst originally employed by us, $Cl_2Pd(PPh_3)_2$, is the most commonly used one to effect the coupling. The coupling is so robust that little investigation of alternative Pd catalysts has been deemed necessary. Among other catalysts, both $Pd(PPh_3)_4$ and $Pd(OAc)_2/PPh_3$ have been used effectively, and it is likely that any of the commonly used Pd(0) or Pd(II) species function equally well in the coupling.

Selective and stepwise couplings of polyiodobenzene with terminal acetylenes are also reported. In the course of the synthesis of rigid, benzene-centered, star-like porphyrin arrays, triply coupled derivative **75** has been prepared by Pd/Cu-catalyzed cross-coupling reactions with different terminal acetylenes under normal conditions from 1,3,5-triiodobenzene **74** in a stepwise manner (**Scheme 29**).[45]



Scheme 29

The cross-coupling of a resin-bound iodobenzoic acid **76** with trimethylsilylacetylene followed by TBAF desilylation provides a polymer-supported arylacetylene. Treatment with an aldehyde and a secondary amine in dioxane in the presence of CuCl catalyst results in the generation of resin-bound propargylamines. The final products **77** are cleaved from the resin and obtained in excellent yields and purity (**Scheme 30**).[46]



R_1	R_2	R_3	Yield(%)	Purity (%)
4-MeC_6H_4	(*E*)-PhCH=CH-CH_2	H	71	95
3-FC_6H_4	2,3-diMeC_6H_3	H	85	>95
4-MeC_6H_4	$PhCH_2$	H	90	>95

[I] Trimethylsilylacetylene (7 equiv)/CuI (10 mol %)/$Pd(PPh_3)_4$ (10 mol %)/THF/Et_3N (1/1), r.t., 40 h.

[II] TBAF, 1.0 M solution in THF, 5 h, r.t.

[III] Aldehyde (4 equiv)/piperidine (4 equiv)/CuCl (10 mol %)/dioxane, 90 °C, 36 h.

[IV] TFA/H_2O (9:1), r.t., 0.5 h.

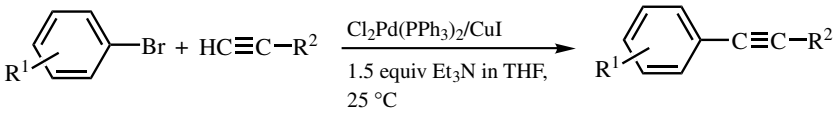
Scheme 30

D.iii. Aryl Bromides

Aromatic bromides react much less readily than the corresponding iodides and generally require solvents at reflux in order to effect the reaction. Whereas with iodides no special care is needed to ensure useful conversions of starting materials to products, the lower reactivity of the bromides requires a more careful choice of reaction conditions. It is advisable in this case to use a high-quality amine solvent (triethylamine most commonly), although vigorous drying is necessary. An important requirement, however, is to deoxygenate the reaction mixture prior to addition of the copper catalysts. It is useful to prevent the decomposition of the Pd catalyst and the oxidative coupling of the acetylenes.

Reliable and practical procedures for the synthesis of arylacetylenes by Pd-catalyzed cross-coupling of aryl bromides with terminal acetylenes have been developed, which

involve the use of THF as solvent.[47] By careful choice of the reaction mixture and the mode of addition of the reactants, even unreactive substrates are converted into the products with good yields at room temperature as shown in **Scheme 31**.



R^1	R^2	Method	Yield (%)
4-CHO	Me_3Si	A	99
4-COMe	Me_3Si	A	92
2-CO_2Me	Me_3Si	B	88
3-CO_2Me	Me_3Si	B	87
4-COMe	^{n}Bu	B	91
4-COMe	Ph	B	87

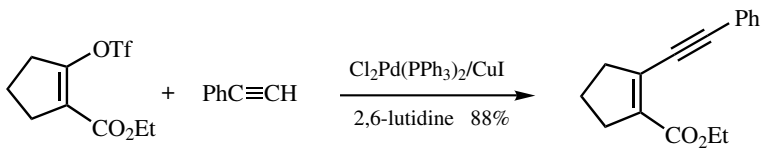
A: $Cl_2Pd(PPh_3)_2$ (4 mol %)/CuI (2 mol%) 1 h

B: $Cl_2Pd(PPh_3)_2$ (5 mol %)/ PPh_3 (2.5 mol %)/CuI (3 mol %) 16 h

Scheme 31

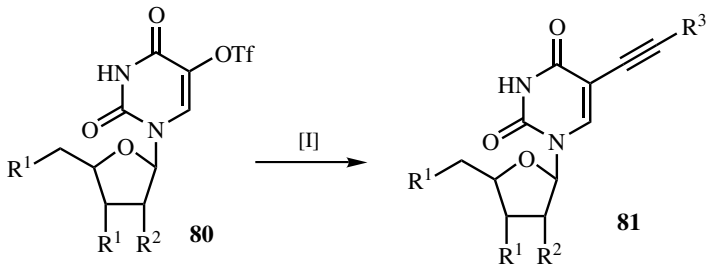
D.iv. Aryl or Vinyl Triflates

Aryl or vinyl triflates, which can easily be prepared from the less expensive and readily available hydroxyl, aldehyde, or ketone derivatives, can undergo Pd-catalyzed cross-coupling reactions with terminal acetylenes. Facile Pd/Cu coupling of vinyl triflates with terminal acetylenes was reported by Cacchi.[48] The cross-coupling of enol triflate with phenyl acetylene proceeds easily under normal conditions (**Scheme 32**).[49] In view of the importance of C5-alkynyl uridine nucleosides as anticancer agents, Pd-catalyzed couplings of terminal acetylenes with 5-(trifluoromethanesulfonyloxy)pyrimidine nucleosides have been investigated. In most cases coupling is observed at room temperature but it is often very slow; slight elevation(55 °C) in the reaction temperature leads to a dramatic increase in the rate of coupling (**Scheme 33**).[50] For the double cross-coupling of aromatic 1,2-bistriflates with trimethylsilylacetylene, the addition of ^{n}Bu_4NI accelerates enediyne formation. Enediyne formation with catechol ditriflate and trimethylsilylacetylene are shown in **Scheme 34**.[51] The coupling under standard conditions gives a 29:71 ratio of **48/49**. Iodide salts (300 mol % of either KI or ^{n}Bu_4NI) greatly accelerate the Pd-catalyzed coupling reaction. Bromide, chloride, or triflate salts do not show the same enhancement.



78 **79**

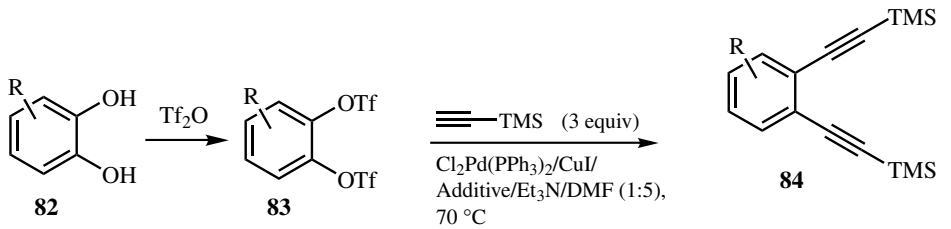
Scheme 32



[I] R^3-C≡CH (1.5 equiv)/$Pd(PPh_3)_4$ (5%)/CuI (10%)/Et_3N (1.5 equiv)/DMF

R^3	Time (h)	Temperature (°C)	Yield (%)
TMS	2.5	50	85
$HOMe_2C$	0.5	55	90
Ph	2.0	55	93

Scheme 33



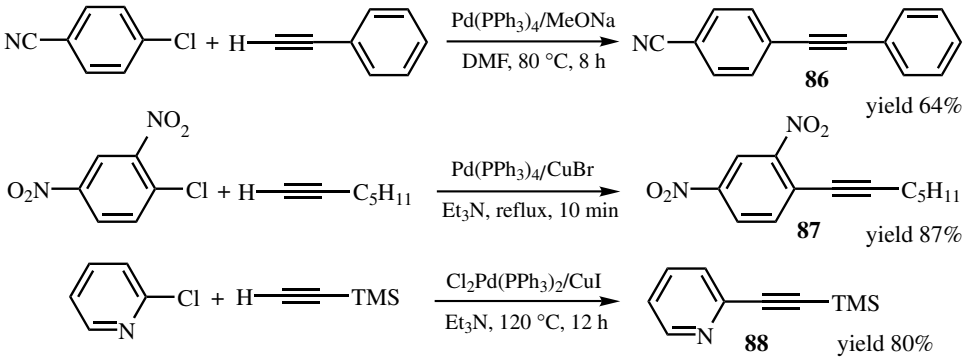
$Cl_2Pd(PPh_3)_2$ (mol %)	CuI	Time (h)	Additive	Additive (mol %)	Product (%)	
10	30	44	none	none	**84/85**	29:71
5	20	20	$^nBu_4NBr$	300	**85**	38
10	25	18	$^nBu_4NBr$	300	**84**	52
10	30	3	$^nBu_4NBr$	300	**84**	91
10	30	4	KI	300	**84**	91

Scheme 34

D.v. Aryl Chlorides

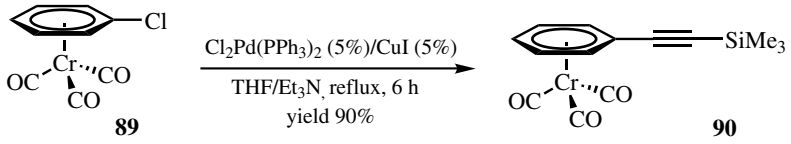
Aryl chlorides are both more readily available and less expensive than aryl bromides or iodides. A few existing methods for the Pd-catalyzed coupling of aryl chloride substrates usually only function well for electron-deficient substrates such as **86** and **87**

(**Scheme 35**).[2],[44],[52] Many heteroaromatic chlorides such as **88** can, however, react quite readily. This situation has changed rapidly in the past few years. For example, in the case of the Heck reaction, noteworthy advances in the use of aryl chlorides have been described by Ohff et al.,[53] Herrmann et al.,[54] and Shaw et al.[55] Recent work by Littke and Fu[56] has established that certain Pd-catalyzed coupling reactions of aryl chlorides can be accomplished efficiently in the presence of sterically hindered, electron-rich phosphines such as P^tBu_3. However, there are no examples of utilization for the coupling reaction of chloroarene with terminal acetylenes.



Scheme 35

On the other hand, even the recently prepared Herrmann–Beller catalyst[34],[57] still requires higher temperatures for efficient coupling rates of the Heck reaction. Interestingly, the complexation of chloroarenes with the $Cr(CO)_3$ fragment activates the arene–chlorine bond considerably toward the oxidative addition. Thus, $Cr(CO)_3$ complexed chloroarenes react about 15 times faster than iodoarenes in Pd-catalyzed cross-coupling reactions under mild conditions, in particular in Pd/Cu-catalyzed cross-couplings with terminal acetylenes in refluxing THF and/or tertiary amines (**Scheme 36**).[57]



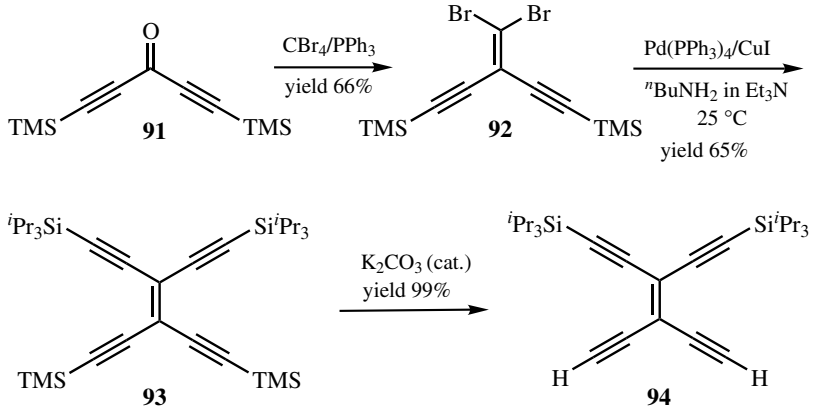
Scheme 36

E. APPLICATIONS

E.i. Synthesis of Terminal Acetylenes

A conjugated terminal acetylene is an important intermediate in organic synthesis. The reaction of acetylene gas with organic halides preferentially gives only internal acetylenes because of the higher reactivity of monosubstituted acetylenes than that of acetylene gas.

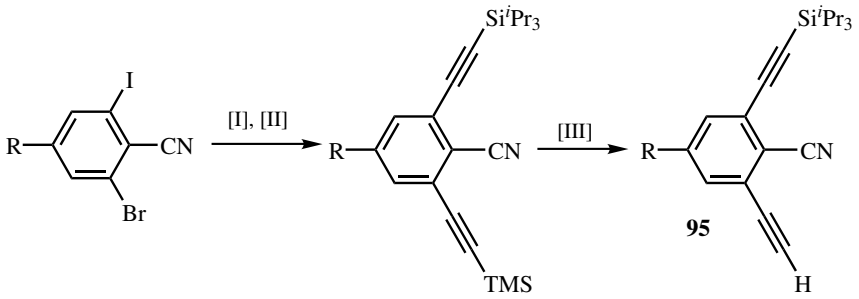
The most commonly used protecting group for acetylenes is the trimethylsilyl (TMS) group.[58] Thus, commercially available trimethylsilylacetylene provides an excellent starting material for the synthesis of aryl and alkenyl acetylenes. Triisopropylsilyl groups are also useful for the step wise deprotection with TMS groups (**Scheme 37**). Cross-coupling of aryl or alkenyl halides with trimethylsilylacetylene proceeds in the presence of a Pd catalyst and CuI, followed by treatment with dilute aqueous KOH[58] or K_2CO_3[6],[60] in MeOH or a source of fluorine, such as KF, KF-crown ether, TASF, or $^nBu_4NF$[66],[78] to give terminal acetylenes. This protocol is applied to the synthesis of the starting monomers for acetylenic nanoarchitectures, such as ring and dendrimer molecules.



Scheme 37

Recently, direct synthesis of terminal acetylenes via Pd-catalyzed cross-coupling of aryl or alkenyl halides with ethynylmetals was developed by Negishi and co-workers (**Section III.2.8.2**).[59]

A combination of selective and stepwise cross-couplings of polyhalides with protected acetylenes and deprotections under various conditions leads to the synthesis of unsymmetrically substituted polyethynylated arenes or olefins as shown in **Schemes 37**,[60] **38**,[61] and **39**.[62]

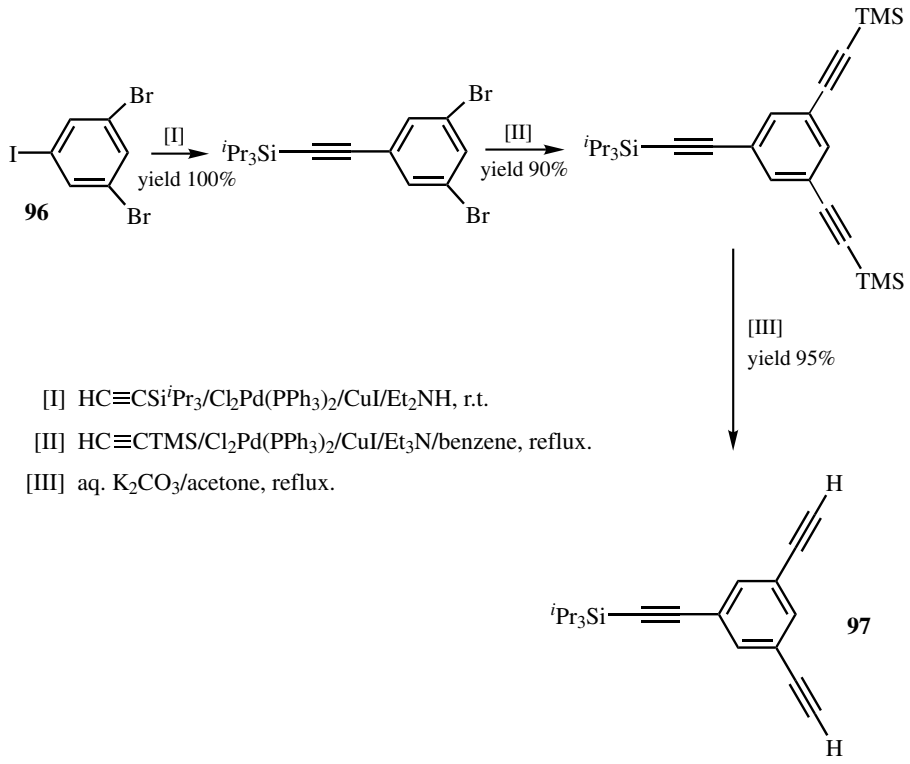


[I] HC≡CSi^{i}Pr$_3$/[Pd$_2$(dba)$_3$]CHCl$_3$/CuI/PPh$_3$/Et$_3$N, 70 °C.

[II] HC≡CTMS/[Pd$_2$(dba)$_3$]CHCl$_3$/CuI/PPh$_3$/Et$_3$N, 70 °C.

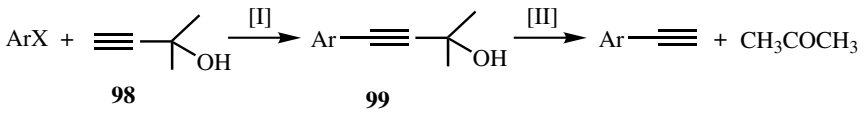
[III] LiOH/THF/H$_2$O, r.t.

Scheme 38



Scheme 39

A relatively inexpensive 2-methyl-3-butyn-2-ol **98** is also a useful protecting reagent for stable and volatile arylalkynes. Base-catalyzed "retro-Favorsky" elimination of acetone from alcohols RC≡CC(CH$_3$)$_2$OH **99** can successfully be applied to prepare terminal acetylenes (**Scheme 40**).[63],[64] Treatment with KOH at elevated temperatures is required for elimination of acetone. Many procedures are reported.



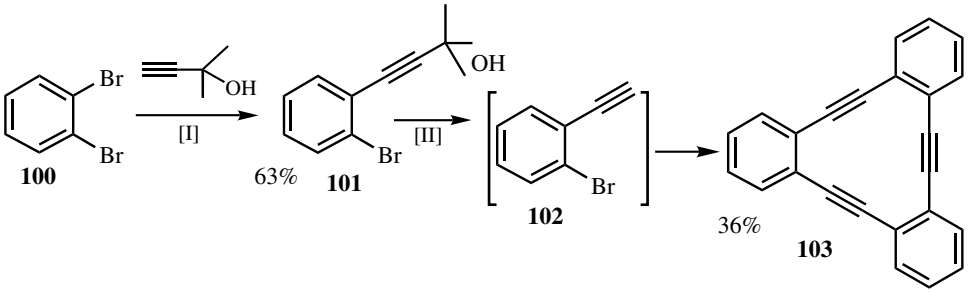
[I] Pd(PPh$_3$)$_4$/CuBr in Et$_3$N or piperidine.

[II] KOH(cat.)/paraffin oil, heat.

Scheme 40

By utilization of this methodology, dehydro[12]annulenes were prepared in two steps (**Scheme 41**).[65]

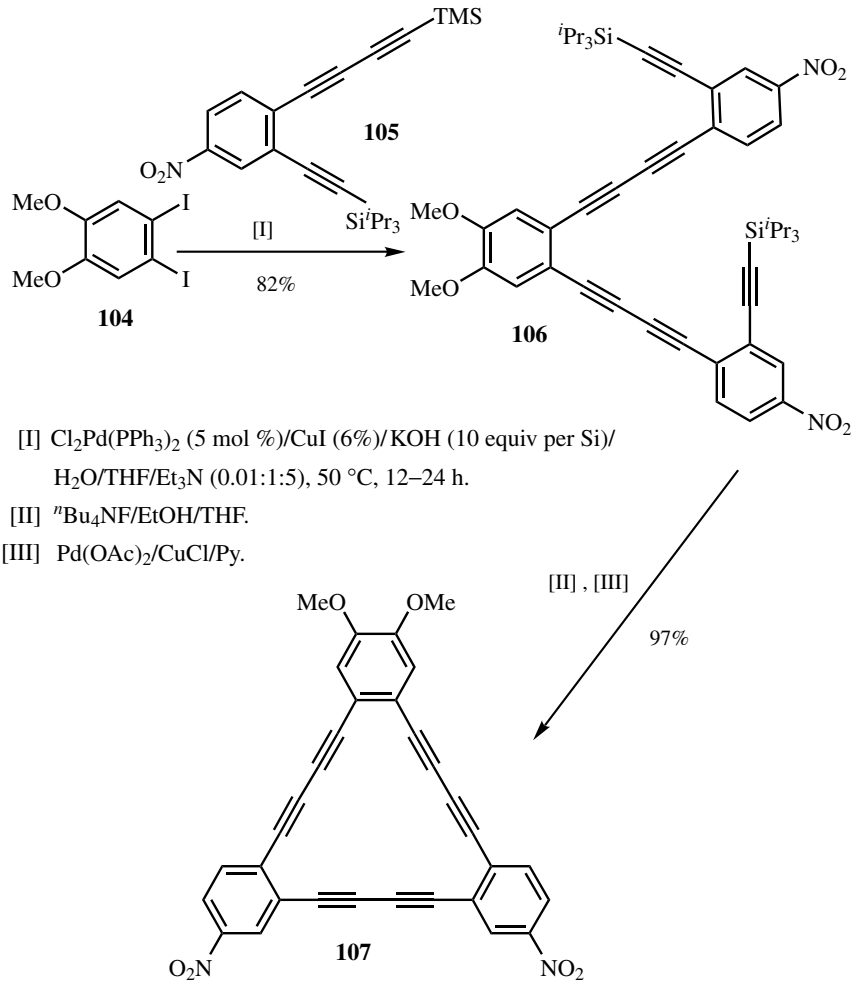
By the *in situ* desilylation/alkynylation reaction diiodoveratrole **104** reacts with trimethylsilylbutadiyne derivative **105** to afford silylated α,ω-polyyne **106**, which is further desilylated by ^{n}Bu$_4$NF in THF/ethanol solution (**Scheme 42**).[66]



[I] $Pd(PPh_3)_4$/CuI in Et_3N, 60 °C, 5 h.

[II] 5N aq. KOH/$Pd(PPh_3)_4$ /CuI/$BnNEt_3Cl$/benzene, 85 °C, 22 h.

Scheme 41



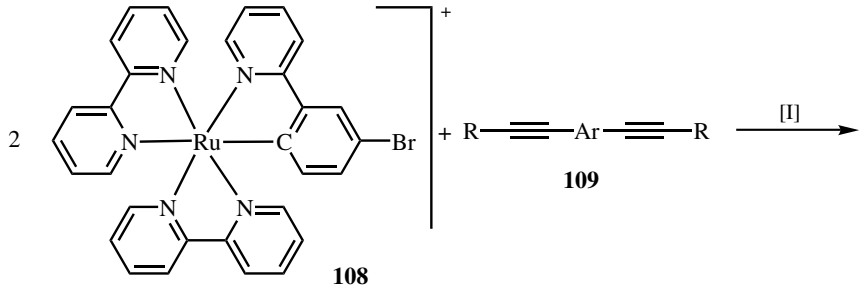
[I] $Cl_2Pd(PPh_3)_2$ (5 mol %)/CuI (6%)/ KOH (10 equiv per Si)/ H_2O/THF/Et_3N (0.01:1:5), 50 °C, 12–24 h.

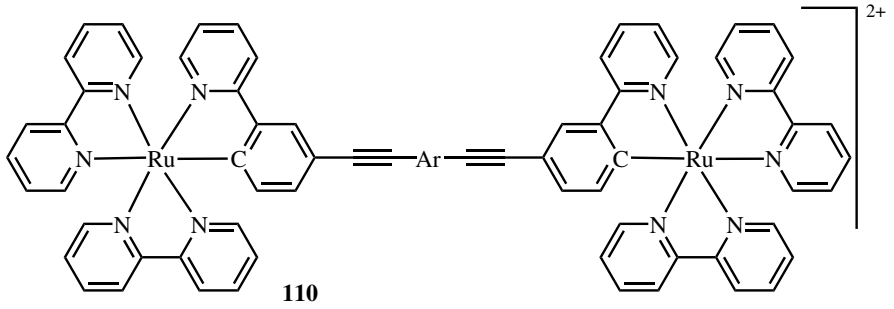
[II] $^nBu_4NF$/EtOH/THF.

[III] $Pd(OAc)_2$/CuCl/Py.

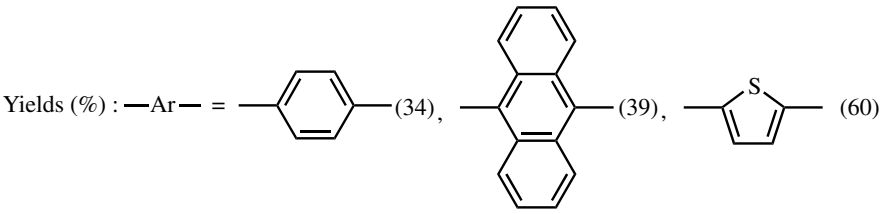
Scheme 42

The cross-coupling of the poorly reactive aryl bromides **108** with sensitive alkynes **109** (R = H) do not proceed under standard conditions. The one-pot desilylation of TMS-protected alkynes **109** (R = TMS) followed by the cross-coupling with a brominated complex allows the use of sensitive diynes and provides an easy access to models of wires (**Scheme 43**).[67]





[I] NaOH/CuI (3%)/$Pd(PPh_3)_4$ (5%)/DMF, 80 °C, 16 h.



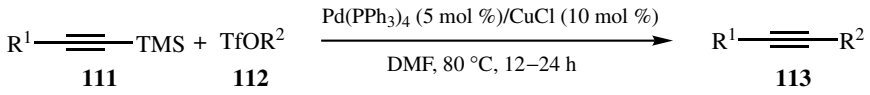
Scheme 43

Alkynylsilanes **111** react with aryl or alkynyl triflates **112** by the Pd–Cu catalyst in DMF to give the cross-coupling, namely, "sila"-Sonogashira–Hagihara coupling, products in good to excellent yields (**Scheme 44** and **Table 1**).[68] The Si—C bond may be cleaved by Cu^+ in a polar solvent. As as application of the coupling, desired unsymmetrical diarylacetylenes **115** starting with trimethylsilylacetylene can be synthesized without isolation of **114** (**Scheme 44**).

TABLE 1. Cross-Coupling Reaction[a] of (Phenylethynyl)trimethylsilane 111 with 4-Acetyl-phenyl Triflate 112 (Scheme 44)

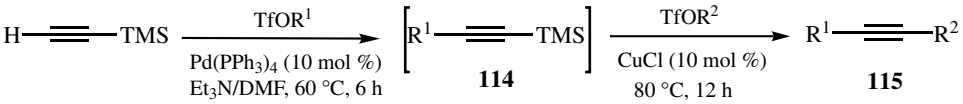
$Pd(PPh_3)_4$ (mol %)	CuCl (mol %)	Time (h)	Yield[b] (%) **113**
5	10	12	97
1	2	24	97
5[c]	5	12	93
0	10	12	0
5	0	12	0

[a]Reactions were carried out using $Pd(PPh_3)_4$ (1.0 mmol) and 4-acetylphenyl triflate (**112**) (1.2 mmol) in DMF (5 mL).
[b]GC yield based on (phenylethynyl)trimethylsilane.
[c]$Cl_2Pd(PPh_3)_2$ was used.



111 **112** **113**

$R^1 = C_6H_5$, 4-NCC_6H_4, 4-$MeOC_6H_4$, 2-thieny; R^2 = 4-$MeCOC_6H_4$, 4-NCC_6H_4, 4-$Me_3CC_6H_4$



114 **115**

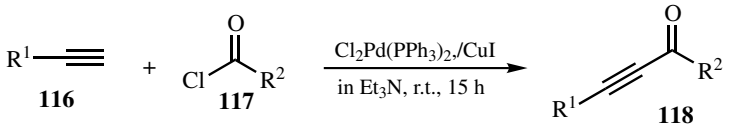
Scheme 44

E.ii. Synthesis of Alkynyl Ketones

α,β-Acetylenic ketones have attracted considerable biological interest because of their utility as synthetic intermediates, particularly for the synthesis of heterocyclic systems. A common route to α,β-acetylenic ketones involves the acylation of metal acetylide. The direct Pd-catalyzed coupling of acyl chloride with terminal acetylenes[69],[70] or (alk-1-ynyl)tributylstannanes[71] to give α,β-acetylenic ketones was reported (**Schemes 45** and **46**). Alkynyltributylstannanes provide a convenient and mild method for synthesizing alkynyl ketones that is complementary to or, when sensitive functional groups such as TMS group are present, superior to the corresponding terminal acetylenes. Alternatively, acetylenic ketones can also be obtained via one-pot formation of two carbon–carbon bonds under Pd-catalyzed carbonylative conditions by reaction of alk-1-ynes with aryl or vinyl halides and vinyl triflates (**Scheme 47**).[72]

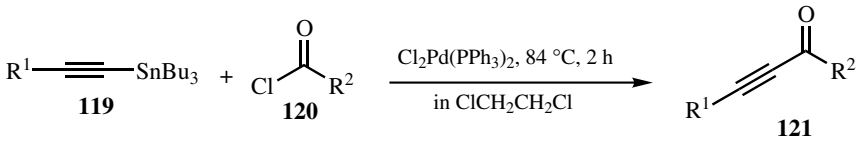
E.iii. Synthesis of Enediyne Macrocycles

Enediynes have attracted attention as substrates for the Bergman cyclization, and as a structural motif found in a variety of DNA-cleaving antitumor antibiotics, such as



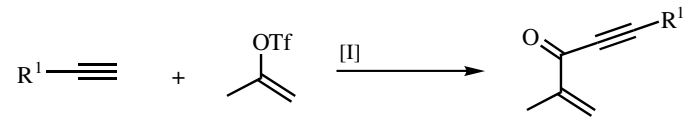
R^1	R^2	Yield (%)	Reference
Ph	Ph	96	[69]
Ph	PhCH=CH−	75	[69]
Ph	^{t}Bu	79	[69]
Me	*o*-BrC_6H_4	33	[70]
^{n}Bu	*o*-BrC_6H_4	71	[70]
Ph	*o*-BrC_6H_4	89	[70]

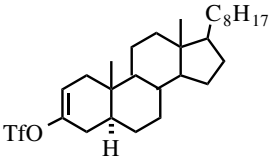
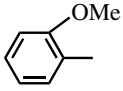
Scheme 45



R^1	R^2	Yield (%)
Ph	Ph	94
Ph	^{i}Pr	69
TMS	Ph	64
TMS	^{i}Pr	71

Scheme 46

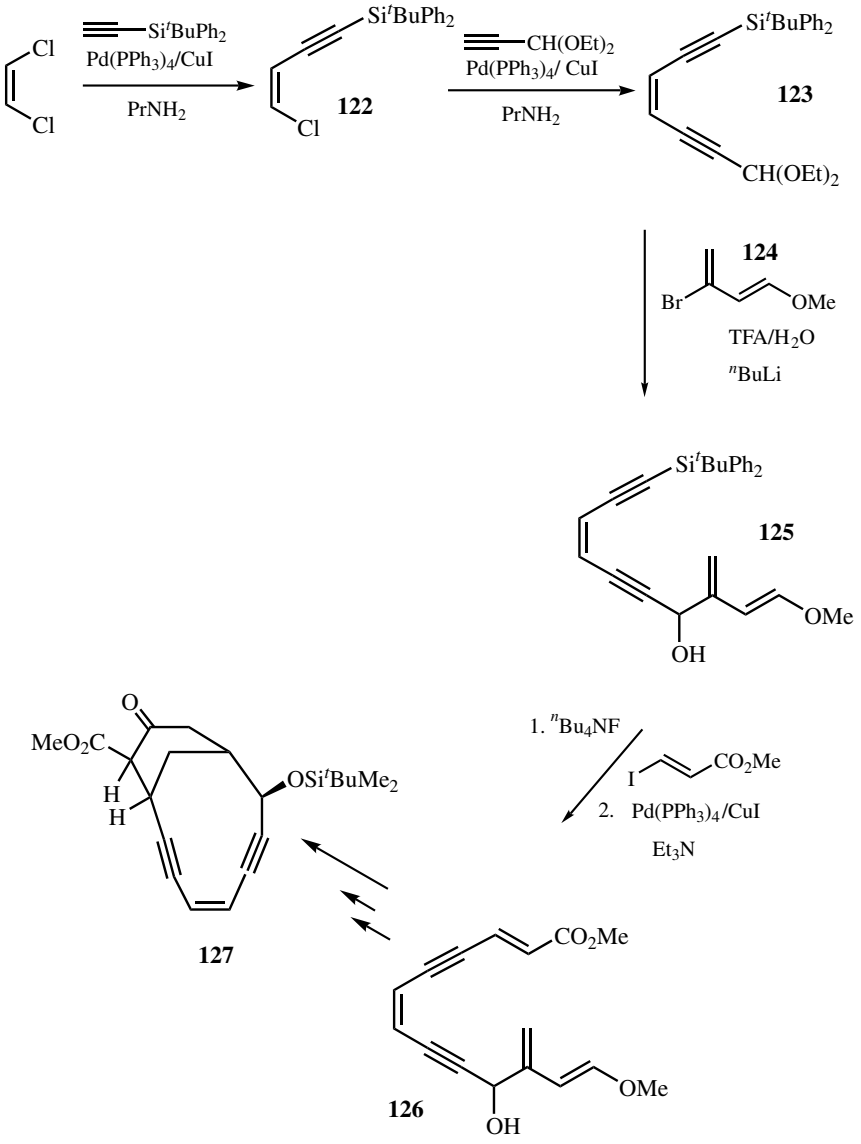


R^1	Enol Triflate	Yield (%)
		83
	"	80

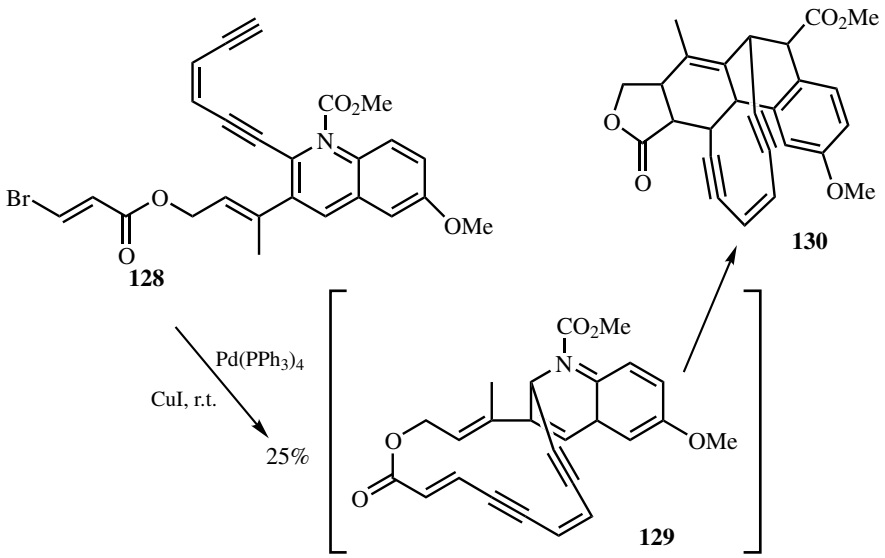
[I] : $Pd(OAc)_3$, dppp,Et_3N, CO(1 atm), 60 °C, 2.5 h

Scheme 47

esperamisins and dynemicins. Conjugated polyeneyne **126** is a model precursor for the intramolecular Diels–Alder cyclization in a biomimetic pathway to the esperamicins **127** (**Scheme 48-1**). This model compound is synthesized via **122**–**123** from *cis*-dichloroethylene by regiocontrolled sequential coupling of three different alkynes using two kinds of appropriate Pd catalysts.[73] Interestingly, the novel intramolecular reaction of the alkenyl bromide with the terminal acetylene in **128**, followed by intramolecular Diels–Alder reaction, affords the highly strained dynemicin A skelton **130** in one step (**Scheme 48-2**).[73],[74]



Scheme 48-1

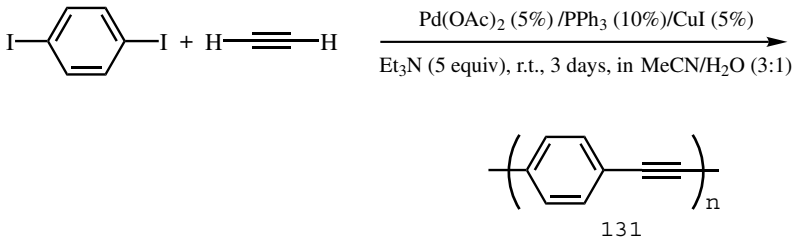


Scheme 48-2

E.iv. Polymer Synthesis by Cross-Coupling

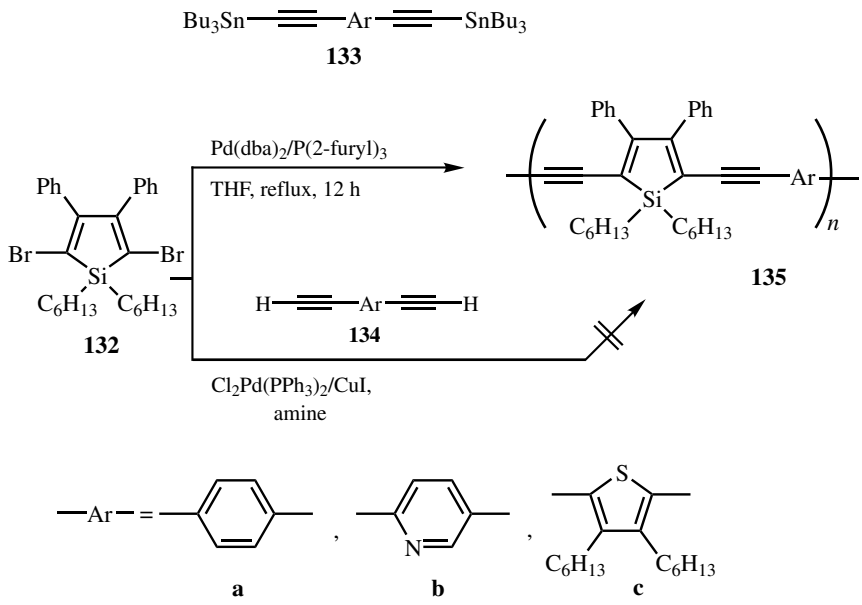
Since the yield of the Pd-catalyzed cross-coupling of aryl iodides with terminal acetylenes is practically quantitatve, the cross-coupling of α,ω-diethynyl would be expected to yield linear aryleneethynylene-conjugated polymers.

Polymers such as polyphenyleneethynylene **131** can be synthesized via polymerization of aryl iodides with acetylene gas in aqueous medium (**Scheme 49**).[75]



Scheme 49

However, the coupling reaction of **132** with terminal acetylenes **134** using a $Cl_2Pd(PPh_3)_2$/CuI catalyst system in amine gives only a complex mixture. Diethynylsilole-based π-conjugated polymers **135** are prepared by the Stille coupling reaction of 2,5-dibromosiloles **132** with bis(stannylethynyl)arenes **133**, as shown in **Scheme 50**. When the phenylene and thienylene derivatives, **133a** and **133b**, are employed, the coupling reaction smoothly proceeds to give a red polymer **135a** and deep violet polymer **135b** in 92% and 68% yields, respectively.[76]

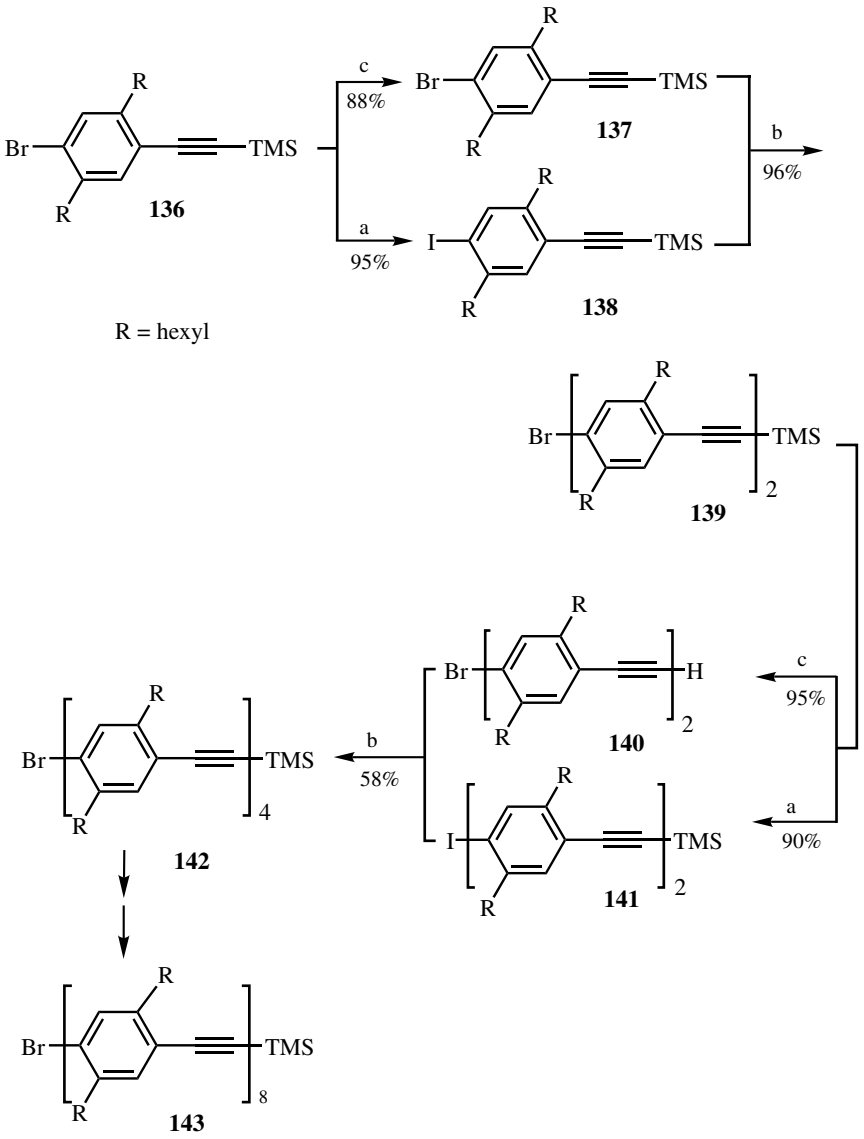


Scheme 50

Currently, increasing interest is being paid to monodisperse, well-defined oligomers as models for polymers. Besides this, the oligomers themselves can be used as modules for nanoscopic architectures, like rings and dendrimers, for example. For this purpose, shape-persistent oligomers like oligo(phenyleneethynylene)s and oligo(phenylenevinylene)s appear especially attractive. Oligo(phenyleneethynylene)s with hexyl or isopentoxy substituents have been prepared in a stepwise manner by Tours as shown in **Scheme 51**.[77] The iterative divergent/convergent binominal strategy is based on the bromine–iodine selectivity of the Pd-catalyzed cross-coupling, the conversion of a bromine substituent into an iodine substituent via halogen metal exchange, and the trimethylsilyl as an acetylene-protecting group. The synthesis is efficient and gives gram amounts of octamers **143**.

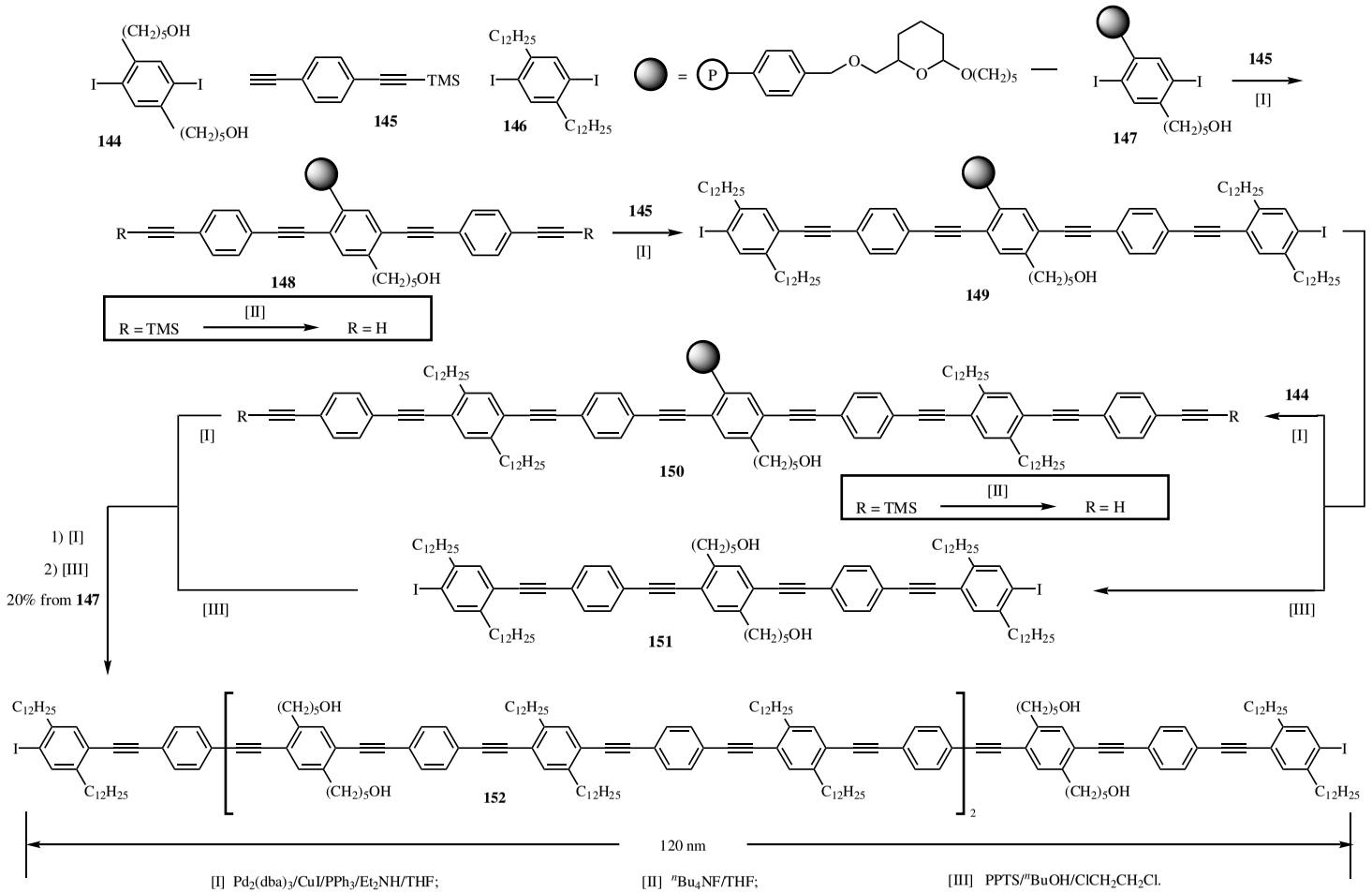
Another synthetic approach to the well-defined π-conjugated oligomers is a reported solid-phase strategy, which is illustrated in **Scheme 52** for the synthesis of the 120-nm long heptadecameric oligo(*p*-phenyleneethynylene) rod **152**. The iterative divergent/convergent synthetic approach is applicable to protocols for solid-phase synthesis. The starting monomer **144** is anchored through the hydroxy group using PPTS in dichloroethane to the dihydropyran-modified Merrifield's resin and is followed by the two steps of cross-coupling to give the extended resin-bound pentamer **149**. Attempts to generate **148** (R = H) directly from **147** and 1,4-diehynylbenzene fail, possibly due to rapid homocoupling of 1,4-diehynylbenzene with trace oxygen present. Compound **148** (R = H) is prepared by the Pd/Cu-catalyzed cross-coupling of **147** with monomer **145** followed by deprotection. Polymer-supported trimer **148** (R = H) is then coupled with **146** {5–6 mol of **146** per mol of **148** (R—H)} to afford polymer-supported pentamer **149**. Excess **146** is easily recovered by filtration. One portion of **149** is coupled with **145** to produce the polymer-supported heptamer **150** (R = TMS). The remaining portion of **149** is treated with acid to liberate pentamer **151**. The

Pd/Cu-catalyzed coupling of **150** with excess of the liberated pentamer **151** affords the polymer supported 17-mer. Directly heating the mixture of **150** and **151** causes a much lower yield, possibly due to decomposition of the α,ω-diyne **150** (R = H). Recovery of excess **151** is simply achieved by filtration from the beads, followed by passage through silica gel. Finally, treatment of anchored **152** with acid liberates the free 120-nm long 17-mer **152**.[78]



a: (1) ^{n}BuLi, (2) ICH_2CH_2I; b:$Cl_2Pd(PPh_3)_2$/CuI/Et_2NH;
c: NaOH/MeOH/THF.

Scheme 51


144
145
146
147
148
149
150
151
152
[I]
[II]
[III]
R = TMS
R = H
1) [I]
2) [III]
20% from 147
120 nm
[I] Pd2(dba)3/CuI/PPh3/Et2NH/THF;
[II] nBu4NF/THF;
[III] PPTS/nBuOH/ClCH2CH2Cl.

Scheme 52

F. SUMMARY

1. Pd/Cu-catalyzed cross-coupling reactions of sp^2-C halides with terminal acetylenes have been shown to be highly useful and established reactions for the synthesis of eneyne compounds.

2. Recent developments of Pd/Cu-catalyzed cross-coupling such as low-temperature coupling, use of long-lived palladacycle catalysts, and coupling reactions in aqueous media were described. Although there have been tremendous developments in Pd-catalyzed systems for Heck-type reactions in the last decade, successful approaches toward the cross-coupling reaction with terminal acetylenes are rare.

3. Several examples of the application of Pd/Cu-catalyzed cross-coupling for synthesis of alkynyl ketones, terminal acetylenes, enediyne macrocycles, and enediyne polymers are given.

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