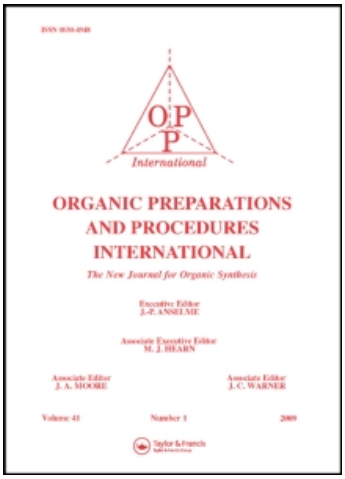


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SELECTIVE TRANSITION METAL-PROMOTED CARBON-CARBON AND CARBON-HETEROATOM BOND FORMATION. A REVIEW

Renzo Rossi[a]; Fabio Bellina[a]
[a] Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Pisa, ITALY

To cite this Article Rossi, Renzo and Bellina, Fabio(1997) 'SELECTIVE TRANSITION METAL-PROMOTED CARBON-CARBON AND CARBON-HETEROATOM BOND FORMATION. A REVIEW', Organic Preparations and Procedures International, 29: 2, 137 — 176
To link to this Article: DOI: 10.1080/00304949709355180
URL: http://dx.doi.org/10.1080/00304949709355180

ORGANIC PREPARATIONS AND PROCEDURES INT., 29 (2), 137-176 (1997)

SELECTIVE TRANSITION METAL-PROMOTED CARBON-CARBON AND CARBON-HETEROATOM BOND FORMATION. A REVIEW

Renzo Rossi* and Fabio Bellina

Dipartimento di Chimica e Chimica Industriale, Università di Pisa
Via Risorgimento 35, I-56126 Pisa, ITALY

SELECTIVE TRANSITION METAL-PROMOTED CARBON-CARBON AND CARBON-HETEROATOM BOND FORMATION. A REVIEW

Renzo Rossi* and Fabio Bellina

Dipartimento di Chimica e Chimica Industriale, Università di Pisa
Via Risorgimento 35, I-56126 Pisa, ITALY

INTRODUCTION

Transition metal-promoted carbon-carbon bond forming reactions, involving (hetero)aryl or alkenyl halides, are essential tools in the arsenal of organic chemist. The great synthetic importance of these reactions is attested to by several recent reviews and monographs on this subject.[1-9] Some chapters of Volume 12 of *Comprehensive Organometallic Chemistry II* (*COMC-II*) also provide useful and precise information on this subject, with particular reference to processes of use in the synthesis of complex molecules. However, as regards to transition metal-promoted cross-coupling reactions, these surveys generally emphasized the characteristics of the different types of organometallic derivatives employed instead of the electrophiles involved in these reactions. Moreover, aspects concerning the regio-, chemo- and stereoselectivity of the carbon-carbon bond forming reactions which involve di- or polyhalo(hetero)arenes and di- or polyhaloethene derivatives, have been almost completely neglected. Only in a chapter of *COMC-II,* which deals with processes based on oxidative addition and transmetallation reactions,[10] are examples of selective reactions involving polychlorinated alkenes and polyhalo(hetero)arenes discussed.

The aim of this review, which covers relevant literature up to April 1996 is to fill in these gaps. Thus, the main synthetic aspects of selective transition metal-promoted carbon-carbon polyhalo(hetero)arenes and di and polyhaloethene derivatives, have been summarized and discussed. Such aspects include the preparation of key intermediates of some relevant naturally-occurring bioactive compounds and their analogues. The discussion will focus on the synthetic aspects of the transition metal-promoted cross-coupling reactions and on the processes wherein organopalladium(II) complexes, which derive from oxidative addition of palladium(0) species to aryl or alkenyl polyhalides, undergo insertion of carbon monoxide or alkenes; it will also deal with the few reported examples involving transition metal-promoted carbon-heteroatom bond forming reactions with dihaloarenes and dihaloethene derivatives. Other transition metal-promoted reaction, such as the cascade reactions, will be only mentioned occasionally. Reports from the patent literature have not been included since the experimental procedures in patents are seldom sufficiently detailed to allow reproduction of the results.

I. CARBON-CARBON BOND FORMATION *via* POLYHALO(HETERO)ARENES

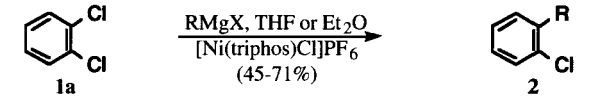
1. Reactions Involving Dichloro-, Trichloro-, Dibromo-, Tribromo- or Diiodo(hetero)arenes

The transition metal-promoted cross-coupling reactions between aryl halides and organometallic compounds such as Grignard reagents, organoaluminum, organozinc, organozirconium, organoboron, organotin and organosilicon compounds have been extensively used to prepare a large variety of synthetically useful and, in some cases, biologically active compounds.[10] Mechanistically, these reactions involve three main steps: oxidative addition, transmetallation and reductive elimination. In particular, the low valent transition metal compound, which is most frequently a palladium(0) or a nickel(0) species stabilized by ligands such as triarylphosphines or triphenylarsine, undergoes oxidative addition with an aryl halide. Then, a transmetallation reaction involving the oxidative addition complex and the organometallic reagent, followed by reductive elimination affords the desired cross-coupled product and regenerates the low valent transition metal catalyst.[11-13] It must be noted that in these reactions the reactivity of aryl halides for the initial oxidative addition of palladium(0) or nickel(0) species is I > Br > Cl.[11-13]

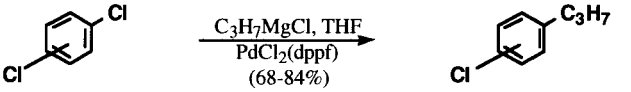
Particularly interesting from a synthetic point of view are the transition metal-promoted cross-coupling reactions involving polyhalo(hetero)arenes and among these, those in which a symmetrically substituted polyhalo(hetero)arene undergoes a selective monoalkylation, mono(hetero)arylation or monobenzylation reaction. For instance, symmetrically substituted dichloro- and dibromo(hetero)arenes such as compounds **1a-c, 4, 6, 8** as well as 1,3,5-trichlorobenzene (**11**) undergo selective coupling reactions at a single position with Grignard reagents.[14-20] The catalyst precursors used for these monoalkylations, mono(hetero)arylations and monobenzylations include $Ni(acac)_2$,[20] $[Ni(triphos)Cl]PF_6$,[14a] $PdCl_2(dppf)$,[15,18,19] $PdCl_2(dppb)$[16] and $Pd(PPh_3)_4$.[17] As expected, the selectivity of these reactions is dependent on the proper choice of the experimental conditions and in particular, on the organometallic reagent/organic polyhalide molar ratio. On the other hand, so far no detailed investigation has been carried out on dependence of the selectivity and yields of these monocoupling reactions on the nature of the catalyst precursor. However, palladium compounds have been extensively used for reactions involving (hetero)aryl polyhalides and, among these catalyst precursors, $PdCl_2(dppf)$ in general gave satisfactory results both in terms of selectivity and yields.

Examples of these monocoupling reactions, in which different types of catalyst precursors and organometallic species have been used to give the desired monocross-coupled products in modest to satisfactory yields, are given in Eqs. 1-7.[14-20]

Modest selectivity and yields have also been obtained in the palladium-promoted reactions of **8**, 3,4-dibromothiophene (**14**), 4,4'-dibromobiphenyl (**16**) and 1,4-dibromobenzene (**18**) with benzylzinc bromide, 2-furylzinc chloride, phenylboronic acid and vinyltributylstannane, respectively (Eqs. 8-11).[16,17,21,22]

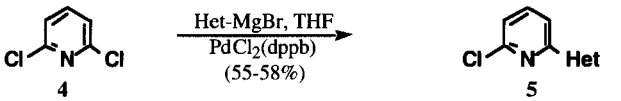


1a 2 (1)



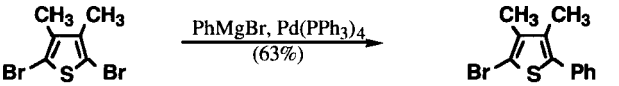
1a-c 3a-c (2)

[a = 2-Cl; b = 3-Cl; c : 4-Cl]

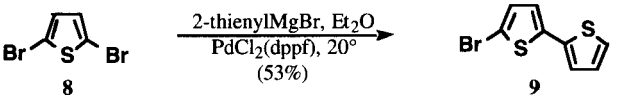


4 5 (3)

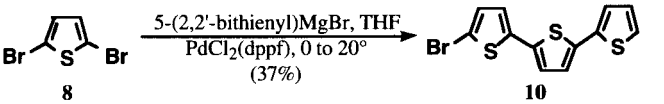
[Het = 2-thienyl; N-methyl-2-pyrrolyl]



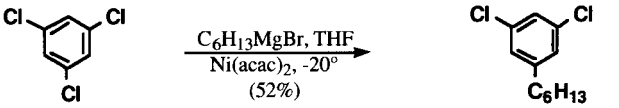
6 7 (4)



8 9 (5)



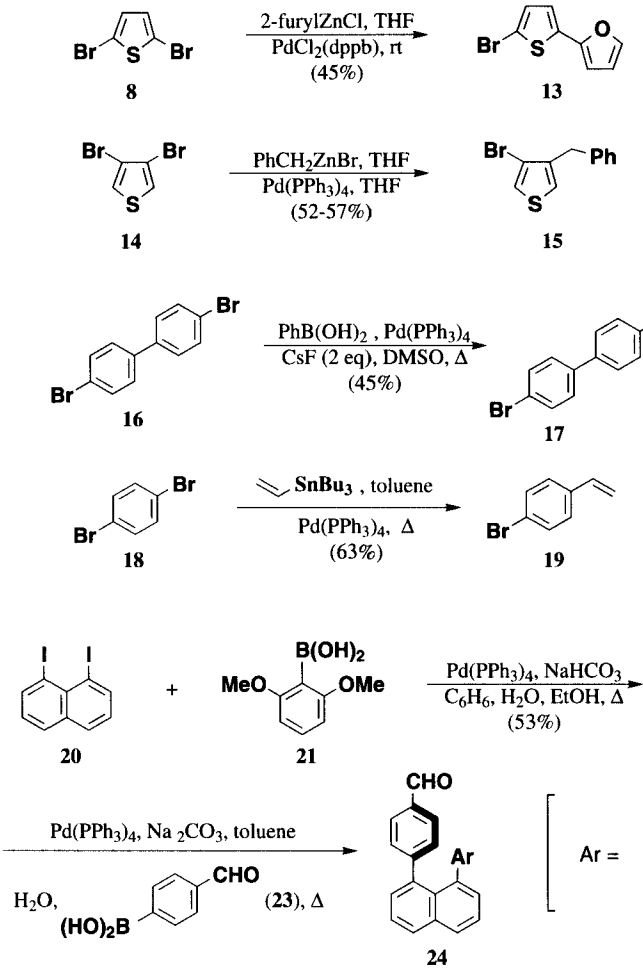
8 10 (6)



11 12 (7)

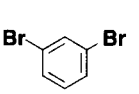
1,8-Diiodonaphtalene (**20**) has also been selectively transformed in 53% yield into the corresponding 8-aryl-1-iodonaphtalene **22** by a palladium-promoted coupling reaction with 2,6-dimethoxyphenylboronic acid (**21**) (Scheme 1).[23] Interestingly, in spite of considerable steric hindrance, this diiodo derivative underwent smooth reaction with 4-phenylboronic acid (**23**) to form **24** (Scheme 1).[23]

This novel NLC-phore, in which an aryl substituent is rendered electron-rich by an electron donor, while the other has reduced electron density as a result of an electron-withdrawing group, represents an alternative to conventional extended conjugated systems for the development of blue-transparent frequency-doubling devices.[23]

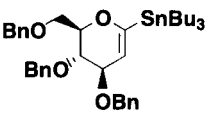


Scheme 1

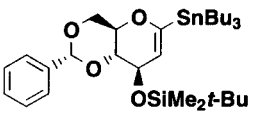
Another interesting example demonstrating the synthetic utility of the transition metal-promoted monoarylation reactions of symmetrically substituted dibromoarenes involves the synthesis of the aryl-bridged C-disaccharide **28** by two sequential cross-coupling reactions of 1,3-dibromobenzene (**25**) with 1-stannylglycals **26** and **27**, respectively, in the presence of a catalytic amount of $Pd(PPh_3)_4$ in toluene. [24] Compound **28**, which was synthesized in 65% overall yield,[24] can be viewed as a trisaccharide mimic.



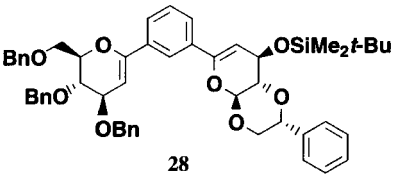
25



26

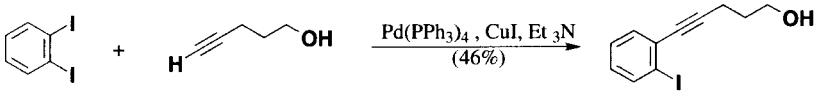


27



28

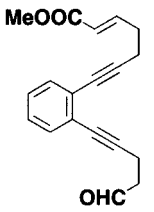
Very selective and high yielding mono-alkynylations also occur when symmetrically substituted dibromo- or diiodo(heteroarenes are reacted with 1-alkynes under Sonogashira conditions[9], *i. e.* in the presence of an alkylamine as base and catalytic amounts of a palladium complex and copper(I)



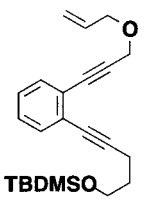
(12)

29a 30 31

iodide.[25-27] Equation 12 illustrates a palladium- and copper-mediated synthesis of 5-(2-iodophenyl)-4-pentyn-1-ol (**31**) from 1,2-diiodobenzene (**29a**) and 4-pentyn-1-ol (**30**).[26] Compound **31** has been subsequently used as a starting material for the selective synthesis of the mixed enediynes **32** and **33**.[28]

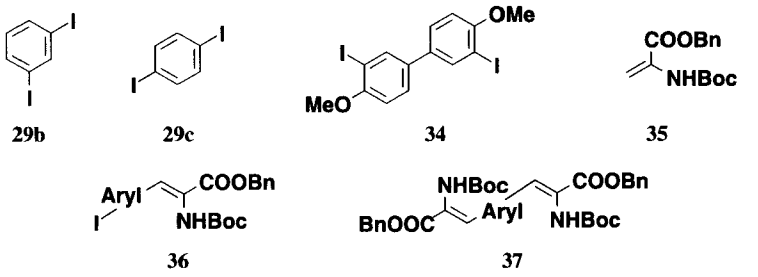


32

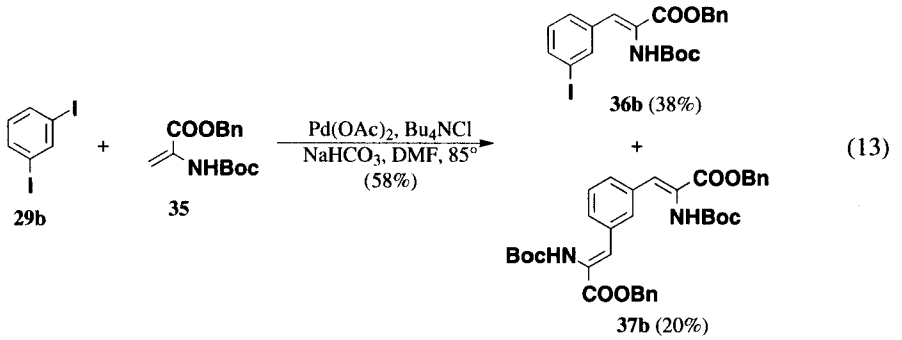


33

On the other hand, very few data have been reported in the literature on the palladium-promoted mono-alkenylations of symmetrically disubstituted dihalo(hetero)arenes. In fact, only quite recently it has been reported[29] that 1,3-diiodobenzene (**29b**), 1,4-diiodobenzene (**29c**) and 3,3'-diiodo-4,4'-dimethoxybiphenyl (**34**) react with 1 equiv of the protected 2-aminoacrylate derivative **35**, under the modified Heck conditions to provide mixtures of the mono- and the *bis*-coupling products of general formula **36** and **37** in a 1:0.52, 0.95:1 and 1:0.37 molar ratio, respectively.[30]



Equation 13 exemplifies the reaction between **29b** and **35**.[30] Interestingly, no reaction occurred between **29a** and **35** under these experimental conditions.[30]

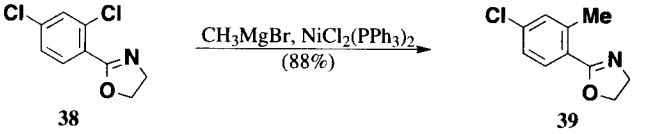


(13)

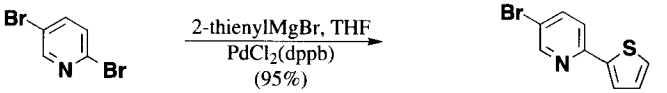
On the contrary, good results both in terms of yield and selectivity have generally been obtained in palladium-mediated monoalkylation[31-34], mono(hetero)arylation,[16,18,33-36] monoalkenylation[33], monoalkynylation[33,37-41] and monoformylation reactions[39] of unsymmetrically substituted di- or trihalo(hetero)arenes by a wide range of organometallic reagents, some of which were formed *in situ* as in the case of the alkynylations carried out using the Sonogashira procedure or its modifications.[9] Interestingly, π-deficient azines chlorinated in the eletrophilic 2- and 4-positions are also suitable for similar selective carbosubstitution reactions under the influence of palladium catalysis.[32] In fact, by treatment of these compounds with trialkylalanes, in the presence of catalytic amounts of $Pd(PPh_3)_4$, chemo- and regioselective alkylations in the more electrophilic 4-position occur.[32]

Some typical examples of highly regioselective reactions involving unsymmetrically substituted di- and trihalo(hetero)arenes are given in Eqs. 14-18.[31,16,33,40,39] The results reveal the following noteworthy features. Firstly, the complete regioselectivity observed in the nickel-mediated methylation of **38**[31] could be ascribed to the presence of an activating substituent in the *ortho*-position to the carbon-chlorine bond involved in the reaction (Eq. 14). Secondly, in compounds **40**, **8** and 2,5-dibromothiazole (**49**) the 2-position was the most reactive.[16,38,18,35] Thirdly, N-benzylated 2,6-dichloropurine **42** and its isomers of general formula **50** underwent palladium-mediated couplings with organotin and organozinc compounds in the 6-position.[33] However, the selectivity observed for the couplings involving **50** was higher than that of similar reactions involving **42** even though the 6-posi-

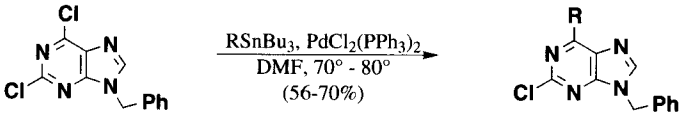
tion in **50** is more sterically hindered than in **42**.[33] Fourthly, the alkynylation reaction of **44** (Eq. 17)[40] involved the carbon-iodine bond in the 4-position to the mesyloxy group. Thus, in this reaction this



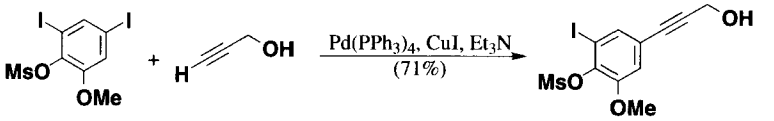
38 39 (14)



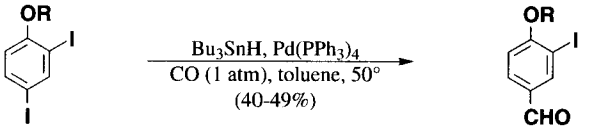
40 41 (15)



42 [R = *trans*-Ph-CH=CH; CH_2=C(OEt)] 43 (16)

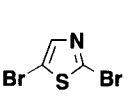


44 45 46 (17)

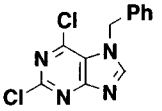


47 [R = Ac; *t*-Boc] 48 (18)

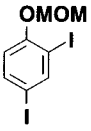
last group exhibited a reactivity much lower than that of the iodo substituent. Fifthly, the protected iodophenols **47** were able to undergo formylation (Eq. 18)[39] as well as alkynylation reactions in the 4-position. However, the high regioselectivity observed in these last reactions was not general for all protected 2,4-diiodophenols. In fact, the MOM derivative **51** underwent coupling with 1-hexyne with little selectivity.[39]



49

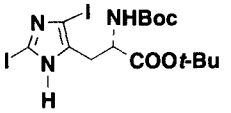


50

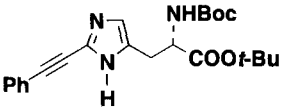


51

Sixthly, the diiodohistidine derivative **52** underwent reaction with 3 equiv of phenylacetylene in the presence of Et_3N and catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI to afford compound **53** in 52% yield , which derives from deiodination and coupling reaction of **52**.[37]



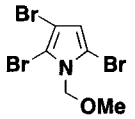
52



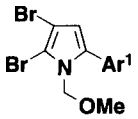
53

The presence of an acidic NH proton in the substrate could be responsible for this unexpected reaction path. Indeed, simple 5-alkyl substituted diiodoimidazoles underwent sluggish, poorly selective dehalogenations under similar conditions.[37]

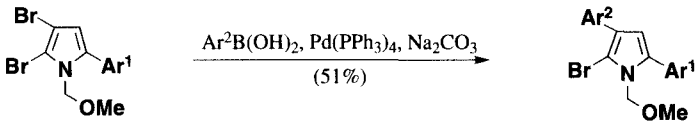
Finally, the products which were obtained from the palladium-mediated reactions of the N-protected 2,4,5-tribromoimidazole derivative **54** with arylzinc chlorides, arylmagnesium chlorides or (hetero)arylboronic acids derived from highly selective arylations in the 2-position of the heteroaryl tribromide.[36] Interestingly, the yields of these products having general formula **55** were higher when (hetero)arylboronic acids were used as organometallic partners.[36] Compounds **55** so obtained underwent regioselective palladium-mediated cross-couplings with arylboronic acids to give the 4-bromo derivatives **56** in high yield (Eq. 19).[36]



54

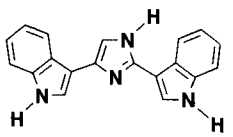


55



55 [Ar^1 = Ph; Ar^2 = Ph, 2-$MeOC_6H_4$] 56 (19)

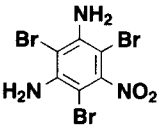
It is also worthwhile mentioning that successive and regioselective arylation reactions, similar to those used to prepare compounds **56** have been employed in a total synthesis of nortopsentin D (**57**), an antifungal marine alkaloid.[36]



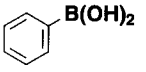
57

Recently, in the course of a study aimed to the development of a new convenient and efficient protocol for the synthesis of polyphenyl mono- and diaminobenzenes, an unexpected selective palladium-promoted diarylation reaction involving an unsymmetrically substituted tribromoarene has been observed.[42] Treatment of 3,5-diamino-2,4,6-tribromonitrobenzene (**58**) with 4 equiv of phenylboronic acid (**59**) in a benzene-ethanol-water mixture containing Na_2CO_3, in the presence of $Pd(PPh_3)_4$ at reflux temperature for 24 hrs under a nitrogen atmosphere, gave 3,5-diamino-4-bromo-2,6-diphenyl-1-nitrobenzene (**60**) in 73% yield.[42] This reaction was also carried out in dimethoxyethane-water using $Ba(OH)_2$ as base. However, a lower yield (21%) of **60** and no formation of the desired 3,5-diamino-2,4,6-triphenyl-1-nitrobenzene (**61**) were obtained.[42] The isolated compound **60** was again subjected to a cross-coupling reaction with an excess amont (2 equiv) of **59**.

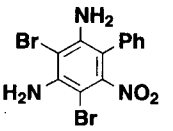
However, the reaction mixture did not contain compound **61**, although compound **60** used was almost completely consumed. This result could be explained by taking into account the fact that the electron-donating amino groups may deactivate the bromo atom *ortho* to the nitro group for the oxidative addition to $Pd(PPh_3)_4$.



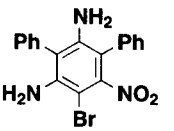
58



59



60



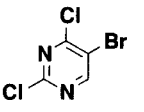
61

2. Di- and Trihalo(hetero)arenes which Contain Different Halogen Substituents

Several investigations have been carried out on highly selective transition metal-promoted carbon-carbon bond forming reactions, which involve di- and trihalo(hetero)arenes having different halogen substituents. These reactions, which have been used to prepare some heavily functionalized molecules, include nickel- or palladium-mediated cross-couplings with a wide range of organometallic reagents, palladium- and copper-mediated cross-couplings with 1-alkynes as well as Heck type reactions.

These reactions are very selective owing to the different reactivity of the halogen substituents present in the substrates which are used as electrophiles. In fact, iodinated positions undergo transition metal-promoted carbon-carbon bond forming reactions more readily than brominated positions and these were much more reactive than chlorinated sites.[43-45] The chemoselectivity of the cross-coupling reactions involving bromochloroarenes was also dependent on the nature of the transition metal catalyst precursor. In fact, the increased chemoselectivity of the palladium-mediated reactions in comparison to the analogous nickel-promoted reactions permitted the monoarylation of 4-bromochlorobenzene.[46]

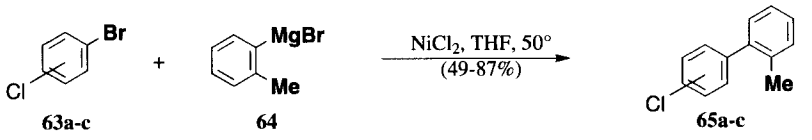
On the other hand, the replacement of a chlorine substituent generally required the presence of a strongly electron-withdrawing group in an activating position or a very electron poor heteroaromatic system linked to this substituent. Thus, the chlorines in activated pyrimidine positions could be replaced by carbon substituents using organotin reagents and palladium catalysis.[47] In particular, the 4(6)-position in pyrimidine was more reactive than the 2-position and regioselective coupling could be achieved. On the other hand, a bromine substituent was required for coupling to take place in the benzenoid 5-position.[47] In 5-bromo-2,4-dichloropyrimidine (**62**), the 4-chlorine was replaced before the 5-bromine and the latter before the 2-chlorine substituent, all in a regioselective manner.[47] Thus, functionalized carbon substituents could be selectively introduced in both activated and non-activated positions in halopyrimidines.



62

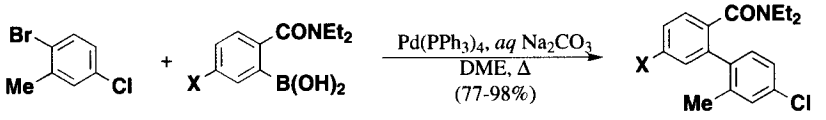
Transition metal-mediated couplings involving di- or trihalo(hetero)arenes have also been employed to prepare in satisfactory yields halogen substituted bi(hetero)aryls. The organometallics used in these reactions include arylmagnesium,[48,49] (hetero)arylboron,[50-55] (hetero)aryltin[65-60] as well as arylsilicon

derivatives.[61] Typical examples of these selective (hetero)aryl-(hetero)aryl couplings are shown in Eqs. 20-24.[49,53,57,59,61]

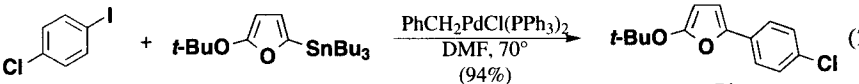


63a-c 64 65a-c (20)

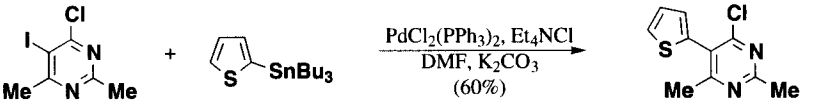
[a = 2-Cl; b = 3-Cl; c = 4-Cl]



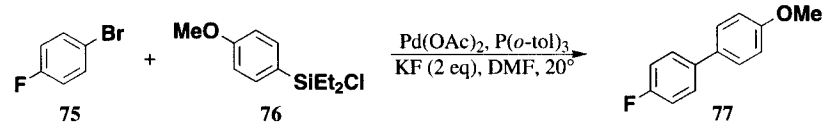
66 67 [X = H, MeO] 68 (21)



69 70 71 (22)

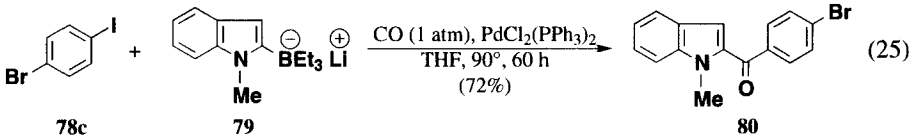


72 73 74 (23)



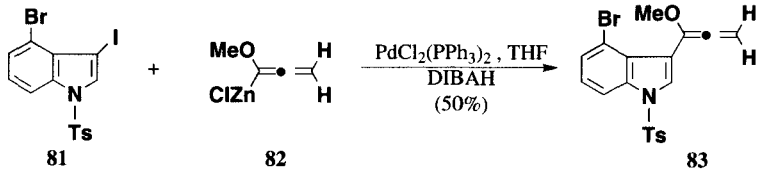
75 76 77 (24)

On the other hand, a palladium-mediated carbonylative cross-coupling reaction between the lithium heteroaryltriethylborate **79** and 4-bromoiodobenzene (**78c**) has been used to prepare 4-bromophenyl-1-methylindol-2-yl ketone (**80**) in good yield (Eq. 25).[62]

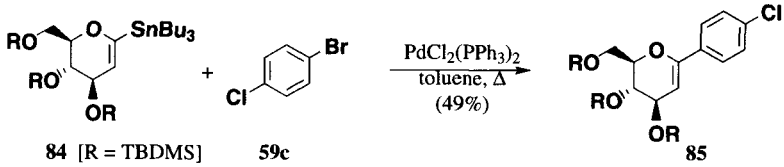


78c 79 80 (25)

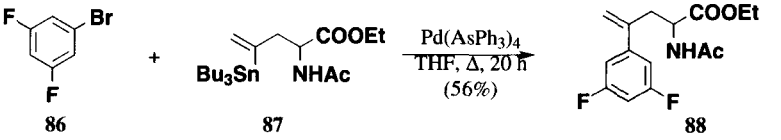
Synthetic utility has also been demonstrated for transition metal-promoted monocouplings of di- or trihalo(hetero)arenes, which are characterized by different halogen substituents, with alkenylzirconium,[63] alkenyl and propadienylzinc[64,65] as well as alkenyltin derivatives.[57,65-72] Significant examples of unsaturated, highly functionalized compounds, which have been prepared by these reactions, are given in Eqs. 26-30.[65,67,70-72]



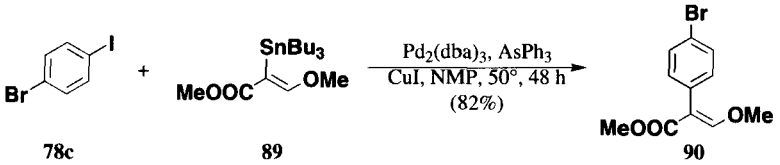
81 82 83 (26)



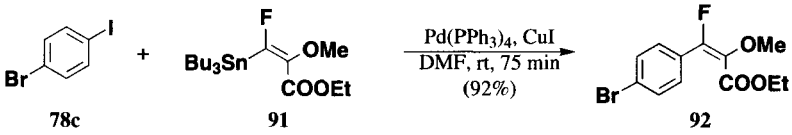
84 [R = TBDMS] 59c 85 (27)



86 87 88 (28)



78c 89 90 (29)

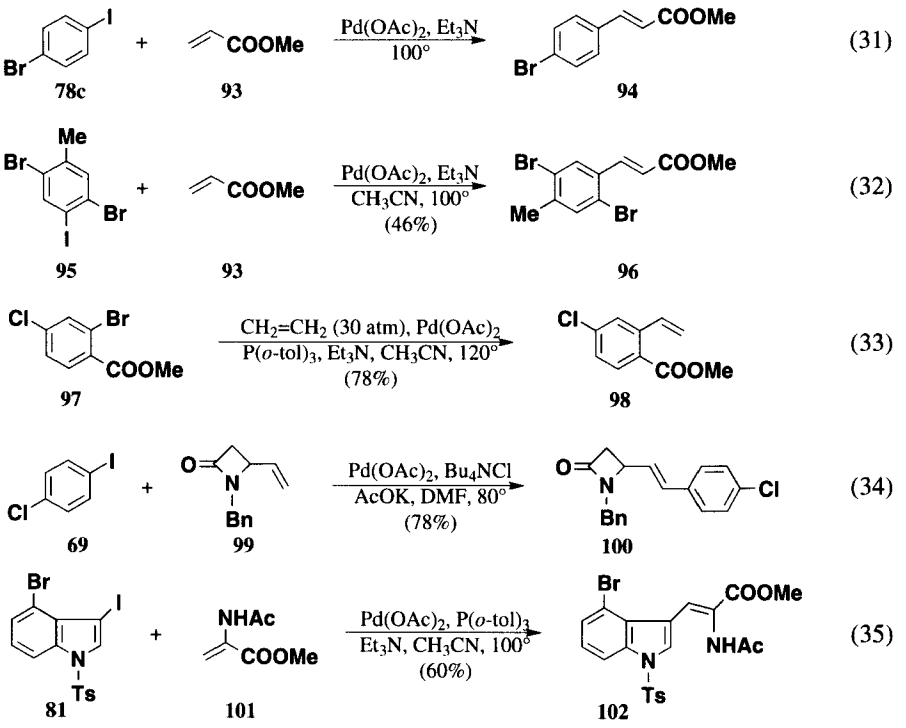


78c 91 92 (30)

Compound **81**[65] is the N-tosyl derivative of a 3-substituted 4-bromoindole in which the functional group, which is present in the 3-position, represents a precursor to a propenoyl group. Compound **85**[67] is a C-aryl glucal and its preparation (Eq. 28) was carried out using a strategy which proved to be suitable for the synthesis of analogues of many C-aryl glycoside antibiotics. Compound **88**[70] is an allylglycine derivative, which is structurally related to some non-proteinogenic α-aminoacids, some of which have been reported to act as irreversible inhibitors of pyridoxal phosphate dependent enzymes.[73,74] Compound **90**[71] is a 2-aryl substituted (*E*)-3-methoxypropenoate, which is structurally related to some highly promising synthetic fungicides characterized by the agrochemically important 3-methoxypropenoate toxophore.[75] Finally, compound **92**[72] is a β-fluoro-α–keto acid derivative, which is valuable precursors to the corresponding β-fluoro-α-aminoacid. It must be noted that β-fluoro-α-aminoacids are currently of great interest in the design of potential therapeutic agents and enzyme inhibitors.[76]

The di- and trihalo(hetero)arenes, which are the subject-matter of this section, also undergo alkenylation reaction at a single position by the Heck procedure[77] or its modifications.[29,78-81] The first example of selective palladium-mediated monoalkenylation of a dihaloarene by treatment with an

alkene derivative was reported in 1979 by Heck and coworkers.[82] They found that, on treatment of 2-bromoiodobenzene (**74a**) or **74c** with methyl propenoate (**93**) in Et_3N at 100° in the presence of $Pd(OAc)_2$, only the iodo substituent of these arene dihalides was involved in the reaction. On the contrary, both bromo and iodo substituents were involved if a triarylphosphine was present in addition to $Pd(OAc)_2$.[83] Subsequently, several other Heck type monoalkenylations of poly-halo(hetero)arenes have been reported.[30,84-91] Some typical examples are illustrated in Eqs. 31-35.[84,85,87,90]



(31)

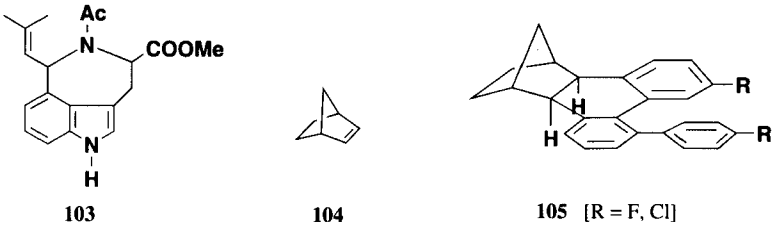
(32)

(33)

(34)

(35)

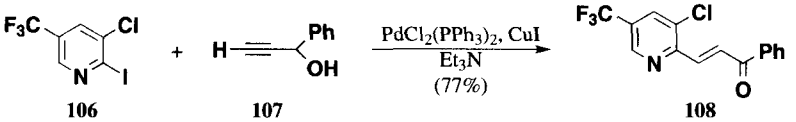
Compound **102**, which was prepared in satisfactory yield by monoalkenylation of **81** (Eq. 36), was used as a precursor to N-acetyl methyl ester of clavicipitic acid (**103**).[90]



Nevertheless, when norbornene (**104**) was used as the olefinic partner in the reaction with **71** or **65**[92] and such reaction was performed using the protocol developed by Jeffery[93] with $Pd(OAc)_2$ as the catalyst precursor, K_2CO_3 as the base in DMF or NMP at 60-100° and in the presence of Bu_4NBr, *exo*-[4-(*p*-halophenyl)-3,6-dihalo-9,10-dihydro-phenanthreno]-2':3',9:10-norbornanes **105** were

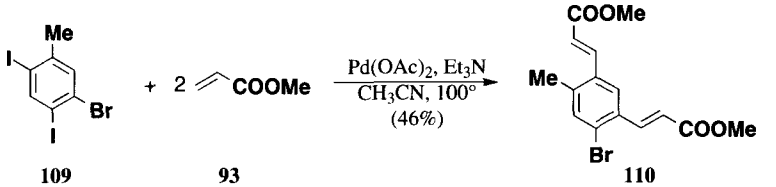
obtained in modest yields.

Interestingly, a one-pot procedure, which complements the Heck reaction, was developed for the synthesis of (*E*)-chalcone **108**. This procedure consisted of a palladium- and copper-mediated cross-coupling between 3-chloro-5-trifluoromethyl-2-iodopyridine (**106**) and **107** and a subsequent base-catalyzed rearrangement (Eq. 36).[94]



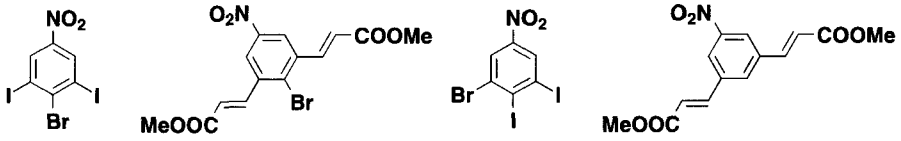
106 107 108 (36)

An investigation has also been carried out on the dialkenylation reaction of bromodiodoarenes by the Heck protocol.[84] Thus, bromodiiodotoluenes could be selectively reacted at the iodo groups. In fact, when compound **109** was treated with **93** in acetonitrile at 100° in the presence of Et_3N and a catalytic amount of $Pd(OAc)_2$, bromodiester **110** was obtained, although in a modest yield (Eq. 37).[84]



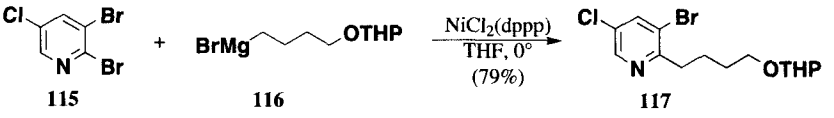
109 93 110 (37)

Similarly, 3,5-diiodo-4-nitrobenzene (**111**), when treated with **93** under similar reaction conditions, gave the desired bromonitrodiester **112** in 34% yield.[84] Nevertheless, the reaction between **113** and **93** gave compound **114** in 10% yield, which derived from the loss of the 4-iodo group and a bis-alkenylation reaction involving an iodo and a bromo group.[84]

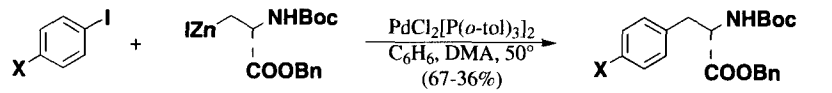


111 112 113 114

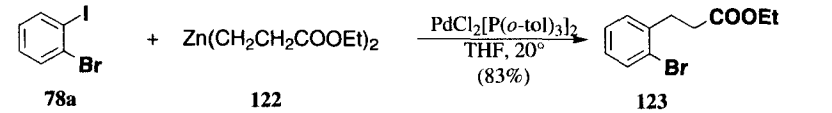
Several selective syntheses of halo(hetero)arenes, which contain functionalized C_{sp3} substituents, starting from di- and trihalo(hetero)arenes have also been reported in the literature.[95-104] These syntheses involve transition metal-promoted reactions of organometallic derivatives, such as Grignard reagents,[95] organozinc[96-100] and organotin derivatives,[101-104] with (hetero)aryl di- or trihalides such as compounds **59a**, **59c**, **71**, **74c**, 2,3-dibromo-5-chloropyridine (**115**), 4-fluoroiodobenzene (**118**) and 2-bromoiodobenzene (**78a**). Examples of these selective reactions are reported in Eqs. 38-41.[95,96,99,103]



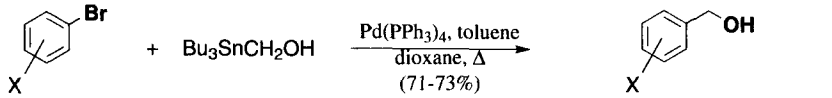
115 116 117 (38)



78c [X = Br] **118** [X = F] **119** **120** [X = Br] **121** [X = F] (39)

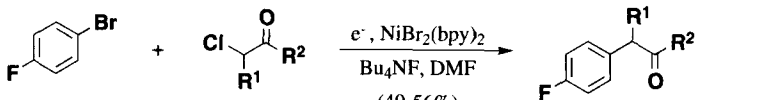


78a **122** **123** (40)



63a [X = 2-Cl] **63c** [X = 4-Cl] **124** **125a** [X = 2-Cl] **125b** [X = 4-Cl] (41)

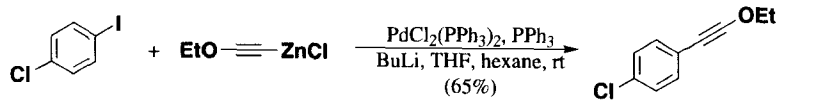
Quite recently, 4-fluorobenzyl ketones of general formula **127** have been prepared by electroreductive coupling of **71** with α-chloroketones of general formula **126** in DMF solution, in the presence of a Zn or Al-sacrificial anode and catalytic quantities of a nickel(II) complex (Eq. 42).[105]



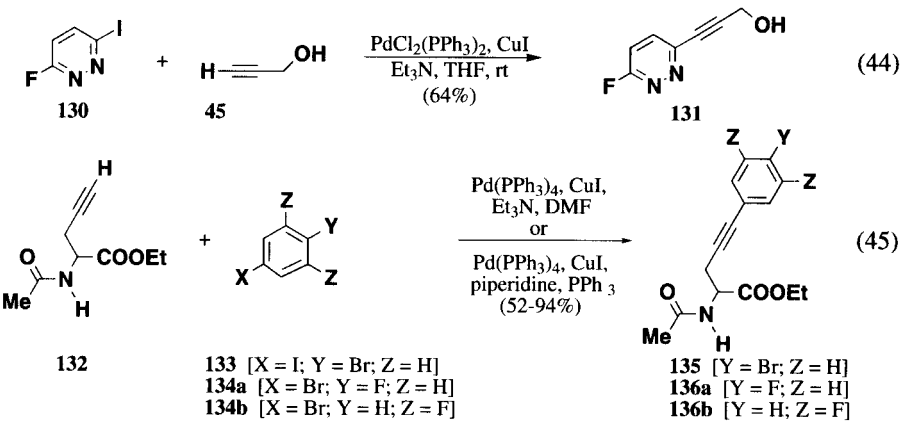
75 **126** **127** (42)

It is worth adding to the end of this section that some examples concerning the selective alkynylation reaction of di and trihalo(hetero)arenes have also been reported in the literature.[68,84,106-110] Again, the order of reactivity of the halogen groups in these transition metal-promoted reactions was I > Br >> Cl >> F.

A selective monoalkynylation of **65** by an alkynylzinc chloride is illustrated in Eq. 43.[106] On the other hand, selective monoalkynylations of dihalo(hetero)arenes, which involve treatment of these substrates with 1-alkynes in the presence of an alkylamine and catalytic quantities of a palladium comples and CuI, are shown in Eqs. 44 and 45.[107,108]



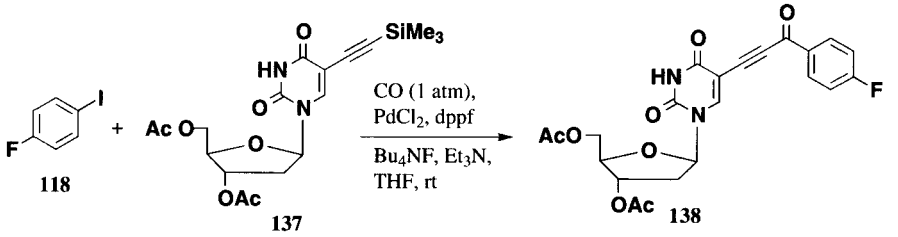
69 **128** **129** (43)



130 45 131 (44)

132 133 [X = I; Y = Br; Z = H] 134a [X = Br; Y = F; Z = H] 134b [X = Br; Y = H; Z = F] 135 [Y = Br; Z = H] 136a [Y = F; Z = H] 136b [Y = H; Z = F] (45)

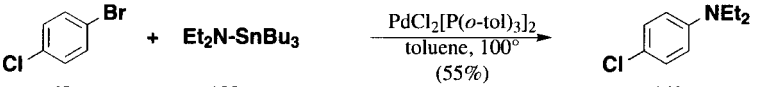
Finally, a selective synthesis of α,β-enynone **138** by carbonylative cross-coupling of compound **118** with 5-(trimethylsilylethynyl)-3,5'-di-O-acetyl-2'-deoxyuridine (**137**), in the presence of Bu_4NF and Et_3N and catalytic quantities of $PdCl_2$ and dppf, is reported in Eq. 46.[109]



118 137 138 (46)

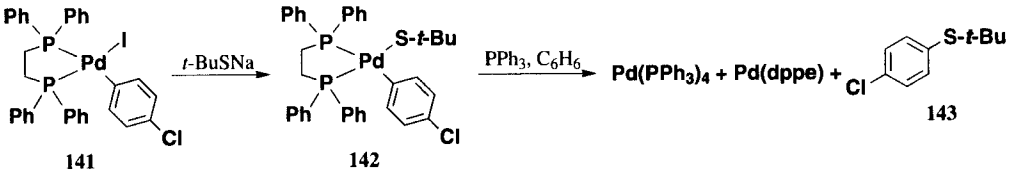
II. CARBON-HETEROATOM BOND FORMATION

Palladium catalysis has been shown to be efficient for the amination of aryl bromides with organotin amines.[111] Aryl chlorides or iodides seem to be unreactive in this type of substitution reaction. In fact, by treatment of compound **59c** with tributylstannyldiethylamine (**139**) in the presence of a catalytic amount of $PdCl_2[P(o\text{-tol})_3]_2$, 4-chlorophenyl-diethylamine (**140**) was selectively obtained (Eq. 47).[111]



63c 139 140 (47)

To the best of our knowledge, this synthesis represents the only example described so far in the literature of a catalytic transition metal-promoted carbon-heteroatom bond forming reaction involving a polyhalo(hetero)arene. However, very recently, it has been reported that addition of sodium *tert*-butyl thiolate to the palladium aryl complex **141** provides the aryl *tert*-butyl thiolate complex **142**, which, when warmed in a benzene solution at 50° in the presence of triphenylphoshine, forms the corresponding *tert*-butyl *p*-chlorophenyl sulfide (**143**) in quantitative yield (Scheme 2).[112]

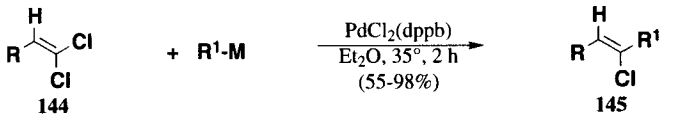


Scheme 2

III. CARBON-CARBON BOND FORMATION *via* POLYHALOGENATED ETHENE DERIVATIVES

1. 1,1-Dichloro-, 1,1-Dibromo- and 1-Chloro-1-iodoethenes and 1,1,2-Trichloroethenes

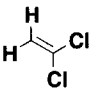
The first success in the regio- and stereoselective monoarylation and monoalkylation of 1,1-dichloro-1-alkenes **144** by Grignard reagents or organozinc reagents in the presence of catalytic amounts of $PdCl_2$(dppb) was reported in 1987.[113] As shown in Eq. 49, 1-substituted (*Z*)-1-chloro-1-ethenes **145** were obtained in 55-98% yield.[113]



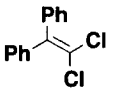
(49)

[R = Ph, 4-$MeOC_6H_4$, 2-thienyl, Me, Cl; R^1 = Ph, 4-ClC_6H_4, 2-thienyl, C_4H_9; M = MgBr, ZnCl]

The presence of the substituent R in compounds **144** was essential for the regio- and stereoselective monocoupling. In fact, parent 1,1-dichloroethene (**146**) produced a comparable amount of diarylation products. Moreover, no reaction took place with 1,1-dichloro-2,2-diphenylethene (**147**).[113]



146

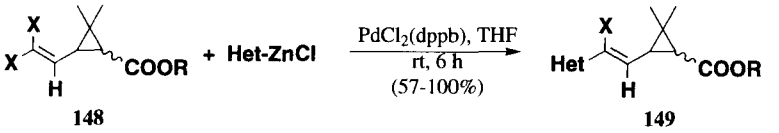


147

The stereoselectivity of the reactions reported in Eq. 49, which could be anticipated on the basis of the known rate difference for the palladium-mediated cross-coupling reactions of (*E*)- *vs* (*Z*)-1-bromo-1-alkenes,[114-121] was ascribed to the steric effect exerted by the vicinal substituent R in (*Z*)-position to a chlorine atom. In fact, electronically different groups such as alkyl, aryl, heteroaryl and chlorine were equally effective. Interestingly, the success of these reactions also depended upon choice of $PdCl_2$(dppb) as a catalyst. In fact, when $PdCl_2(PPh_3)_2$ was used as a catalyst, diarylation products were mainly obtained.[112] Interestingly, compounds **145** reacted with Grignard reagents or organozinc halides in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ to give stereospecifically trisubstituted ethene derivatives.[113]

A versatile method for the modification of commercial synthetic pyrethroids was also based on the fact that the *E* halogen atom in 1,1-dichloro-1-alkenes exhibits higher reactivity than the *Z*

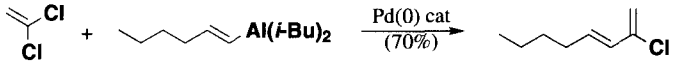
halogen.[122] This method consisted of a highly regio- and stereoselective reaction between *cis*- or t*rans*-(2,2-dihaloethenyl)dimethylcyclopropane carboxylates **148** and (hetero)arylzinc chlorides in the presence of catalytic quantities of $PdCl_2$(dppb) (Eq. 50).[122] A variety of structurally modified pyrethroids of general formula **149** were so obtained in 57-100% yield.[122]



148 149 (50)

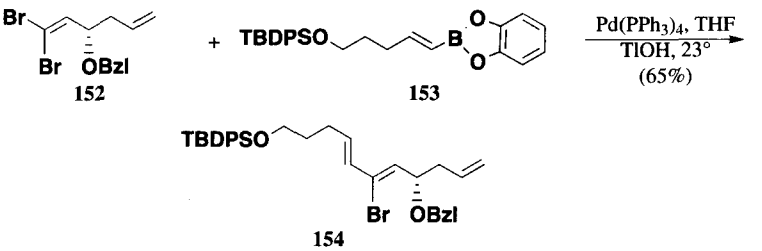
[X = Cl, Br; Het = Ph, 4-ClC_6H_4, 3-ClC_6H_4, 4-FC_6H_4, 2-thienyl, 2-furyl]

Linstrumelle and coworkers[123] found that compound **146** underwent selective monoalkenylation by treatment with (*E*)-1-hexenyldiisobutylalane (**150**) in the presence of a palladium(0) catalyst (Eq. 51).



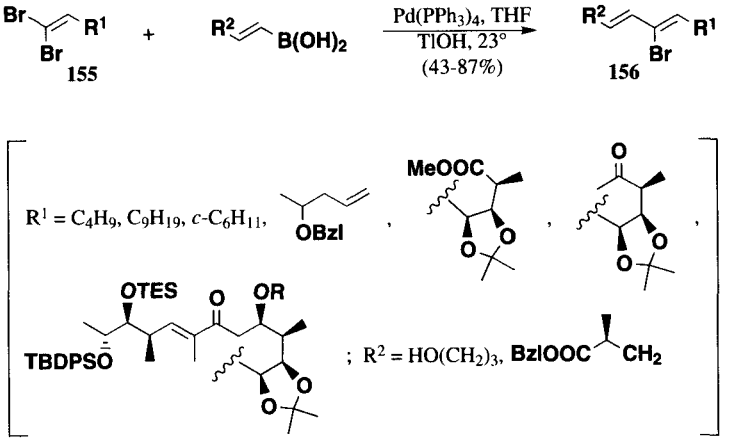
146 150 151 (51)

A key step of an enantioselective synthesis of the bottom half of chlorotricholide was also based on a highly regio- and stereoselective alkenylation of a chiral and stereodefined 1,1-dibromo-1-alkene.[124] Thus, reaction of **152** with **153**, using the modification of the Suzuki reaction[125] which was developed by Kishi,[126] afforded compound **154** in 65% yield (Eq. 52).[124] Interestingly, the yields of the selective monoalkenylations of 1,1-dibromo-1-alkenes, in general, could be improved when vinylboronic acids were employed rather than catechoborane derivatives.[127]



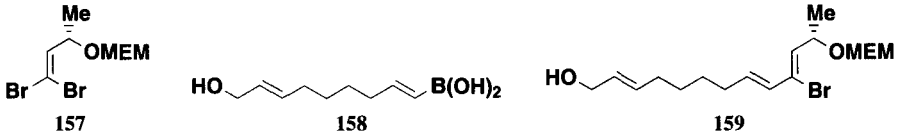
152 153 154 (52)

As shown in Eq. 53, a large variety of (*Z*,*E*)-2-bromo-1,3-dienes of general formula **156** have been synthesized according to this improved procedure.[127]

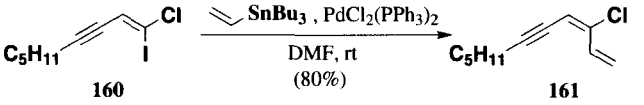


(53)

More recently, a similar selective monoalkenylation has been employed to prepare compound **159** from **157** and **158**.[128]

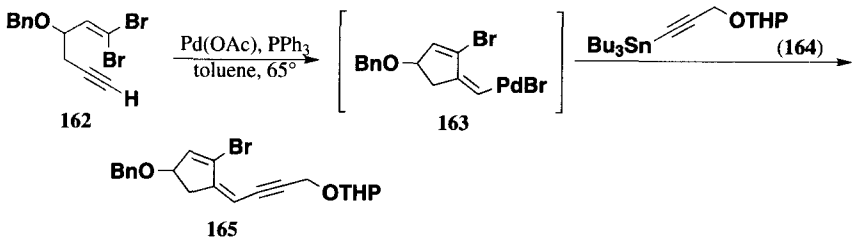


Very recently, it has also been reported that (*Z*)-1-chloro-1-iodo-1-en-3-yne **160** undergoes a highly selective and stereospecific monoalkenylation by treatment with vinyltributylstannane, in the presence of a palladium(II) catalyst precursor, to give (*E*)-3-chloro-1,3-dien-5-yne **157** in good yield (Eq. 54).[129] The fact that in this case the *Z* halogen substituent was more reactive than that in the *E*-position can be explained taking into account that an alkenyl iodide is much more reactive than an alkenyl chloride in this type of reaction.[42]



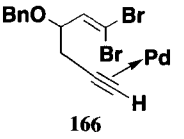
(54)

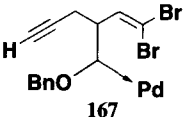
A more striking exception to the rule that in a 1,1-dihalo-1-alkene the *E* halogen atom is more reactive than that in the *Z*-position was reported by Torii and coworkers.[130] They found that dienyne **165** could be synthesized by a palladium-mediated process which involved intramolecular insertion of dibromide **162** followed by a cross-coupling of **163** with **164** (Scheme 3).[130]



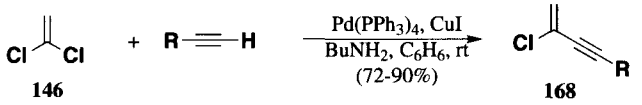
Scheme 3

The formation of **165** indicated that this process proceeds through oxidative-addition of the bromine present in the *Z*-position of **162**. As illustrated in **166** and **167**, such a predominant oxidative-addition, which affords **163**, is probably assisted by the initial coordination of the triple bond or the oxygen atom of the benzyloxy group of compound **162**.



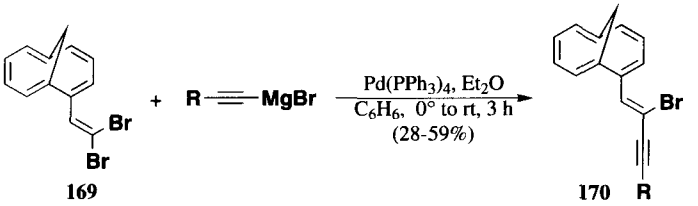


Finally, it must be mentioned that success was also obtained in the selective monoalkynylation of 1,1-dichloro- and 1,1-dibromo-1-alkenes.[123,131] Thus, by treatment of a very large molar excess (5 equiv) of **146** with 1-alkynes, in the presence of a benzene solution of butylamine and catalytic amounts of $Pd(PPh_3)_4$ and CuI, 2-chloro-1-en-3-ynes **168** were obtained in good yield (Eq. 55).[123]



(55)

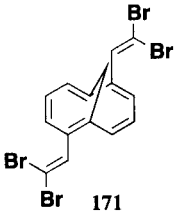
More recently, some 2-(2-bromo-1-alken-3-ynyl)bicyclo[4.4.1]undeca-1,3,5,7,9-pentaenes of general formula **170** have been synthesized by palladium-mediated coupling between 2-(2,2-dibromovinyl)bicyclo[4.4.1]undeca-1,3,4,7,9-pentaenes (**169**) and 1-alkynylmagnesium bromides (Eq. 56).[131]



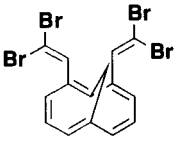
(56)

Interestingly, compounds **170** could not be obtained by palladium- and copper-mediated reaction between **169** and 1-alkynes in the presence of butylamine. Under these conditions only prod-

ucts which resulted from the homocoupling of the starting 1-alkynes were isolated.[131] On the other hand, mixtures of cross-coupled products were produced when either compound **171** or **172** were reacted with 1.66 - 2 equiv of phenylethynylmagnesium bromide in the presence of a catalytic amount of $Pd(PPh_3)_4$.[131]



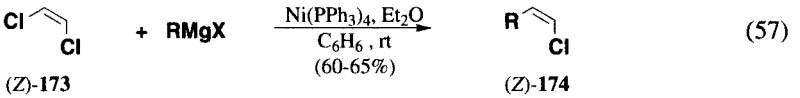
171



172

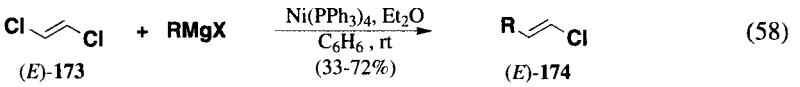
2. *Symmetrically and Unsymmetrically Substituted 1,2-Dihaloethenes and 1,1,2-Trihalo-1-alkenes*

(*Z*) and (*E*)-1,2-Dichloroethene, (*Z*)- and (*E*)(**173**), undergo selective and stereospecific monocoupling reactions with alkylmagnesium chlorides in the presence of catalytic amounts of $Ni(PPh_3)_4$.[132] When 5 equiv of (*Z*)- and (*E*)-**173** were employed, these reactions provided the desired (*Z*)- and (*E*)-1-chloro-1-alkenes, (*Z*) and (E)-**174**, respectively, in good yield (Eqs. 57 and 58).[132]



(*Z*)-**173** [R = $Ph(CH_2)_3$, C_8H_{17}] (57)

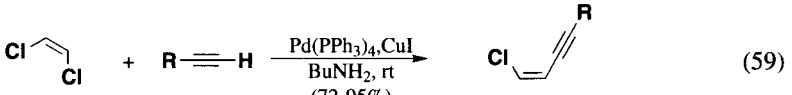
(*Z*)-**174**



(*E*)-**173** [R = $THPO(CH_2)_6$, $Ph(CH_2)_3$, C_8H_{17}] (58)

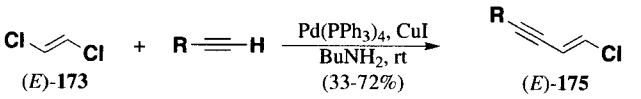
(*E*)-**174**

Compounds (*Z*) and (*E*)-**173** proved also to be efficient precursors to 1-chloro-1-en-3-ynes **175**.[132] In fact, when treated with 1-alkynes, in the presence of butylamine and catalytic quantities of $Pd(PPh_3)_4$ and CuI, these dihalides (5 equiv) afforded compounds (*Z*)- and (*E*)-**175** in high yield (Eqs. 59 and 60).[132]



(*Z*)-**173** [R = C_5H_{11}, CH_2OTHP, CH_2OAc, CH_2SCH_3] (59)

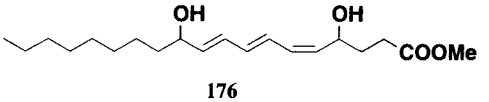
(*Z*)-**175**



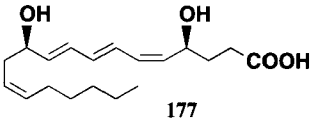
(60)

[R = C_5H_{11}, CH_2OTHP, CH_2OAc, CH_2SCH_3]

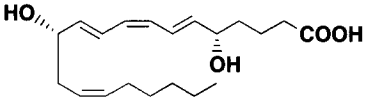
Similar monoalkynylation reactions have been employed to prepare a large variety of stereoisomerically pure, functionalized 1-chloro-1-en-3-ynes **175**,[133-143] some of which have been used as precursors to naturally-occurring bioactive compounds such as methyl (6*Z*,8*E*,10*E*)-5,15-dihydroxyeicosa-6,8,10-trienoate (**176**),[134] which is a compound of the LTB family, leukotriene B_4 (**177**)[137] and (5S,12S)-diHETE (**178**).[138]



176

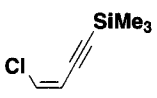


177

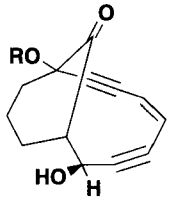


178

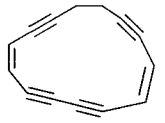
Other stereodefined 1-chloro-1-en-3-ynes so prepared have found remarkable synthetic applications. Thus, compound (*Z*)-**175a** was used as a precursor in the stereospecific synthesis of 12-β-hydroxybicyclo[7.3.1]-enediyne **179**,[135] cyclodeca-3,9-diene-1,5,7,11-tetrayne (**180**),[144] and the cyclic enediyne **181**, which represents a model compound of dynemicin A.[145] On the other hand, compound



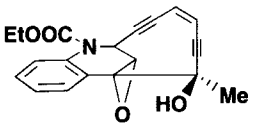
(*Z*)-**175a**



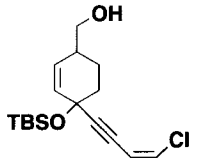
179



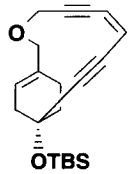
180



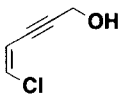
181



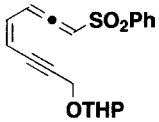
(*Z*)-**175b**



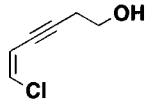
182



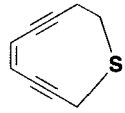
(*Z*)-**175c**



183



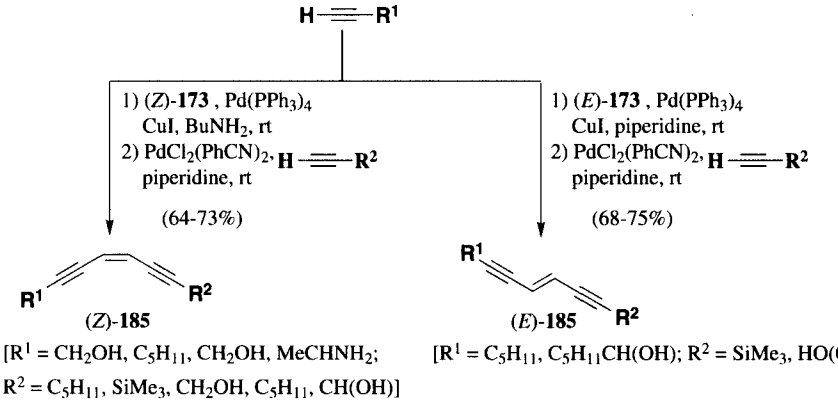
(*Z*)-**175d**



184

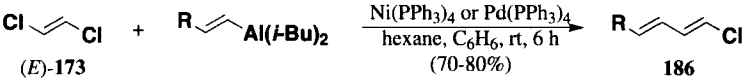
(*Z*)-**175b** was an intermediate in the synthesis of **182**, which possesses the bicyclo[7.3.1]tridecaenediyne system characteristic of the enediyne antibiotics calicheamicin and esperamicin,[139] and compound (*Z*)-**175c** was employed in the synthesis of enyne-allene-sulfone **183**, which serves as an excellent Michael acceptor and probably possesses DNA-cleaving properties.[140] Finally, compound (*Z*)-**175d** was used as a precursor to the 10-membered heterocyclic enediyne **184**.[143]

It is important to note that both the nature of the amine and the catalyst are critical for the success of the monoalkynylation of (*Z*)- or (*E*)-**173**. In fact, when these compounds were reacted with 1-alkynes in the presence of diethylamine and catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI, low yields of compounds (*Z*)- and (*E*)-**175** were obtained.[146] On the contrary, reaction of (*E*)-**173** with 1-alkynes in benzene containing piperidine and catalytic amounts of $Pd(PPh_3)_4$ and CuI gave high yields of compounds (*E*)-**175**.[146] In the case of (*Z*)-**173**, the use of butylamine, instead of piperidine, was preferable and gave compounds (*Z*)-**175** in 76-98% yield.[146] However, a large molar excess of (*Z*)- or (*E*)-**173** was always necessary in order to avoid the formation of the undesired symmetrically disubstituted cross-coupled products. It is also worth noting that the high yield and selectivity of the monoalkynylation reactions carried out under these experimental conditions allowed a simple straightforward one-pot synthesis of functionalized unsymmetrical (*Z*)- and (*E*)-enediynes of general formula **185** by the procedure illustrated in Scheme 4.[147]



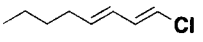
Scheme 4

(*E*)-1,2-Dichloroethene, (*E*)(**173**), underwent selective and stereospecific monocoupling reaction with (*E*)-1-alkenyldiisobutylalanes, in the presence of catalytic amounts of $Ni(PPh_3)_4$ or $Pd(PPh_3)_4$, to give (*E*)-1-chloro-1,3-dienes **186** (Eq. 61).[148] Also in this case, the yields and the selectivity of the reactions were high when a large molar excess (5 equiv) of (*E*)-**173** was used.[148]

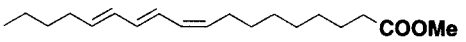


(61)

(1*E*,3*E*)-1-Chloro-1,3-octadiene (**186a**) so prepared was used as a precursor to methyl α-eleostearate B (**187**), a feeding deterrent for the boll weevil on cotton.[148]

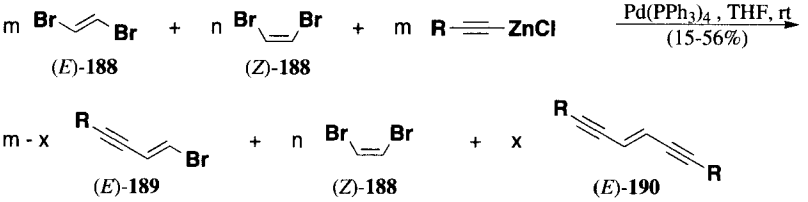


186a



187

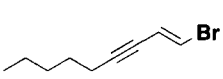
Unfortunately, selective and stereospecific monoalkenylation and monoalkynylation reactions, similar to those involving (*Z*)- and (*E*)-**173**, can not be employed for the preparation of stereoisomerically pure (1*Z*,3*E*)- and (1*E*,3*E*)-1-bromo-1,3-dienes as well as (*Z*)- and (*E*)-1-bromo-1-en-3-ynes starting from (*Z*)- and (*E*)-1,2-dibromoethene (**188**), respectively. In fact, these dibromo derivatives undergo stereomutation very easily to give stereoisomeric mixtures rich in both the stereoisomers. However, when a commercially available stereoisomeric mixture of **188**, which contained m equiv of (*E*)-**188** and n equiv of (*Z*)-**188**, was reacted with m equiv of a 1-alkynylzinc chloride in the presence of a catalytic amount of $Pd(PPh_3)_4$, (*E*)-1-bromo-1-en-3-ynes (*E*)(**189**) having very high stereoisomeric purity were stereoselectively obtained (Eq. 62).[115,119]



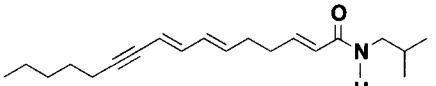
(62)

[R = C_4H_9, C_5H_{11}, 2-thienyl]

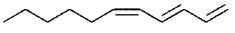
An improved diastereoselective monoalkynylation reaction was accomplished by using 0.5 equiv of 1-alkynylzinc chloride: the yields of compounds (*E*)-**189** increased to 56% in the case of R = butyl and R = pentyl. However, when a similar procedure was used in the case of R = 2-thienyl, mono- and di-alkynylated compounds were obtained in 15 and 56% yields, respectively.[119] Compound (*E*)-**189a**, which was prepared according to this protocol, was used as a starting material for the stereocontrolled synthesis of (2*E*,6*E*,8*E*)-N-(2-methylpropyl)-2,6,8-hexadecatrien-10-ynamide (**191**), a naturally-occurring acetylenic substance,[149] as well as a precursor to (3*E*,5*Z*)-1,3,5-undecatriene (**192**), a substance isolated from the essential oil of *Ferula galbaniflua*, which is also present in the male attracting essential oil of the seaweeds *Dictyopteris plagiogramma, D. australis* and *D. membranacea.*[116]



(*E*)-**189a**



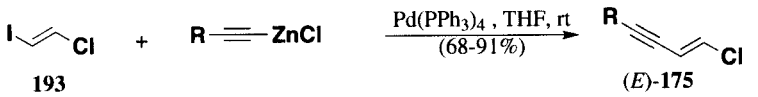
191



192

It is interesting to note that Negishi and coworkers[150] described a method for preparing compounds (*E*)-**175**, which complements that reported by Ratovelomanana and Linstrumelle.[132] This method involves a clean, selective and stereospecific monocoupling reaction between 1-alkynylzinc chlorides and (*E*)-1-chloro-2-iodoethene (**193**), which is easily available by treating acetylene with ICl

and 6 N HCl, in the presence of catalytic quantities of $Pd(PPh_3)_4$ (Eq. 63).[150]



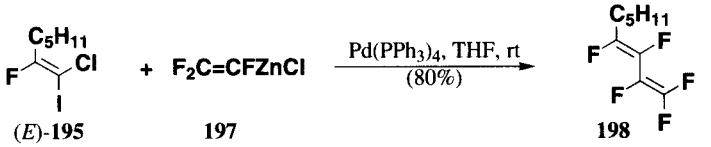
193 (*E*)-175 (63)

[R = C_5H_{11}, C_6H_{13}, Ph, CH_2=$C(CH_3)$, C_6H_{13}-C≡C]

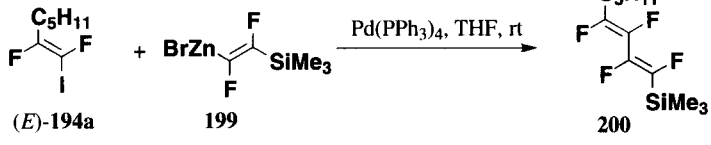
Selectivities similar to those registered for this reaction have been recorded for palladium-mediated monocoupling reactions involving trihaloethenes and unsymmetrically substituted dihaloethene such as (*Z*)-1,2-difluoro-1-iodo-1-alkenes (*Z*)-**194**,[151-153], their stereoisomers, (*E*)-**194**,[153-155] (*E*)-1-chloro-2-fluoro-1-iodo-1-alkenes (*E*)-**195**[152] and 2-substituted or 1,2-disubstituted (*Z*)- and (*E*)-1-bromo-2-fluoroethenes of general formula **196**.[156]

(*Z*)-**194** (*E*)-**194** (*E*)-**195** **196**

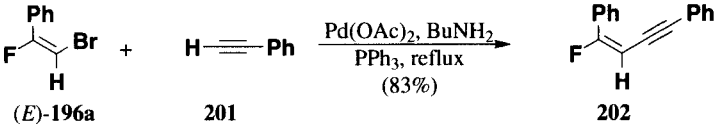
Examples of these selective and stereospecific reactions are given in Eqs. 64-67.[151,154,156]



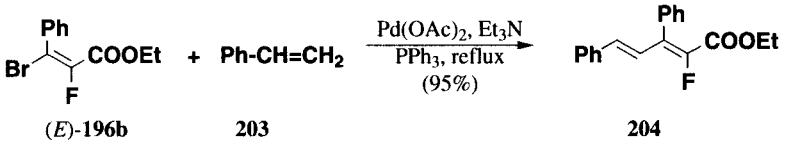
(*E*)-**195** **197** **198** (64)



(*E*)-**194a** **199** **200** (65)



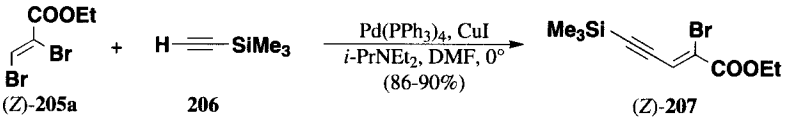
(*E*)-**196a** **201** **202** (66)



(*E*)-**196b** **203** **204** (67)

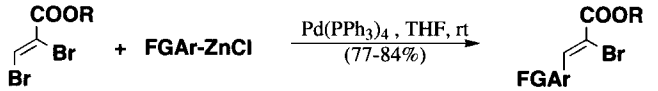
On the contrary, until few years ago not much attention had been paid to the study of regioselective and stereospecific transition metal-promoted carbon-carbon bond forming reactions which involve stereodefined, 1,2-dichloro, 1,2-dibromo- or 1,2-diiodoethene derivatives characterized by a functional group in the α-position to their carbon-carbon double bond. In 1989 Myers and coworkers[157] reported the first example of this type of reactions. In particular, it was found that, when

ethyl (*Z*)-2,3-dibromopropenoate, (*Z*)-**205a**, was reacted at 0° with a DMF solution of trimethylsilylacetylene (**206**) in the presence of *i*-Pr_2NEt and catalytic amounts of $Pd(PPh_3)_4$ and CuI, (*Z*)-bromoenyne **207** was obtained in 86-90% yield (Eq. 68).[157]



(68)

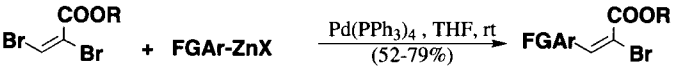
Subsequently, in the context of an in-depth investigation on the selectivity and the synthetic usefulness of palladium-mediated reactions which involve easily available alkyl (*Z*)- and (*E*)-2,3-dibromopropenoates, (*Z*)- and (*E*)-**205**, the regioselective and stereospecific high yielding synthesis of multigram quantities of (*Z*)- and (*E*)-2-bromo-3-(hetero)arylpropenoates, (*Z*) and (*E*)-**208** was reported.[158] The procedure consisted of a reaction between (hetero)arylzinc halides and (*Z*)- and (*E*)-**205**, respectively, in THF at 20° in the presence of catalytic amounts of $Pd(PPh_3)^4$ (Eqs. 69 and 70).[158]



(*Z*)-**205** (*Z*)-**208**

(69)

[FGAr = Ph, 2-thienyl, 4-FC_6H_4, 3,4-methylenedioxyphenyl]



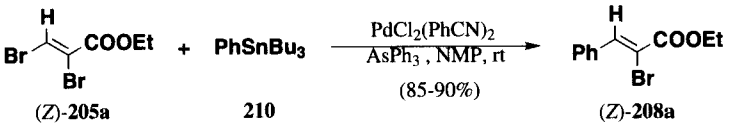
(*E*)-**205** (*E*)-**208**

(70)

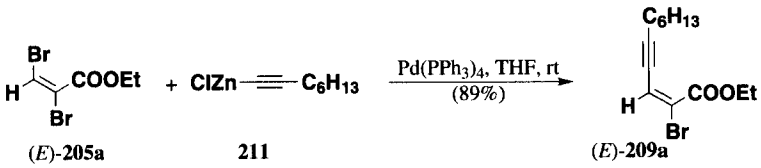
[FGAr = Ph, 4-$MeOC_6H_4$, 4-$EtOOCC_6H_4$; X = Cl, Br]

It was demonstrated that a new catalyst precursor consisting of a mixture of 10% palladium on carbon and 3.9 equiv of $AsPh_3$ as well as that obtained by treatment of $Pd(OAc)_2$ with 4 equiv of $AsPh_3$ in THF at 60° can conveniently replace the more expensive and air unstable $Pd(PPh_3)_4$ in efficiently promoting either the above mentioned coupling reactions or those involving organozinc derivatives and organic electrophiles different from compounds **205**, which contain an electron-withdrawing substituent linked to their carbon-carbon double bond.[159] Compounds (*Z*)- and (*E*)-**208** can be stereospecifically and regioselectively prepared by palladium-promoted reaction of aryltributylstannanes with (*Z*)- and (*E*)-**205**.[160] Moreover, 3-(1-alkynyl) substituted alkyl (*Z*)- and (*E*)-2-bromopropenoates, (*Z*)- and (*E*)-**209**, can be selectively prepared in satisfactory yields by palladium-promoted reactions of these dibromides with 1-alkynylzinc chlorides.[160]

Examples of these reactions are shown in Eqs. 71 and 72.[160]

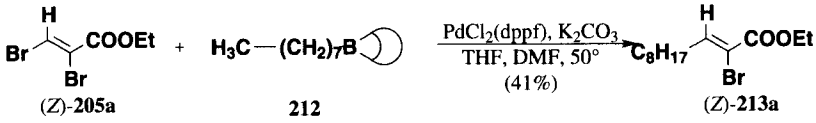


(71)



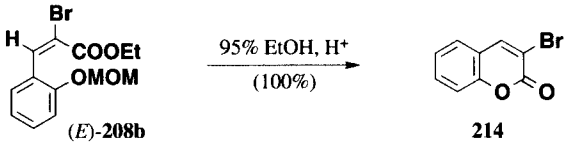
(72)

On the other hand, a representative alkyl (Z)-3-alkyl-2-bromopropenoate, *i.e.* **213a**, was prepared by reaction of a 9-alkyl-9-BBN derivative with (Z)-**205a**, in the presence of K_2CO_3 and a catalytic quantity of $PdCl_2$(dppf) (Eq. 73).[160]

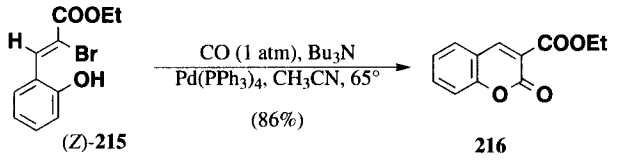


(73)

Some applications demonstrated the synthetic utility of the compounds prepared according to these protocols. Thus, (*E*)-**208b** was easily converted to 3-bromocoumarin (**214**) (Eq. 74)[160] and (Z)-**211**, which was obtained by acidic hydrolysis of the corresponding MOM derivative, underwent a palladium-mediated intramolecular carbonylative reaction to give **216** in high yield (Eq.75).[160]



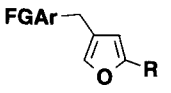
(74)



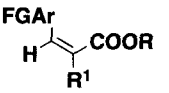
(75)

Moreover, compounds (Z)- and (*E*)-**208** proved to be suitable precursors to 2,4-disubstituted furans of general formula **217**[161] as well as to trisubstituted α,β-unsaturated esters of general formula (*Z*) and (*E*)-**218**.[160]

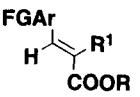
The high yield and selectivity of the palladium-mediated monoarylations of compounds (Z)-**205** also allowed a direct access to trisubstituted α,β-unsaturated esters (Z)-**218** by a one-pot procedure, which involved two sequential palladium-mediated arylations (Eq. 76).[160]



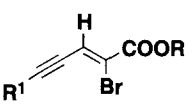
217 [R = alkyl]



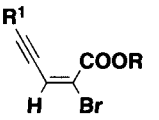
(*Z*)-**218** [R^1 = Ph, Me, $CH{=}CH_2$]



(*E*)-**218** [R^1 = 3,4-methylenedioxyphenyl, 2-$MOMOC_6H_4$, $CH_2{=}CH$, Ph-C≡C]

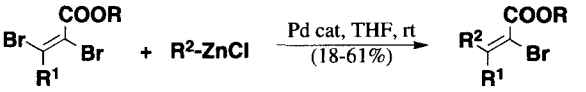


(*Z*)-**209**



(*E*)-**209**

To conclude this section it must also be mentioned that 3-alkyl, 3-aryl and 3-alkoxycarbonyl substituted (*E*)-2,3-dibromopropenoates **219** underwent highly regioselective palladium-mediated cross-coupling reactions with aryl- and 1-alkynylzinc chlorides (Eq. 77).[162]

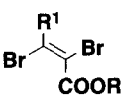


(77)

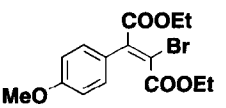
(*E*)-**219** **220**

[R^1 = CH_3, C_5H_{11}, Ph, COOEt; R = Me, Et; R^2 = 4-$MeOC_6H_4$, 2-$MOMOC_6H_4$, 4-FC_6H_4,C_6H_{13}-C≡C]

Interestingly, the stereospecificity of these reactions was dependent on the type of dibromide used. In fact, when 3-alkyl substituted (*E*)-2,3-dibromopropenoates were employed, the desired cross-coupled products were stereoisomerically pure. On the other hand, crude compounds **220**, which were prepared by palladium-mediated arylation of **219c** were contaminated by *ca.* 7% of the corresponding stereoisomers. Moreover, a still higher percentage of undesired stereoisomer (20%) contaminated the cross-coupled product **220d**, which was obtained by reaction between diethyl 2,3-dibromofumarate (**219d**) and 4-methoxyphenylzinc chloride.[162]



(*E*)-**219a** [R^1 = C_5H_{11}; R = Me]
(*E*)-**219b** [R^1 = Me; R = Et]
(*E*)-**219c** [R^1 = Ph; R = Et]
(*E*)-**219d** [R^1 = EtOOC; R = Et]



220d

The modest yields of cross-coupled products which were obtained in these couplings were at least in part due to a side reaction which produced α,β-acetylenic esters **221** corresponding to the dibromides used.[162] As confirmed by stoichiometric reactions involving $Pd(PPh_3)_4$ and compounds (*E*)-**219**, these acetylenic esters derived from a *trans*-elimination reaction involving the oxidative-addition complexes which regioselectively resulted from **219** and the palladium(0) species present in the reaction mixtures.[162]

R^1—≡—COOR
221

Finally, it is worth mentioning that the very high regioselectivity observed in the monocoupling reactions involving (*Z*)- and (*E*)-**205** as well as (*E*)-**219**, has been explained by supposing that the mesomeric effect of the alkoxycarbonyl group present in these dibromides overcomes its inductive effect.[163] Thus, this group might be able to render the carbon-bromine bond in the 3-position more electron poor than that in their 2-position and, therefore, more suitable for the oxidative-addition reaction with the palladium(0) species present in the reaction mixtures.[163] On the other hand, the results obtained in the reactions involving (*E*)-**219** show that the presence of an aryl or an alkyl group in the 3-position of alkyl 2,3-dibromopropenoates does not affect the regiochemistry of the couplings.[162] Nevertheless, these groups render the palladium-promoted cross-coupling reactions slower than the corresponding reactions involving (*E*)-**205**.[163]

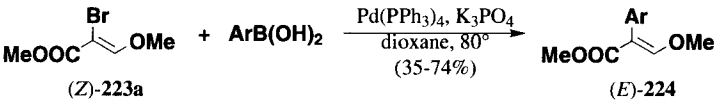
IV. CARBON-HETEROATOM BOND FORMATION *via* POLYHALOGENATED ETHENE DERIVATIVES

Transition metal-promoted reactions to construct carbon-heteroatom bonds starting from alkenyl halides are limited. Several years ago, it was noted that alkenyl sulfides could be prepared by reaction of alkenyl bromides with lithium aryl- or alkylthiolates in the presence of a palladium(0)[164] or a nickel(II) catalyst precursor.[165] Subsequently, it was found that trialkyltin sulfides could be conveniently used as valuable sulfur-centered nucleophiles in palladium[166,167] hetero-cross-coupling reactions. It was also reported that in the palladium-mediated reactions (*E*)-1-bromo-1-alkenes were more reactive than the corresponding (*Z*)-stereoisomers.[120] However, only very recently, similar palladium-mediated reactions involving stereodefined, functionalized 1,2-dihaloethene derivatives have been investigated.[168,169] In particular, it has been found that alkyl (*Z*)- and (*E*)-2,3-dibromopropenoates (**205**) react stereospecifically, regio- and chemoselectively with 1.15 equiv of alkoxy-, alkylthio- and arylthiotributylstannanes of general formula **222** in NMP at 20°, in the presence of 5 mol % $Pd(PPh_3)_4$ to give 3-alkoxy, 3-alkylthio and 3-arylthio substituted alkyl (*Z*)- and (*E*)-2-bromopropenoates **223**, respectively, in satisfactory to high yields (Eq. 78).[168,169]

$$\underset{\textbf{205}}{\overset{Z \text{ or } E}{\textbf{Br-CH=CBr-COOR}}} + \underset{\textbf{222}}{\textbf{R}^1\textbf{XSnBu}_3} \xrightarrow[(39\text{-}86\%)]{Pd(PPh_3)_4,\ NMP,\ rt} \underset{\textbf{223}}{\overset{Z \text{ or } E}{\textbf{R}^1\textbf{XCH=CBr-COOR}}} \qquad (78)$$

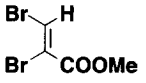
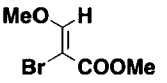
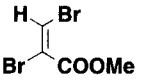
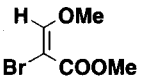
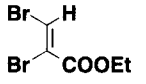
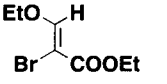
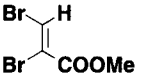
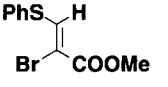
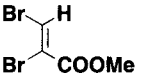
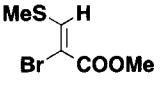
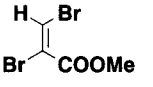
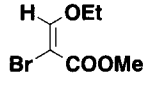
[R^1 = Me, Et; X = O, S]

Some typical results are summarized in Table 1. Interestingly, the reaction between (*Z*)-**223a** so prepared and (hetero)arylboronic acids in dioxane at 80°, in the presence of K_3PO_4 and catalytic amounts of $Pd(PPh_3)_4$, produced some 2-(hetero)aryl substituted (*E*)-3-methoxypropenoates **224** in satisfactory yields, which represent structural analogues of broad-spectrum systemic fungicides (Eq. 79).[168,169]



(*Z*)-**223a** (*E*)-**224** (79)

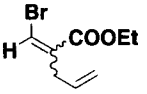
TABLE 1. Palladium-mediated Carbon-Oxygen and Carbon-Sulfur Bond-forming Reactions[a]

Entry	Substrate	Tin derivative	Reaction time (hrs)	Products	Yield (%)
1	 (*Z*)-**205b**	Bu_3SnOMe **222a**	96	 (*Z*)-**224a**	63
2	 (*Z*)-**205b**	Bu_3SnOMe **222a**	71	 (*Z*)-**224a**	46
3	 (*Z*)-**205a**	Bu_3SnOEt **222b**	172	 (*Z*)-**224b**	45
4	 (*Z*)-**205b**	Bu_3SnSPh[b] **222c**	24	 (*Z*)-**224c**	84
5	 (*Z*)-**205b**	Bu_3SnSMe **222d**	5	 (*Z*)-**224d**	86
6	 (*E*)-**205b**	Bu_3SnOEt **222b**	168	 (*Z*)-**224e**	39

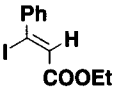
a) Reactions performed in NMP at room temperature using 1.15 equiv of the organotin reagent and 5 mol% $Pd(PPh_3)_4$. b) Reaction performed using 2.5 equiv of Bu_3SnSPh.

Finally, it must be noted that the palladium-mediated carbon-oxygen bond forming reaction, which worked well with alkoxytributylstannanes and compounds **205**, did not afford the desired 3-alkoxy derivatives starting from a stereoisomeric mixture of 3-bromo-2-allylpropenoate (**225**) or 3-bromocoumarin (**214**). In fact, these bromides did not react under the experimental conditions used to prepare compounds **223a,b**.[170]

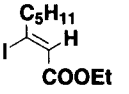
On the other hand, under these conditions, ethyl (Z)-3-iodo-3-phenylpropenoate (**226**) and methyl (Z)-3-iodo-2-octenoate (**227**) were converted to the corresponding α,β-acetylenic esters.[170]



225

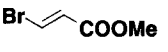


226

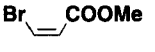


227

On the contrary, when stereoisomerically pure methyl (*E*)- and (*Z*)-3-bromopropenoate, (*E*)- and (*Z*)(**228**), were reacted with 1.15 equiv of (methylthio)tributylstannane (**222d**) in NMP solution at 20° for 5 hrs, methyl (*E*)- and (*Z*)-3-(methylthio)propenoate, (*E*)- and (*Z*)(**229**), were stereospecifically obtained in 85 and 90% yield, respectively.[169] Very recently, these new stereoisomerically pure electrophiles have been used as direct precursors to a variety of unsual sulfur-containing naturally-occurring carboxyamides, which are characterized by a methylthio substituent linked to their stereodefined carbon-carbon double bond.[169]

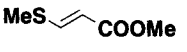


(*E*)-**228**

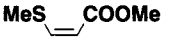


(*Z*)-**228**

222d



(*E*)-**229**



(*Z*)-**229**

Similarly, the palladium-mediated reaction between compound **227** and phenylthiotributylstannane (**222c**) afforded stereospecifically the desired 3-phenylthio substituted product in good yield.[170]

REFERENCES

1. N. A. Bumagin and I. P. Beletskaya, *Russ. Chem. Rev.*, **59**, 1174 (1990).

2. Y. Hatanaka and T. Hiyama, *Synlett,* 845 (**1991**).

3. A. Erdik, *Tetrahedron,* **48**, 9557 (1992).

4. T. N. Mitchell, *Synthesis,* 803 (**1992**).

5. V. N. Kalinin, *ibid.*, 413 (**1992**).

6. C.-J. Li, *Chem. Rev.*, **93**, 2033 (1993).

7. L. Hegedus, *J. Organomet. Chem.*, **477**, 269 (1994).

8. H. M. Colquhoun, D. J. Thomson and M. V. Twigg, *Carbonylation,* Plenum Press, New York, (1991).

9. R. Rossi, A. Carpita and F. Bellina, *Org. Prep. Proc. Int.*, **27**, 127 (1995).

10. V. Farina, in *Comprehensive Organometallic Chemistry II,* E. W. Abel, F. G. A. Stone, G. Wilkinson, L. S. Hegedus, Eds., Pergamon, Oxford, Vol 12, 161-240 (1995).

11. J.-F. Fauvarque and A. Jutard, *Bull. Chim. Soc. Fr.,* 765 (**1976**).

12. D. Milstein and J. K. Stille, *J. Am. Chem. Soc.,* **101**, 4981 (1979).

13. A. Gillie and J. K. Stille, *ibid.,* **102**, 4933 (1980).

14. G. S. Reddy and W. Tam, *Organometallics,* **3**, 630 (1984).

15. T. Katayama and M. Umeno, *Chemistry Lett.,* 2073 (**1991**).

16. A. Minato, K. Suzuki, K. Tamao and M. Kumada, *Chem. Commun.,* 511 (**1984**).

17. A. Minato, K. Tamao, K. Suzuki and M. Kumada, *Tetrahedron Lett.,* **21**, 4017 (1980).

18. A. Carpita and R. Rossi, *Gazz. Chim. Ital.,* **115**, 575 (1985).

19. R. Rossi, A. Carpita, M. Ciofalo and V. Lippolis, *Tetrahedron,* **47**, 8443 (1991).

20. K. C. Eapen, S. S. Dua and C. Tamborski, *J. Org. Chem.,* **49**, 478 (1984).

21. S. W. Wright, D. L. Hageman and L. D. Mc Clure, *ibid.,* **59**, 6095 (1994)

22. D. R. Mc Kean, G. Parrinello, A. F. Renaldo and J. K. Stille, *ibid.,* **52**, 422 (1987).

23. A. Bahl, W. Grahn, S. Stadler, F. Feiner, G. Bourhill, C. Bräuchle, A. Reisner and P. G. Jones, *Angew. Chem. Int. Ed. Eng.,* **34**, 1485 (1995).

24. E. Dubois and J. M. Beau, *Chem. Commun.*, 1191 (**1990**)

25. L. Brandsma and H. D. Ver Kruijsse, *Synth. Commun.,* **20**, 2275 (1990).

26. J. W. Grissom, T. L. Calkins and M. Egan, *J. Am. Chem. Soc.,* **115**, 11744 (1993).

27. Q. Zhou, P. J. Carrol and T. M. Swager, *J. Org. Chem,.* **59**, 1294 (1994).

28. J. W. Grissom, T. L. Calkins, D. Huang and H. McMillen, *Tetrahedron,* **50**, 4635 (1994).

29. S. Cacchi, P. G. Ciattini, E. Morera and G. Ortar, *Tetrahedron Lett.,* **28**, 3039 (1987)

30. A.-S. Carlström and T. Frejd, *J. Org. Chem.,* **56**, 1289 (1991).

31. L. N. Pridgen, *ibid.,* **47**, 4319 (1982).

32. I. Mangalagiu, T. Benneche, K. Undheim, *Tetrahedron Lett.*, **37**, 1309 (1996).

33. a) L. L. Gundersen, G. Langli and F. Rise, *ibid.*, **36**, 1945 (1995); b) G. Langli, L.-L. Gundersen and F. Rise, *Tetrahedron*, **52**, 5625 (1996).

34. I. Klement, P. Knochel, K. Chau and G. Cahiez, *Tetrahedron Lett.*, **35**, 1177 (1994).

35. A. Dondoni, M. Fogagnolo, A. Medici and E. Negrini, *Synthesis*, 185 (**1987**).

36. I. Kaswasaki, M. Yamashita and S. Ohta, *Chem. Commun.*, 2085 (**1994**).

37. D. A. Evans and T. Bach, *Angew. Chem. Int. Ed. Engl.*, **32**, 1326 (1993).

38. J. W. Tilley and S. Zawoiski, *J. Org. Chem.*, **53**, 386 (1988).

39. R. W. Bates, C. J. Gabel and J. Ji, *Tetrahedron Lett.*, **35**, 6993 (1994).

40. R. W. Bates and T. Rama-Devi, *Synlett*, 1151 (**1995**).

41. S. Torii, L. H. Xu and H. Okumoto, *ibid.*, 515 (**1992**).

42 Y. Miura, H. Oka and M. Momoki, *Synthesis*, 1419 (**1995**).

43. A. M. Echavarren and J. K. Stille, *J. Am. Chem. Soc.*, **109**, 5478 (1987)

44. Y. Yang and A. R. Martin, *Synth. Commun.*, **22**, 1757 (1992)

45. B. C. Soderberg, in *Comprehensive Organometallic Chemistry II*, Pergamon, Oxford, Vol 12, 241-297 (1995).

46. B. M. Trost and T. R. Verhoeven, in *Comprehensive Organometallic Chemistry*, Pergamon, Oxford, Vol 8, 799-938 (1982).

47. J. Solberg and K. Undheim, *Acta Chem. Scand.*, **A43**, 62 (1989).

48. A. Sekiya and N. Ishikawa, *J. Organomet. Chem.*, **118**, 349 (1976).

49. Y. Ikoma, K. Ando, Y. Naoi, T. Akiyama and A. Sugimori, *Synth. Commun.*, **21**, 481 (1991).

50. N. Miyaura, T. Yanagi and A. Suzuki, *ibid.*, **11**, 513 (1981).

51. J. C. Anderson and H. Namli, *Synlett*, 765 (**1995**).

52. T. Watanabe, N. Miyaura and A. Suzuki, *ibid.*, 207 (**1992**).

53. J-m. Fu, M. J. Sharp and V. Snieckus, *Tetrahedron Lett.*, **29**, 5459 (1988).

54. M. C. Unrau, M. G. Cambell and V. Snieckus, *ibid.*,**33**, 2773 (1992).

55 R. C. Larock, N. G. Barrios-Peña, C. A. Fried, *J. Org. Chem.* **56**, 2615 (1991).

56. A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici and P. Pedrini, *Synthesis,* 693 (**1987**).

57. B. C. Pierce, *Synth. Commun.,* **22**, 1627 (1992).

58. J. Solberg and K. Undheim, *Acta Chem. Scand.,* **A41**, 712 (1987).

59. Y. Kondo, R. Watanabe, T. Sakamoto and Y. Yamanaka, *Chem. Pharm. Bull. Jpn.,* **37**, 2814 (1989).

60. V. P. Baillargeon and J. K. Stille, *J. Am. Chem. Soc.,* **108**, 452 (1986).

61. Y. Hatanaka, K. Goda, Y. Okahara and T. Hiyama, *Tetrahedron,* **50**, 8301 (1994).

62. M. Ishikura and M. Terashima, *J. Org. Chem.,* **59**, 2634 (1994).

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

64. P. L. Heinze and D. J. Burton, *J. Org. Chem.,* **53**, 2714 (1988).

65. L. S. Hegedus, M. R. Sestrick, E. T. Michaelson and P. J. Harrington, *ibid.,* **54**, 4141 (1989).

66. M. Kosugi, T. Sumiya, Y. Obara, M. Suzuki, H. Sano and T. Migita, *Bull. Chem. Soc. Jpn.,* **60**, 767 (1987).

67. R. W. Freisen and C. F. Sturino, *J. Org. Chem.,* **55**, 2572 (1990).

68. F. Marsais, Ph. Pineau, F. Nivolliers, M. Mallet, A. Turck, A. Godard and G. Queguiner, *ibid.,* **57**, 565 (1992).

69. H. B. Kwon, B. H. McKee and J. K. Stille, *ibid.,* **55**, 3114 (1990).

70. G. T. Crisp, and P. T. Glink, *Tetrahedron,* **50**, 3213 (1994).

71. D. M. Hodgson, J. Witherington, B. A. Moloney, I. C. Richards and J.-L. Brayer, *Synlett,* 32 (**1995**).

72. G. Shi, Z. Cao and X. Zhang, *J. Org. Chem.,* **60**, 6608 (1995).

73. P. N. Lopwe and A. F. Rowe, *Comp. Biochem. Physiol., B: Comp Biochem.,* **88B**, 223 (1987).

74. C. Walsh, *Tetrahedron,* **38**, 871 (1982).

75. J. M. Clough, *Nat. Prod. Rep.,* **10**, 565 (1993).

76. J. T. Welch and S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry,* J. Wiley & Sons, New York, **1990**.

77. R. Heck, *Palladium Reagents in Organic Synthesis,* Academic Press, London, **1985**.

78. A. Spencer, *J. Organomet. Chem.,* **258**, 101 (1983).

79. T. Jeffery, *Chem. Commun.,* 1287 (**1984**)

80. C. A. Merlic and M. F. Semmelhack, *J. Organomet. Chem.,* **391**, C23 (1990).

81. C. Amatore, M. Azzabi and A. Jutand, *J. Am. Chem. Soc.,* **113**, 8375 (1991)

82. J. E. Plevyak, J. E. Dickerson and R. F. Heck, *J. Org. Chem.,* **44**, 4078 (1979).

83. N. Cortese and R. F. Heck, *ibid.,* **42**, 3907 (1977).

84. W. Tao, S. Nesbitt, and R. F. Heck, *ibid.,* **55**, 63 (1990).

85. T. Izumi, Y. Nishimoto, K. Kohei and A. Kasahara, *J. Heterocycl. Chem.,* **27**, 1419 (1990).

86. P. C. Amos and D. A. Whiting, *Chem. Commun.,* 510 (**1987**).

87. A. Satake, K. Okano, I. Shimizu and A. Yamamoto, *Synlett,* 839 (**1994**).

88. T. Satoh, T. Itaya, K. Okuro, M. Miura and M. Nomura, *J. Org. Chem.,* **60**, 7267 (1995).

89. J. J. Chen, J. A. Walker II, W. Liu, D. S. Wise and L. B. Towsend, *Tetrahedron Lett.,* **36**, 8363 (1995).

90. P. J. Harrington, L. S. Hegedus and K. F. McDaniel, *J. Am. Chem. Soc.,* **109**, 4335 (1987).

91. T. Jeffery, *Tetrahedron Lett.,* **33**, 1989 (1992).

92. K. Albrecht, O. Reiser, M. Weber, B. Knieriem and A. de Meijere, *Tetrahedron,* **50**, 383 (1994).

93. T. Jeffery, *Tetrahedron Lett.,* **26**, 2667 (1985).

94. K. Minn, *Synlett,* 115 (**1991**).

95. G. J. Quallich, D. E. Fox, R. C. Friedmann and C. W. Murtiashaw, *J. Org. Chem.,* **57**, 761 (1992).

96. R. F. Jackson, N. Wishart, A. Wood, K. James and M. J. Wythes, *ibid.,* **57**, 3397 (1992).

97. J. L. Fraser, R. F. W. Jackson and B. Porter, *Synlett,* 379 (**1994**).

98. Y. Tamaru, H. Ochiai, T. Nakamura and Z. Yoshida, *Tetrahedron Lett.*, **27**, 955 (1986).

99. E. Nakamura, S. Aoki, K. Sekiya, H. Oshino and I. Kuwajima, *J. Am. Chem. Soc.*, **109**, 8056 (1987).

100. I. Klement, P. Knochel, K. Chau and G. Cahiez, *Tetrahedron Lett.*, **35**, 1177 (1994).

101. M. Kosugi, M. Suzuki, I. Hagiwara, K. Goto; K. Saitoh and T. Migita, *Chemistry Lett.*, 939 (**1982**).

102. M. Kosugi, M. Ishiguro, Y. Negishi, H. Sano and T. Migita, *ibid.*, 1511 (**1984**).

103. M. Kosugi, T. Sumiya, K. Ohhashi, H. Sano and T. Migita, *ibid.*, 997 (**1985**).

104. M. Kosugi, Y. Negishi, M. Kameyama and T. Migita, *Bull. Chem. Soc. Jpn.*, **58**, 3383 (1985).

105. M. Durandetti, S. Sibille, J?-Y. Nédélec and J. Péridiou, *Synth. Commun.*, **24**, 1245 (1994).

106. A. Löffler and G. Himbert, *Synthesis,* 495 (**1992**).

107. T. L. Draper and T. R. Bailey, *J. Org. Chem.*, **60**, 748 (1995).

108. G. T. Crisp and T. A. Robertson, *Tetrahedron,* **48**, 3239 (1992).

109. A. Arcadi, S. Cacchi, F. Marinelli, P. Pace and G. Sanzi, *Synlett,* 823 (**1995**).

110. M. J. Chapdelaine, P. J. Warwick and A. Shaw, *J. Org. Chem.*, **54**, 1218 (1989).

111. M. Kosugi, M. Kameyama and T. Migita, *Chemistry Lett.*, 927 (**1983**).

112. D. Barañano and J. F. Hartwig, *J. Am. Chem. Soc.*, **117**, 2937 (1995).

113. A. Minato, K. Suzuki and T. Tamao, *ibid.*, **109**, 1257 (1987).

114. R. Rossi and A. Carpita, *Tetrahedron Lett.*, **27**, 2529 (1986).

115. A. Carpita and R. Rossi, *ibid.*, **27**, 4351 (1986).

116. B. P. Andreini, A. Carpita and R. Rossi, *ibid.*, **27**, 6633 (1986).

117. B. P. Andreini, M. Benetti, A. Carpita and R. Rossi, *Tetrahedron,* **43**, 4591 (1987).

118. B. P. Andreini, A. Carpita and R. Rossi, *Tetrahedron Lett.*, **29**, 2239 (1988).

119. B. P. Andreini, M. Benetti, A. Carpita and R. Rossi, *Gazz. Chim. Ital.*, **118**, 469 (1988).

120. A. Carpita, R. Rossi and B. Scamuzzi, *Tetrahedron Lett.*, **30**, 2699 (1989).

121. B. P. Andreini, A. Carpita, R. Rossi and B. Scamuzzi, *Tetrahedron,* **30**, 5621 (1989).

122. A. Minato, *J. Org. Chem.,* **56**, 4052 (1991).

123. V. Ratovelomanana, A. Hammoud and G. Linstrumelle, *Tetrahedron Lett.,* **28**, 1649 (1987).

124. W. R. Roush and R. Riva, *J. Org. Chem.,* **53**, 710 (1988).

125. N. Miyaura, K. Yamada, H. Suginome and A. Suzuki, *J. Am. Chem. Soc,* **107**, 972 (1985).

126. J. Uenishi, J.-M. Beau, R. W. Armstrong and Y. Kishi, *ibid.,* **109**, 4576 (1987).

127. W. R. Roush, K. J. Moriarty and B. B. Brown, *Tetrahedron Lett.,* **31**, 6509 (1990).

128. J. E. Baldwin, R. Chesworth, J. S. Parker and A. T. Russell, *ibid.,* **36**, 9551 (1995).

129. M. Alami, B. Crousse and G. Linstrumelle, *ibid.,* **36**, 3687 (1995).

130. S. Torii, H. Okumoto, T. Tadokoro, A. Nishimura and Md. A. Rashid, *ibid.,* **34**, 2139 (1993).

131. A. Bryant-Friederich and R. Neidlein, *Synthesis,* 1506 (**1995**).

132. V. Ratovelomanana and G. Linstrumelle, *Tetrahedron Lett.,* **22**, 315 (1981).

133. D. Guillerm and G. Linstrumelle, *ibid.,* **26**, 3811 (1985).

134. D. Guillerm and G. Linstrumelle, *ibid.,* **27**, 5857 (1986).

135. P. Magnus , H. Annoura and J. Harling, *J. Org. Chem.,* **55**, 1709 (1990).

136. C. Creusy and J.-M. Beau, *Tetrahedron Lett.,* **32**, 3171 (1991).

137. M. Avignon-Tropis, J. M. Berjeaud, J. R. Pougny, I. Fréchard-Ortuno, D. Guillerm and G. Linstrumelle, *J. Org. Chem.,* **57**, 651 (1992).

138. D. Chemin, M. Alami and G. Linstrumelle, *Tetrahedron Lett.,* **33**, 2681 (1992).

139. H. Audrain, T. Skrydstrup, G. Ulibarri, C. Riche, A. Chiaroni and D. S. Grierson, *Tetrahedron,* **50**, 1469 (1994).

140. M.-J. Wu, C.-F, Lin, J.-S. Wu and H.-T. Chen, *Tetrahedron Lett.,* **35**, 1879 (1994).

141. T. Nishikawa, A. Ino and M. Isobe, *Tetrahedron,* **50**, 1449 (1994).

142. G. McGaffin and A. de Meijere, *Synthesis,* 583 (**1994**).

143. Y. Sakai, E. Nishiwaki, K. Shishido, M. Shibuya and M. Kido, *Tetrahedron Lett.,* **32**, 4363

(1991).

144. D. Elbaum, T. B. Nguyen, W. L. Jorgesen and S. L. Schreiber, *Tetrahedron,* **50**, 1503 (1994).

145. T. Nishikawa, A. Ino and M. Isobe, *ibid.,* **50**, 1449 (1994).

146. D. Chemin and G. Linstrumelle, *ibid.,* **50**, 5335 (1994)

147. M. Alami, B. Crousse and G. Linstrumelle, *Tetrahedron Lett.,* **35**, 3543 (1994).

148. V. Ratevelomanana and G. Linstrumelle, *ibid.,* **25**, 6001 (1984).

149. A. Carpita, D. Neri and R. Rossi, *Gazz. Chim. Ital.,* **117**, 503 (1987).

150. E. Negishi, N. Okukado, S. F. Lovich and F-T. Luo, *J. Org. Chem.,* **49**, 2629 (1984).

151. J. P. Gillet, R. Sauvêtre and J. F. Normant, *Tetrahedron Lett.,* **26**, 3999 (1985)

152. F. Tellier, R. Sauvêtre and J. F. Normant, *J. Organomet. Chem.,* **303**, 309 (1986).

153. F. Tellier, R. Sauvêtre and J. F. Normant, *ibid.,* **328**, 1 (1987).

154. F. Tellier, R. Sauvêtre and J. F. Normant, *ibid.,* **367**, 1 (1989).

155. F. Tellier, R. Sauvêtre and J. F. Normant, *ibid.,* **292**, 19 (1985).

156. S. Eddarir, H. Mestdagh and C. Rolando, *Tetrahedron Lett.,* **32**, 69 (1991).

157. A. G. Myers, M. M. Alauddin, M. A. M. Fuhry, P. S. Dragovich, N. S. Finney and P. M. Harrington, *ibid.,* **30**, 6997 (1989).

158. a) F. Bellina, A. Carpita, M. De Santis and R. Rossi, *ibid.,* **35**, 6913 (1994); b) F. Bellina, A. Carpita, M. De Santis and R. Rossi, *Tetrahedron,* **50**, 12029 (1994).

159. R. Rossi, F. Bellina, A. Carpita and R. Gori, *Synlett,* 344 (**1995**).

160. R. Rossi, F. Bellina, A. Carpita and R. Gori, *Gazz. Chim. Ital.,* **125**, 381 (1995).

161. F. Bellina, A. Carpita and R. Rossi, Convegno Nazionale su *Orientamenti e Metodologie in Chimica Farmaceutica, Organica e Bioorganica,* Numana (AN), Italy, June 2-6, 1995, Atti del Convegno, 021.

162. R. Rossi, F. Bellina, A. Carpita and F. Mazzarella, *Tetrahedron,* **52**, 4095 (1996).

163 R. Rossi and F. Bellina, manuscript in preparation.

164. S. Murahashi, M. Yamamura, K. Yanagisawa, N. Mita and K. Kondo, *J. Org. Chem.,* **44**, 2408

(1979).

165. H. J. Cristau, B. Chabaud, B. Labaudiniere and H. Christol, *J. Org. Chem.*, **51**, 875 (1986).

166. N. A. Bumagin, Yu. V. Gulevich and I. P. Beletskaya, *Izv. Akad Nauk SSSR, Ser. Khim.*, **4**, 953 (1984).

167. M. Kosugi, T. Ogata, M. Terada, H. Sano and T. Migita, *Bull. Soc. Chem. Jpn.*, **57**, 1863 (1984).

168. R. Rossi, F. Bellina and A. Carpita, *Synlett,* 356 (**1996**).

169. R. Rossi and F. Bellina, Invited lecture at the *1st Korea-Italy Symposium in Medicinal Chemistry,* Seoul, Korea, May 24-25, 1996.

170. R. Rossi and F. Bellina, Unpublished results.

(Received June 3, 1996; in revised form September 23, 1996)