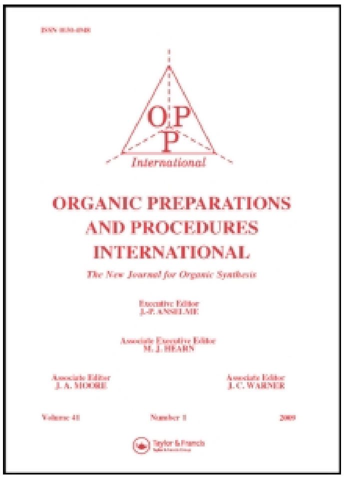

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PALLADIUM- AND/OR COPPER-MEDIATED CROSS-COUPLING REACTIONS BETWEEN 1-ALKYNES AND VINYL, ARYL, 1-ALKYNYL, 1,2-PROPADIENYL, PROPARGYL AND ALLYLIC HALIDES OR RELATED COMPOUNDS. A REVIEW

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INTRODUCTION

The reaction between 1-alkynes and aryl or vinyl halides, in the presence of a base and a palladium(II) or a palladium(0) catalyst as well as of copper(I) iodide as an effective cocatalyst, is known as the *Sonogashira reaction*.[1] The reaction, which was developed in 1975, tolerates the presence of several types of functional groups and has proven to be very useful for the efficient and convenient synthesis of a large variety of disubstituted acetylene derivatives and heterocycles, which include biologically active compounds, as well as for the preparation of naturally-occurring substances and their precursors. No general review has been published on this reaction except for a brief discussion in a chapter of *Comprehensive Organic Synthesis* (1991) devoted to the coupling reactions between sp^2- and sp-carbon centers,[2] which contained references only up to 1989 and in a more recent article (in Japanese) also devoted to a survey of palladium-catalyzed coupling reactions between sp- and sp^2-carbon centers.[3]

The goal of the present review is to discuss in concise fashion the main synthetic aspects of this very useful reaction, including those related to the preparation of key intermediates of some relevant natural products and their analogues, and will emphasize issues of reactivity, chemoselectivity and stereoselectivity. Modifications and alternatives of this coupling reaction such as the palladium-copper mediated reaction between 1-alkynes and aryl or vinyl halides under phase-transfer conditions, the palladium mediated reaction between 1-alkynes and functionalized iodoarenes under carbonylative conditions, the palladium-copper mediated alkynylation of vinyl or aryl perfluoroalkanesulfonates, as well as palladium(0) and/or copper(I) mediated cross-coupling reactions between 1-alkynes and other types of organic electrophiles (*e.g.* 1-alkynyl, 1,2-propadienyl, propargyl and allylic halides) will be also surveyed.

The focus of this survey will be on the synthetic aspects of carbon-carbon bond forming reactions rather than the mechanisms of the reactions discussed. However, we also cover several reactions that generate carbon-heteroatom bonds and are very useful for the synthesis of various types of heterocycles. Moreover, when well-studied cases are available, details on the effects of the type of catalyst, substrate, base and solvent on the reaction outcomes will be given. Since the literature on these coupling reactions is very extensive, the present review is intended to be representative rather than comprehensive and the selection of material, which includes papers published prior to March

1994, reflects the interests and/or prejudices of the authors. However, every attempt has been made to include the most important studies on these reactions and their applications, even though reports from the patent literature have not been reviewed since patents are rarely sufficiently detailed to allow reproduction of the reported results. Moreover, palladium-copper mediated reactions between 1-alkynes and acyl halides have not been discussed, too.

I. SYNTHESIS OF DISUBSTITUTED ACETYLENES *via* PALLADIUM-COPPER MEDIATED REACTION OF 1-ALKYNES WITH sp^2-CARBON HALIDES

In 1975 three different research groups found independently that disubstituted acetylenes of general formula **1** could be conveniently and efficiently synthesized by reaction of 1-alkynes with aryl, heteroaryl or alkenyl halides, in the presence of a palladium catalyst and a base.[1,4,5]

$$R-\equiv-R^1$$

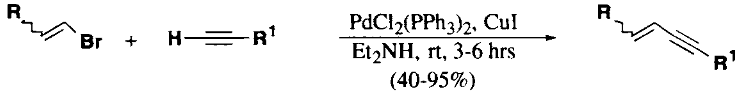
1

[R = aryl, alkyl, alkenyl; R^1 = aryl, heteroaryl]

The palladium complexes used as catalysts were $Pd(PPh_3)_4$,[1] $PdCl_2(PPh_3)_2$[1] or $Pd(OAc)_2(PPh_3)_2$[5] and the base was an alkali metal alkoxide dissolved in DMSO[4] or an amine which also served as the solvent.[1,5]

Sonogashira and coworkers[1] discovered that the activity of the catalyst system could be greatly improved by addition of copper(I) iodide as a cocatalyst and these authors found that the optimal molar ratio between CuI and the palladium complex was at least 2 : 1, respectively. In these experimental conditions and using Et_2NH as base and solvent, the coupling reaction could efficiently be carried out at room temperature (Eqs 1 and 2).[1]

$$2\ Ar-X\ +\ H-\equiv-H\ \xrightarrow[\substack{Et_2NH,\ rt,\ 3\text{-}6\ hrs\\(60\text{-}85\%)}]{PdCl_2(PPh_3)_2,\ CuI}\ Ar-\equiv-Ar \qquad (1)$$



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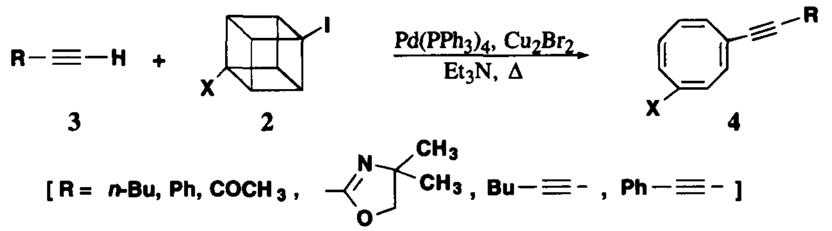
It must be noted that this coupling reaction, which has been used to prepare arylacetylenes,[1] tolanes[5,6] and heteroarylacetylenes[7-9] in mild experimental conditions, is unsuitable for the preparation of dialkylacetylenes. In fact, normally saturated alkyl halides are unsuitable electrophiles as β-elimination reactions compete with the desired coupling. Nevertheless, quite recently it has been found that iodocubanes **2**, which are characterized by carbons having high percentage of s-character and undergo to β-elimination reactions most difficulty, react with 1-alkynes **3** in refluxing Et_3N, in the presence of Cu_2Br_2 and $Pd(PPh_3)_4$.[10] Howewer, the products, isolated in about 50% yield, were not alkynylcubanes but were instead the first examples of alkynyl-1,3,5,7-cyclooctatetraenes (**4**) (Eq. 3).[10]



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The mechanism of the coupling reaction between 1-alkynes and sp^2-carbon halides in the presence of catalytic amounts of a palladium(II) complex and CuI appears to involve: (*i*) reduction of the palladium(II) complex to a palladium(0) species by CuI-promoted reaction with the 1-alkyne in the presence of the base (*e.g.* Et_2NH); (*ii*) oxidative addition of the organic halide to the palladium(0) species followed by alkynylation of the resulting complex to give an aryl- or a vinylpalladium(II) derivative; and (*iii*) a reductive elimination reaction, which affords the desired cross-coupled product **1**.[1] However, when a palladium(II) complex is used as the catalyst precursor, 1,4-disubstituted 1,3-butadiynes **5** are formed along with the desired compounds **1**.[11] Such diynes, which are formed in an equimolar amount with the palladium(II) complex when arylacetylenes are employed as the starting materials,[11] derive from a reductive elimination reaction of the dialkynylpalladium(II) derivatives (*e. g.* **6**) formed in the first step of the reaction.[1,11]

$R-\equiv-\equiv-R$

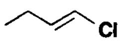
5

$(PPh_3)_2Pd(C{\equiv}C{-}R)_2$

6

Interestingly, the formation of compounds **5** (R = Ar) can occur catalytically and in high yields when arylacetylenes are reacted with 2 mol % of $Pd(PPh_3)_4$, 7.6 mol % of CuI and 0.2 equiv of Et_3N in the presence of 1 equiv of chloroacetone.[11] Conversely, the formation of compounds **5** in the Sonogashira reaction could be avoided using a palladium(0) derivative as the catalyst. Besides Et_2NH[1,12-15], amines such as pyrrolidine,[16] Et_3N,[13,17-33] *i*-Pr_2NH,[17,34-39] morpholine,[17] *n*-$BuNH_2$,[38,40-48] *n*-$PrNH_2$,[41,49-51,54] EtN(*i*-Pr)$_2$,[52,53] *t*-$BuNH_2$,[55] piperidine[5] and DBU[56] have been used in the *Sonogashira reaction*. Sometimes these amines have been employed in solvents such as benzene,[54,56] toluene,[33] Et_2O[48] or DMF.[26] However, although it has been reported that the nature of the amine can be critical for the reaction,[16] no data are available from the literature on the influence of the nature of the solvent on the reaction outcome. On the contrary, it is well known that the rate of the coupling reaction is strongly affected by the nature of the halogen present in the alkenyl or aryl halide used as the electrophilic partner. In particular, for alkenyl halides it has been found that generally alkenyl chlorides show a lower reactivity than alkenyl bromides or iodides.[41,43,57] Nevertheless, alkenyl chlorides such as (*E*)-1-chloro-1-butene (**7**),[58] 1,1-dichloroethylene (**8**),[38] as well as (*Z*)- and (*E*)-1,2-dichloroethylene (**9**) and (**10**), respectively,[41-43] can react very rapidly with 1-alkynes using a modification of the original procedure in which benzene is used as the solvent, $Pd(PPh_3)_4$ or a mixture of this complex with CuI is employed as the catalyst and an amine such as *n*-$PrNH_2$[49] or *n*-$BuNH_2$[41-

43 (1.5 - 2.0 equiv) is the base. However, such reactions, which give rise to conjugated enynes, must be carried out using a molar excess of compounds **8**-**10** (2-5 equiv) to avoid the formation of enediynes.[41-43,50]



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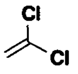

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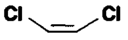

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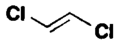

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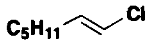
A second procedure, which allows the preparation of conjugated enynes in quite short reaction times (0.5-4 hrs), in high yields and at room temperature starting from alkenyl chlorides such as (*E*)-1-chloro-1-heptene (**11**), or compounds of general formula **12**, involves treatment of these



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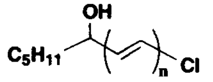
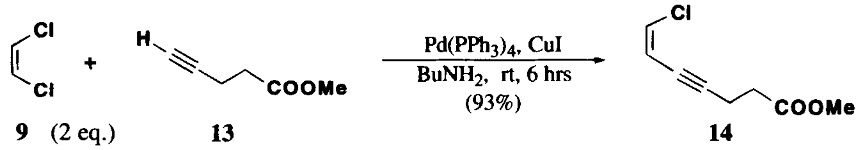


12

chlorides with 1-alkynes (2 equiv) in piperidine, in the presence of $PdCl_2(PhCN)_2$ and CuI (Cu/Pd molar ratio = 2 : 1).[58] Some examples of coupling reactions involving alkenyl chlorides are given in Eqs 4 - 8.[43,38,42,38,52]



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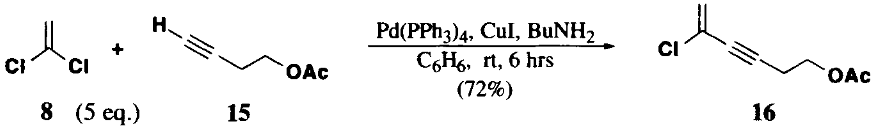

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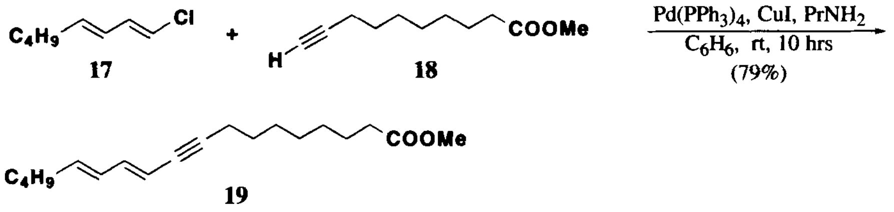

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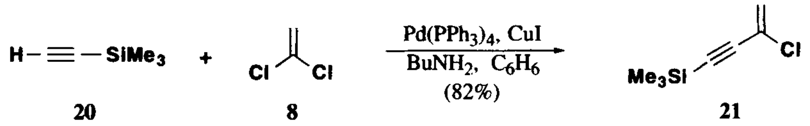

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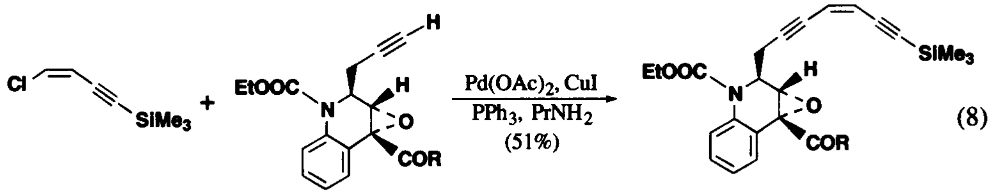
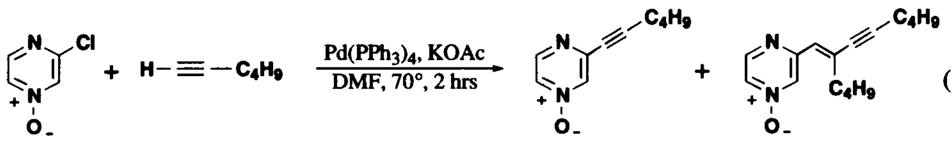


22 23 24

(8)

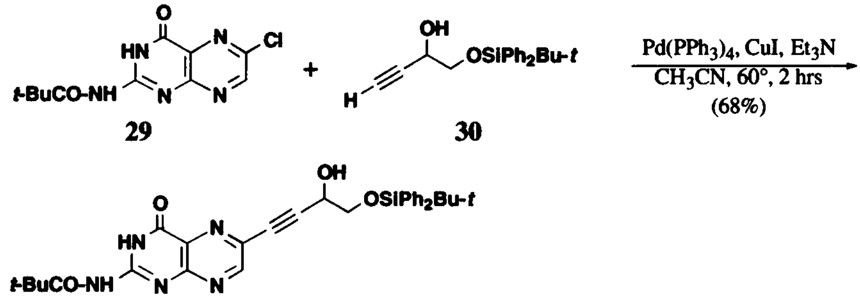
Other examples in the literature show that (hetero)aryl chlorides are unsuitable electrophiles in cross-coupling reactions with 1-alkynes under the standard condition in which CuI is used as the cocatalyst and an alkylamine is the base and/or the solvent;[59-60] 3-chloropyrazine-1-oxide (**25**) is one of these halides.[59] Nevertheless, treatment of **25** with 1.5 equiv of 1-hexyne (**26**) and potassium acetate in DMF at 70° for 2 hrs, in the presence of 5 mol % of Pd(PPh$_3$)$_4$, affords a 78% yield of the desired cross-coupled product **27** along with a 8% yield of the codimeric product **28** (Eq.9).[59]



25 26 27 28

(9)

Moreover, compound **29** reacts with the functionalized 1-alkyne **30** at 60°, in the presence of catalytic amounts of Pd(PPh$_3$)$_4$ and CuI and using Et$_3$N as the base, to give the cross-coupled product **31** in 68% yield (Eq. 10).[61]

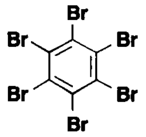


29 30

(10)

31

On the other hand, aryl polybromides such as hexabromobenzene (**32**) have proven to be suitable electrophiles in palladium-copper mediated reactions with 1-alkynes carried out under standard conditions to afford, albeit in modest yields, electron-rich polyalkynyl aromatics such as **33**.[33,62] These hydrocarbons with high C/H ratios are very interesting since they could generate novel discotic liquid crystals or could be precursors to new organic solids with unusual properties. Eqs 4-10 also illustrate a particularly attractive feature of the cross-coupling reactions between 1-alkynes and sp^2-carbon halides, namely that they tolerate a variety of functionalities in each partner of the coupling.



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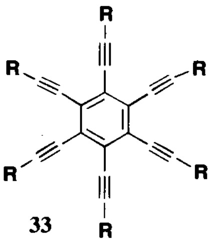
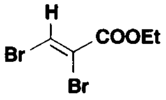


33

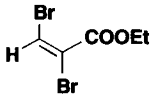
[R = $C(CH_3)_2OH$, $SiMe_3$, $Me_3Si{-}{\equiv}{-}$,
t-Bu-C ≡ C–, $Me_2CHCMe_2SiMe_2{-}{\equiv}{-}$]

These functionalities include hydroxyl,[14,16,27,36,43,47,48,54,61,63-68] t-butyldimethylsilyloxy,[69] carbonyl,[19,36,43,52,56,70-72] ethylenedioxy,[73] methoxy,[13,35] carboxyamido,[74] fluoro,[35,76,77] trifluoromethyl,[75] tetrahydropyranyloxy,[41,44] amino,[26,29,60,77] benzo- and aza-crown ether,[78] acyloxy,[78] cyano,[71,72,80] carboxy,[34] N-alkyl-carboxyamido,[2,81,82] alkoxycarbonyl,[19,36,54,69,70] sulphoxide,[56] nitro,[29] phenylimido[17] and acetal groups.[28,45-47]

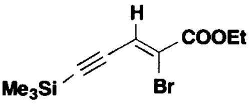
Another synthetically important aspect of these reactions is that those which involve stereodefined alkenyl halides generally proceed with complete retention of the stereochemistry of the double bonds present in the cross-coupling partners.[24,41,43,56,63,69,80,83] Nevertheless, it has been reported that treatment of (Z)- or (E)-ethyl 2,3-dibromopropenoate, (Z)- and (E)-**34**, with 1.7 equiv of trimethylsilylaceylene and 1.7 equiv of i-Pr_2NH in THF, in the presence of catalytic amounts of $Pd(PPh_3)_4$ and CuI leads to the (Z)-coupled product **35** is obtained.[84]



(Z)-**34**

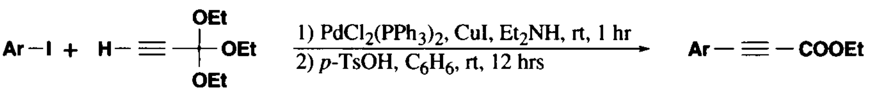


(E)-**34**



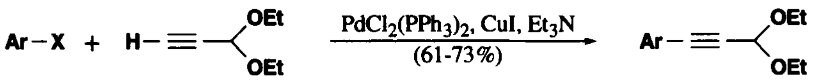
35

All the above mentioned data seem to indicate that in general the coupling reactions between 1-alkynes and sp^2-carbon bromides or iodides do not suffer significant limitations. However, disappointingly, 1-alkynes containing an electron-withdrawing group directly attached to the ethynyl carbon atom hardly react with aryl halides.[28] Nevertheless, ethyl arylpropiolates **38** can be prepared in 33-88% yield by reaction between aryl iodides **36** and 3,3,3-triethoxy-1-propyne (**37**) in Et_2NH at room temperature, in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI, followed by treatment of the products obtained with p-toluenesulfonic acid in benzene (Eq. 11).[28] Aryl halides also to



$$\underset{\mathbf{36}}{Ar{-}I} + \underset{\mathbf{37}}{H{-}{\equiv}{-}C(OEt)_3} \xrightarrow[2)\ p\text{-TsOH},\ C_6H_6,\ rt,\ 12\ hrs]{1)\ PdCl_2(PPh_3)_2,\ CuI,\ Et_2NH,\ rt,\ 1\ hr} \underset{\mathbf{38}}{Ar{-}{\equiv}{-}COOEt} \qquad (11)$$

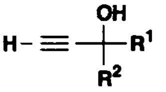
react with 3,3-diethoxy-1-propyne (**39**) in Et_3N at room temperature, in the presence of $PdCl_2(PPh_3)_2$ and CuI, to give 3,3-diethoxy-1-aryl-1-propynes (**40**) (Eq. 12).[28]



(12)

39 **40**

It is also worth mentioning that, depending on the substrates, the palladium-copper mediated reactions between 1-alkynes and sp^2-carbon halides can lead to anomalous products. Thus, even though (hetero)arylalkynols **42** can be synthesized from (hetero)aryl iodides **36** and propargyl alcohols **41**,[11,22,67,76] heteroaryl iodides containing a nitrogen attached to the carbon bearing the iodine atom, on reaction with 3-phenyl-1-propyn-3-ol (**43**) do not give compounds of general formula **42** as the final products.[85]



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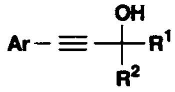

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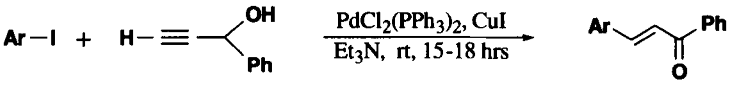
In fact, these reactions give rise to (*E*)-chalcones **44** with an *E*-selectivity greater than



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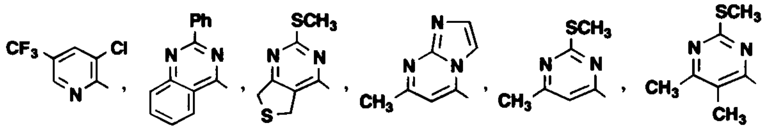
36 **43** **44**

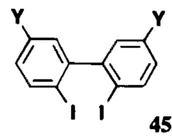
[Ar =



, etc]

95% (Eq. 13).[85] Compounds **44** seem to arise from a combined palladium-catalyzed alkynylation and a base-catalyzed isomerization of the arylalkynols so obtained.

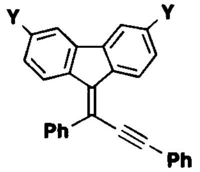
Unexpected products have also been obtained from the palladium-mediated phenylethynylation of 2,2'-dihalobiphenyls.[86] In fact, 2,2'-diiodobiphenyl (**45a**) and 5,5'-dinitro-2,2'-dihalobiphenyls (**45b**) undergo palladium-mediated phenylethynylation with 2 equiv of phenylacetylene (**46**) to give 3-(fluoren-9-ylidene)-1,3-diphenylpropyne (**47a**) and 3-(3,6-dinitrofluoren-9-ylidene)-1,3-diphenylpropyne (**47b**) respectively.[86]



45a [Y = H]
45b [Y = NO_2]

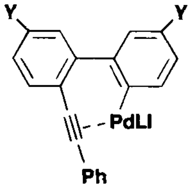
$Ph-\equiv-H$

46



47a [Y = H]
47b [Y = NO_2]

The mechanism of this reaction presumably involves the palladium(II) species **48** and **49**.[86]



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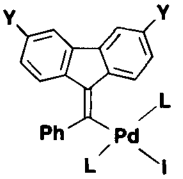
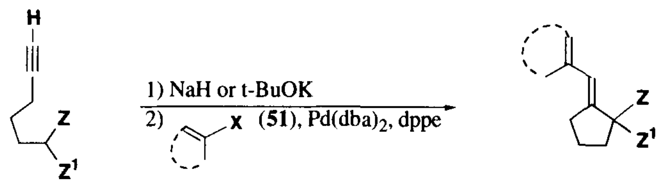


49

Compounds different from acetylene derivatives have also been obtained by reaction between enolates of δ-acetylenic β-diesters, β-ketoesters and β-sulfonylesters of general formula **50** and aryl or vinyl halides **51**, in the presence of 5 mol % of Pd(dba)$_2$ and 5 mol % of diphenylphosphinoethane (dppe) in DMSO at 80°.[87] In fact, such reaction produces stereoselectively arylidene- or allylidenecyclopentanes **52** in quite good yields (Eq. 14).[87]

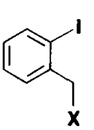


50 **52** (14)

[Z = COOMe; Z^1 = COOMe, COMe, SO$_2$Ph]

The formation of these cyclization products has been rationalized by a mechanism involving a nucleophilic attack of the enolate on the triple carbon-carbon bond activated by the electrophilic palladium(II) complex which is formed in the oxidative addition of **51** to the catalytically active palladium(0) species.[87]

On the other hand, 3-substituted 2-arylidene-2,3-dihydro-1H-inden-1-ones **54** instead of the expected *o*-alkoxycarbonylmethylene or alkylamidomethylene substituted benzoyl-arylacetylenes **55** have been obtained from the reaction between *o*-alkoxycarbonylmethylene or alkylamidomethylene substituted aryl iodides **53** with arylacetylenes in anisole at 80° and at atmospheric pressure of carbon monoxide, in the presence of potassium acetate and a catalytic quantity of Pd(PPh$_3$)$_4$.[88]



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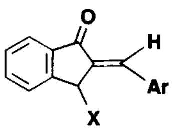

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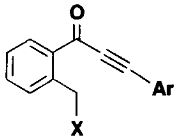
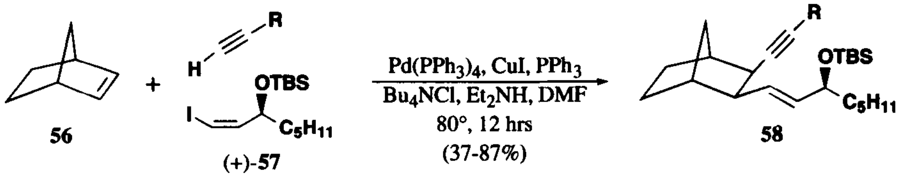


55

[X = COOMe, COOiPr, CONEt$_2$, COOMe; Ar = Ph, 4-CH$_3$OC$_6$H$_4$, THPOC(Me)$_2$]

Compounds **54** derive from sequential oxidative addition of **53** to Pd(PPh$_3$)$_4$, carbon monoxide insertion, reductive coupling with 1-alkynes, nucleophilic attack by the activated methylene group, and protonation with metal elimination.[88]

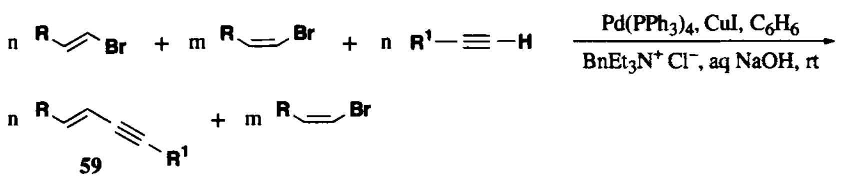
Finally, it has been reported that a number of 2,3-disubstituted bicyclo[2.2.1]heptanes of general formula **58**, pivotal to PGH analogues, can be synthesized by diastereoselective tandem carbon-carbon bond formation involving the palladium-copper mediated coupling of norbornene (**56**), the (+)(*Z*)-alkenyl iodide **57** and various terminal acetylenes (Eq. 15).[89]



(15)

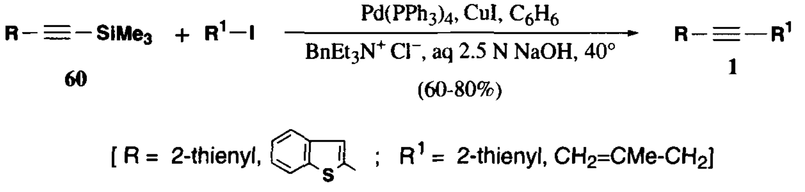
[R = Me_2COH, CH_2OCH_2COOMe, $CH_2O(CH_2)_2COOEt$, CH_2OAc, Me_2CNHAc, $(CH_2)_3OAc$, $(CH_2)_3COOMe$, ]

To conclude this section devoted to the general aspects and some illustrations of the palladium-copper mediated reactions between 1-alkynes and sp^2-carbon halides, it must also be mentioned that the technique of phase-transfer catalysis which has been employed in a variety of metal-catalyzed reactions,[90,91] has also been successfully used for these palladium/copper mediated couplings.[27,57,92-95] The procedure, which offers distinct advantages over methods involving the use of amines as solvents or organometallic reagents such as 1-alkynylzinc halides,[2] consists in reacting 1-alkynes with alkenyl or aryl halides in the presence of benzyltriethylammonium chloride (1 mol %) as the phase-transfer agent, a large excess of aqueous NaOH as the base, benzene as the organic solvent and a mixture of $Pd(PPh_3)_4$ (1 mol %) and CuI (2 mol %) as the catalyst.[27,57,92-95] Interestingly, under these experimental conditions, the reaction rate of (*E*)-1-bromo-1-alkenes with 1-alkynes is quite higher than that of the corresponding (*Z*)-stereoisomers.[27,57,92,93] Thus, starting from stereoisomeric mixtures of 1-bromo-1-alkenes it is possible to synthesize conjugated (*E*)-enynes, **59**, having very high stereoisomeric purity (Eq. 16).[27,92-94]



(16)

The technique of phase-transfer catalysis has also been used for the direct preparation either of unsymmetrically disubstituted acetylenes **1** from 1-trimethylsilyl-1-alkynes **60** and heteroaryl or allyl iodides (Eq.17)[94] or of symmetrically disubstituted diarylacetylenes **61** from trimethylsilylacetylene (**20**) and aryl iodides **36** (Eq. 18).[96]



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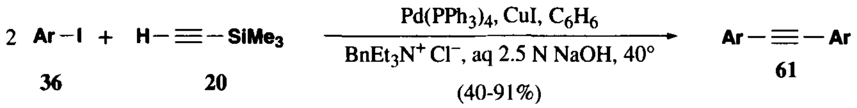
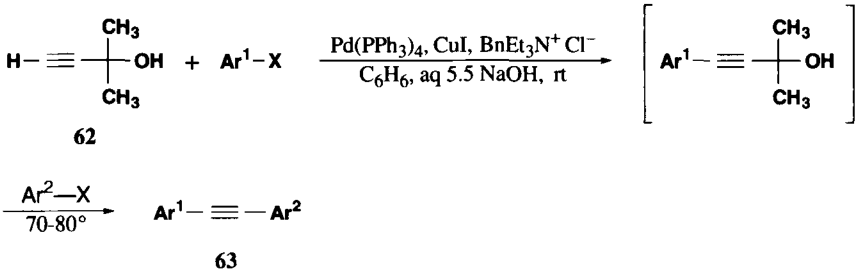


(18)

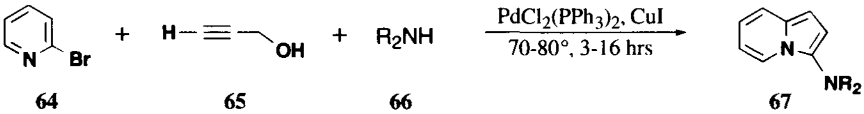
A similar procedure has been employed to prepare oligo(thienylalkyne)s in a stepwise manner[97] as well as in an efficient one-pot synthesis of unsymmetrically disubstituted diarylacetylenes **63** starting from commercial and cheap 2-methyl-3-butyn-2-ol (**62**) as the protected acetylene starting material (Scheme 1).[95]

SCHEME 1



II. SYNTHESIS OF HETEROCYCLES *via* PALLADIUM-COPPER MEDIATED REACTIONS OF 1-ALKYNES WITH (HETERO)ARYL HALIDES

Aminoindolizines of general formula **67** have been synthesized in one step (11-49% yield) by reaction of 2-bromopyridine (**64**) with propargyl alcohol (**65**) and a secondary amine **66** at 70-80° for 3-16 hrs, in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI (Eq. 19).[98] The mechanism appears to involve formation of compound **68** and its isomerization to the α,β-unsaturated aldehyde **69**, followed by ring closure of the corresponding immonium derivative **70**.[98]



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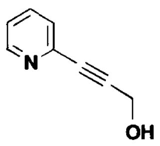

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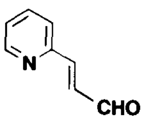

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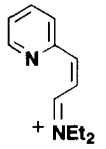
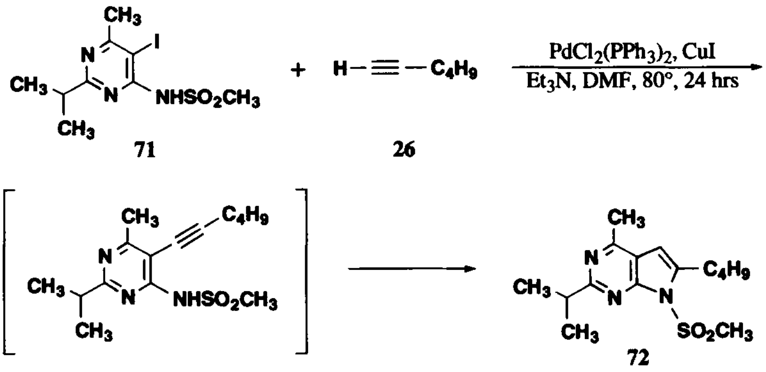
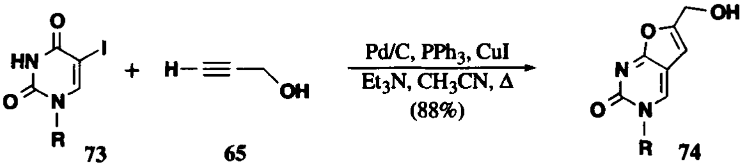


70

Pyridopyrimidines, pyrimidines fused with five- or six-membered heterocycles, *e.g.* **72**, and furo-[3,3-*d*]pyrimidin-2[3H]-ones, *e. g.* **74**, have been prepared by palladium/copper mediated cross-coupling of halopyrimidines with 1-alkynes followed by ring closure of intermediate alkynylpyrimidines (Scheme 2[102] and Eq. 20[20]).[20,99-102]

SCHEME 2

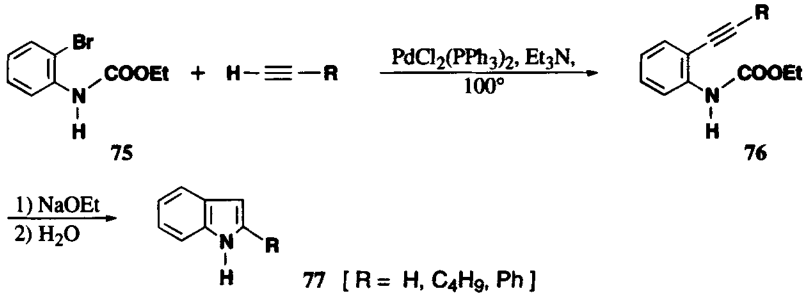




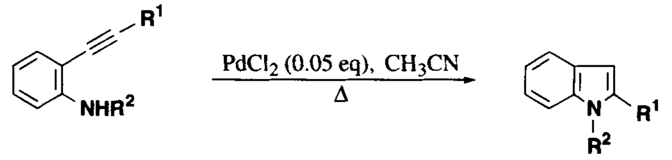
(20)

o-Alkynylanilines such as **76**, which were prepared by palladium-mediated coupling of 1-alkynes with *o*-haloanilines, have been cyclized to 2-substituted indoles **77** in the presence of a base (Scheme 3).[103,104]

SCHEME 3



Alternatively, 2-substituted indoles **77a** or N-acetylindoles **77b** have been synthesized in satisfactory yields by treatment of *o*-alkynylanilines **78** with a catalytic amount of $PdCl_2$ in acetonitrile at 70° (Eq. 21)[77,105] or with catalytic quantities of $PdCl_2(PPh_3)_2$ and CuI in Et_3N.[106]



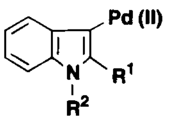
(21)

78a (R^2 = H)
78b (R^2 = Ac)

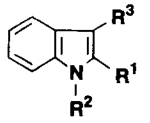
77a (R^2 = H)
77b (R^2 = Ac)

[R^1 = alkyl, Ph, Me_3Si, etc]

This intramolecular aminopalladation reaction, which presumably involves an organometallic intermediate such as **79**, has also been used to prepare either 3-allyl substituted indoles of general formula **80a** starting from *o*-1-alkynyl-N-acetylanilines, **78b**,[105] or 2-substituted 3-acyl indoles **80b** by treatment of 2-(1-alkynyl)trifluoroacetanilides **78c** (R^2 = $COCF_3$) with aryl iodides in the presence of K_2CO_3 and $Pd(PPh_3)_4$ in acetonitrile at 45° under an atmosphere of carbon monoxide.[107]



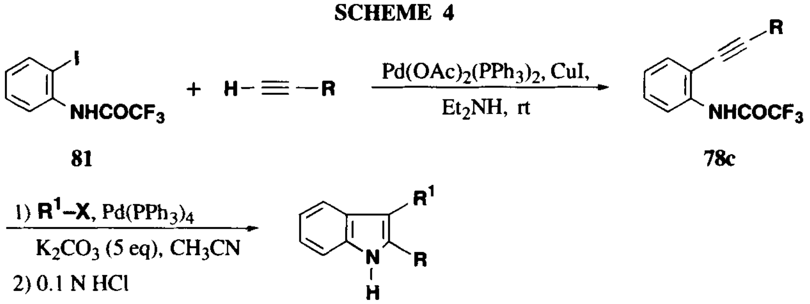
79



80a [R^2 = Ac; R^1 = alkyl, aryl; R^3 = $CH(R^3)CR^4{=}CHR^5$
80b [R^2 = H; R^1 = alkyl, (hetero)aryl, alkenyl; R^3 = ArCO]

2,3-Disubstituted indoles **82**, which are characterized by an aryl or an alkenyl group in the 3-position, have also been synthesized according to a similar strategy (Scheme 4).[108]

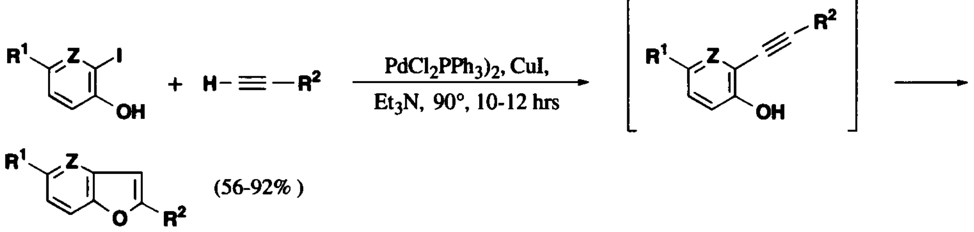
SCHEME 4



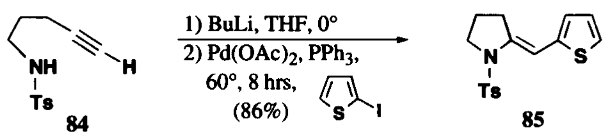
82 [R^1 = aryl, alkenyl]

Similar palladium(II)-mediated cyclizations involving acetylene derivatives which contain a tethered nucleophilic center have been employed for the synthesis of 2-substituted and 2,5-disubstituted benzo[b]furanes and homologues **83** (Scheme 5),[21] 2-alkylidene-1-sulfonyl-pyrrolidines such as **85** (Eq. 22),[109] (*Z*)-3-alkylidenephtalides (*e. g.* **88**) (Eq. 23),[18] isocoumarines,[110] thienopyridines,[111] furopyridines,[111] the marine alkaloid asptamine,[112] γ-(*Z*)-alkylidene butenolides **90** (Eq. 24)[113] and 2,3,5-trisubstituted furans **92** (Eq. 25).[114] It must be noted that the acetylene derivatives characterized by a nucleophilic center near to the alkynyl group can be the starting materials or represent reaction intermediates.

SCHEME 5



83 [Z = CH, N; R^1 = H, Me, Cl; R^2 = Ph, MeCOH, CH_2OTHP, C_6H_{13}]



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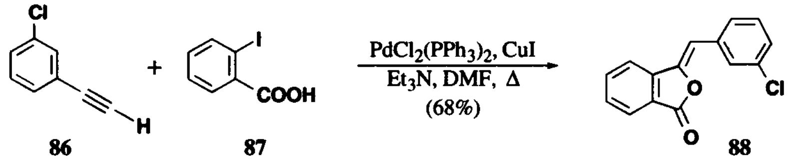

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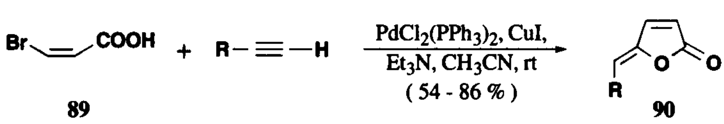

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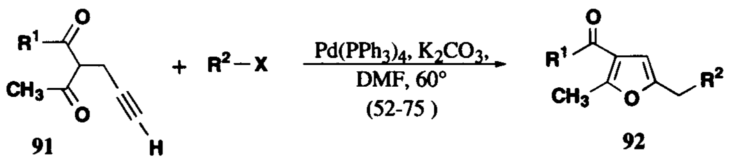
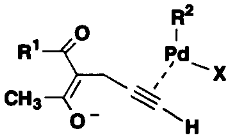


(25)

[R^1 = Me, EtO; R^2 –X = aryl or vinyl halide or triflate]

Mechanistically, the formation of compounds **92** could proceed through formation of the η^2-palladium complex **93** and generation of the σ-vinylpalladium complex **94** via *trans*-addition of oxygen and palladium across the triple carbon-carbon bond, followed by reductive elimination to give compounds **95** and final isomerization of **95** to **92**.[114]



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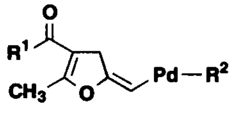

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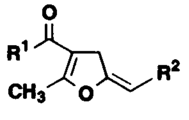
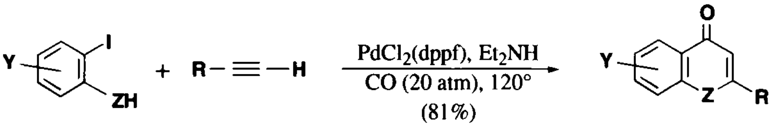


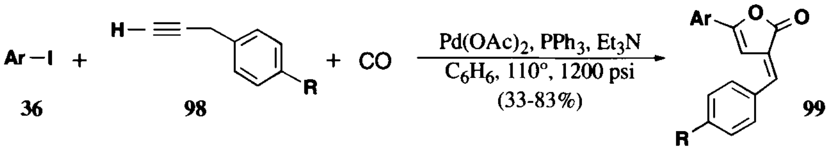
95

Several heterocyclic compounds have also been synthesized by carbonylative coupling of 1-alkynes with sp^2-carbon halides in the presence of palladium(0) or palladium(II) complexes.[22,115-119] Thus, 2-substituted chromones and 4-quinolones of general formula **97** have been prepared in high yields by reaction of *o*-iodophenols or *o*-iodoanilines **96** with 2 equiv of 1-alkynes in Et_2NH heated under stirring in an autoclave at 120° for 2 hrs under a carbon monoxide atmosphere (20 atm), in the presence of a catalytic amount of $PdCl_2(dppf)$ (Eq. 26).[115,116]



96 [Z = O, NH] **97** [Z = O, NH] (26)

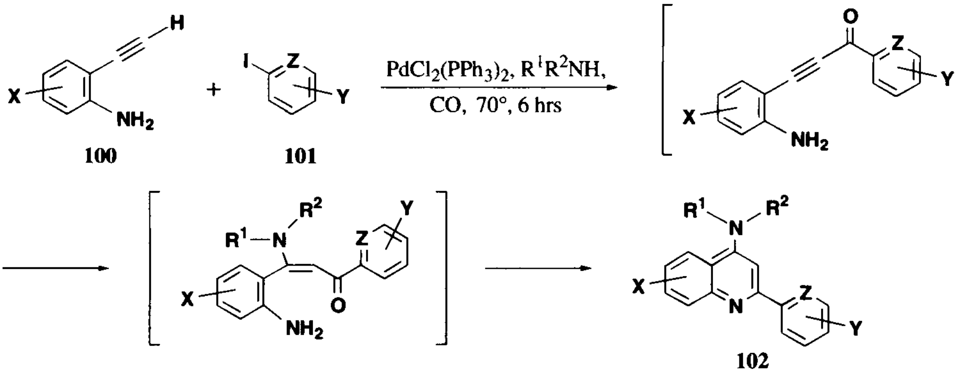
Analogously, (*E*)-3-arylidene-5-aryl-2-(3H)-furanones **99** have been synthesized in 33-83% yield as illustrated in Eq. 27.[22]



36 **98** **99** (27)

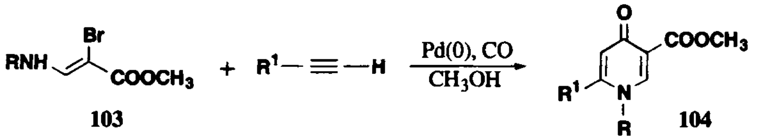
On the other hand, palladium-carbonylative coupling of 2-aminoacetylenes **100** with aryl iodides **101** under a carbon monoxide atmosphere (10 Kg/cm^2) at 70°, gives 2-aryl-4-dialkylamino-quinolines **102** in 43-86% yield (Scheme 6).[117]

SCHEME 6



100 **101** **102**

Finally, compounds **104** and **106** have been conveniently synthesized by carbonylative coupling of 1-alkynes with 2-bromo-3-aminoacrylates **103** and o-haloanilines **105** respectively (Eqs 28 and 29).[118,119]



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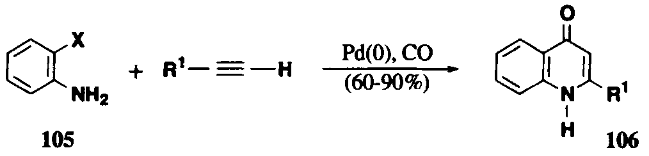
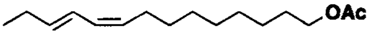


(29)

III. APPLICATION OF THE PALLADIUM-COPPER-MEDIATED REACTION OF 1-ALKYNES WITH sp^2-CARBON HALIDES TO THE SYNTHESIS OF NATURAL PRODUCTS AND THEIR ANALOGUES

The palladium-copper-mediated reaction between 1-alkynes and sp^2-carbon halides has proved to be extremely useful for the synthesis of key intermediates of a large variety of naturally-occurring substances which include some insect pheromone components[41,50,92,93] (*e. g.* compounds **107** and **108**), pheromone components of algae[120] (*e. g.* **109**), polyacetylenes[27,121] (*e. g.* **110** and **111**), insecticidally active isobutylamides[2] (*e. g.* **112**), bullatenone (**113**) and the antitumor agent geiparvarin (**114**),[122] the feeding deterrent for the boll weevil on cotton, methyl α-eleostearate (**115**),[42] the diketone **116** representing rings A-D of the fungal metabolite fredericamycin A,[52] which is a very powerful antitumor agent, (+)(15,16,19,20,23,24)-*hexepi*-uvaricin (**117**),[123] which is a *bis*(tetrahydrofuranyl) annonaceous acetogenin analogue, racemic depospho Form A (**118**),[124] nucleosides[79] and 5-(acylethenyl)uracils,[25,125] which have been found to have antitumor properties, model compounds of enediyne anticancer antibiotics or highly functionalized core structures of such compounds[45,47,126-129]



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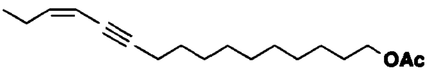

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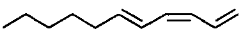

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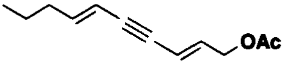

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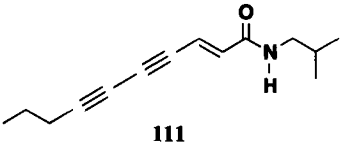

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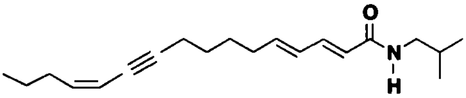

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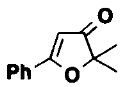

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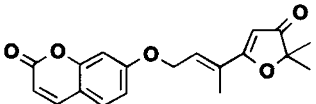

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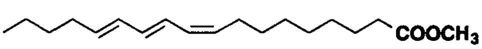
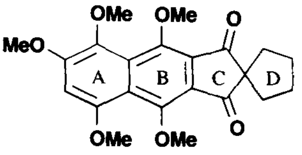


115

(*e. g.* compound **119**), eicosanoids[55,69,130-133] (*e. g.* compounds **120** and **121**) as well as two novel allenic side-chain analogues of 1α,25-dihydrovitamin D_3, **122a** and **122b**, respectively.[134]



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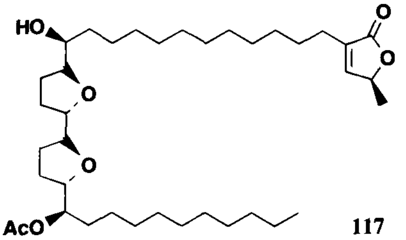

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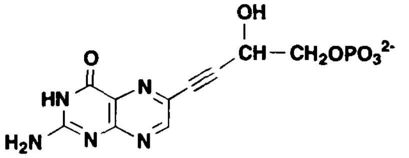

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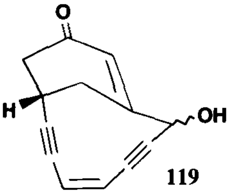

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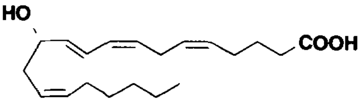

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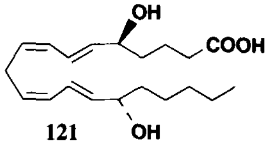

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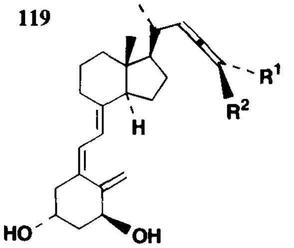
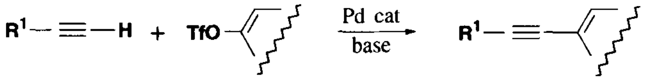


122a [$R^1 = CMe_2OH$; $R^2 = H$]
122b [$R^1 = H$; $R^2 = CMe_2OH$]

IV. PALLADIUM-MEDIATED CROSS-COUPLING REACTIONS BETWEEN 1-ALKYNES AND VINYL OR ARYL PERFLUOROALKANESULFONATES

1-Alkynes have also been found to be able to react with vinyl triflates in the presence of a palladium catalyst and a base to give conjugated enynes in quite good yields (Eq. 30).[16,78,135-158]



(30)

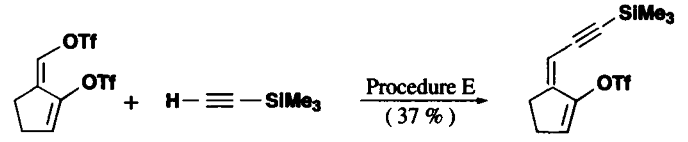
Some common procedures (Methods A-L) used for this reaction are listed in Table.

Some examples of conjugated enynes synthesized according to these procedures are reported in Eqs 31-36.[78,138,144,151,152,158]

TABLE. Pd-mediated Coupling Reaction between 1-Alkynes and Vinyl Triflates

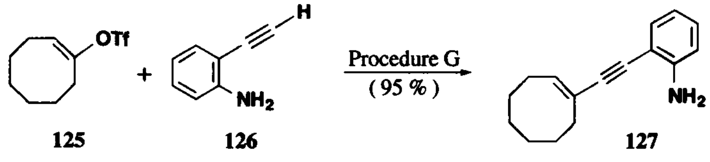
Procedure	Base	Solvent	Catalyst	Conditions (hrs/°C)	Ref.
A	Bu_3N	DMF	$Pd(OAc)_2(PPh_3)_2$	0.5 - 1.0 / rt	136
B	Et_2NH	DMF	$Pd(OAc)_2(PPh_3)_2$ / CuI^a	1.0 - 1.5 / rt	136
C	NaOAc	DMF	$Pd(OAc)_2(PPh_3)_2$	1.0 / 60	136
D	Et_3N	DMF	$PdCl_2(PPh_3)_2$	0.5 - 24 / 75	137, 140, 145, 150, 152
E	i-Pr_2NH	THF	$PdCl_2(PPh_3)_2$ / $CuI^{a,b}$	1.0 - 51 / rt	61, 139, 151, 157
F	Et_3N	DMF	$Pd(PPh_3)_4$ / CuI^a	15.0 / rt	142
G	Et_2NH	DMF	$Pd(PPh_3)_4$	20.0 - 48.0 / rt	79
H	Piperidine or pyrrolidine		$Pd(PPh_3)_4$	0.5 - 1.0 / 25	16
I	K_2CO_3	DMF	$Pd(PPh_3)_4$	3.5 / 60	115
J	Et_2NH or i-Pr_2NH	DMSO	$Pd(OAc)_2(PPh_3)_2$ / CuI^a	20.0 - 48.0 / rt	138
K	Et_2NH	DMF	$Pd(PPh_3)_4$ / CuI^a	0.4 - 5.0 / rt	108, 143, 158
L	Et_2NH	DMF	$PdCl_2(PPh_3)_2$ / CuI^a	2.0 - 4.0 / rt	144

a) Cu/Pd molar ratio = 2 : 1; b) Cu/Pd molar ratio = 3 : 1; c) Cu/Pd molar ratio = 1.5 : 1.



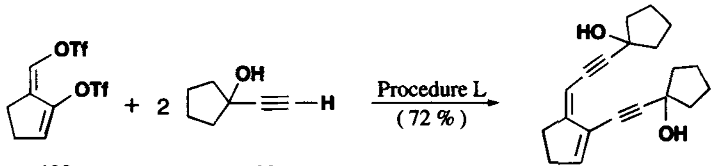
123 **20** **124**

(31)



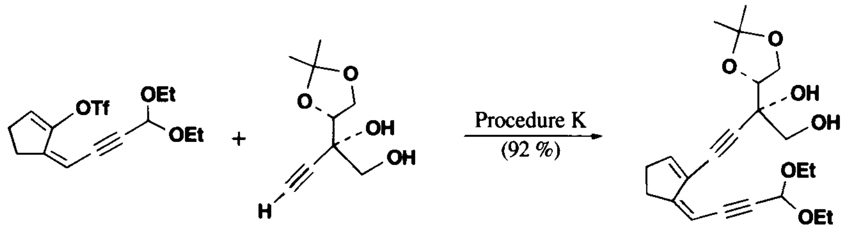
125 **126** **127**

(32)



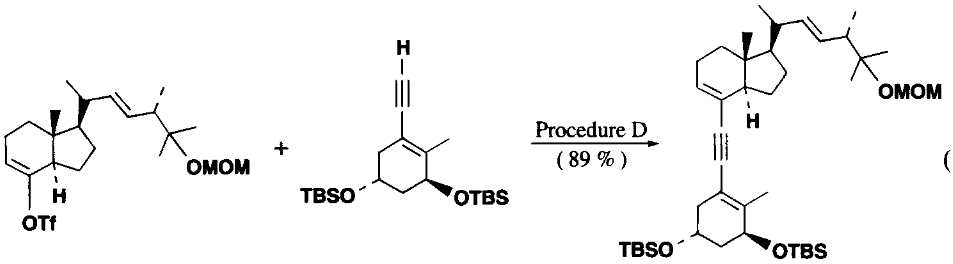
123 **128** **129**

(33)



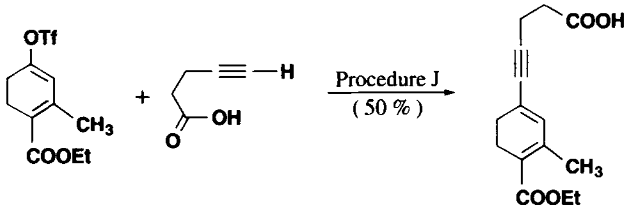
130 **131** **132**

(34)



133 **134** **135**

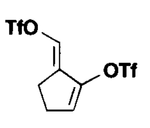
(35)



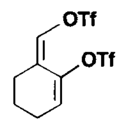
136 **137** **138**

(36)

Interestingly, the Z-configurated bistriflate **123** couples with terminal alkynes in THF/*i*-Pr_2NH (3:1), in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ and CuI, regioselectively at the exocyclic (*i. e.* less hindered) triflate moiety (Eq. 31).[151] Surprisingly, the isomeric E-configurated bistriflate **139** couples under the same conditions preferentially at the semicyclic (*i. e.* more hindered) triflate site.[135] On the other hand, the six-membered analogue **140** of **123** couples with the opposite regiochemical preference.[157]



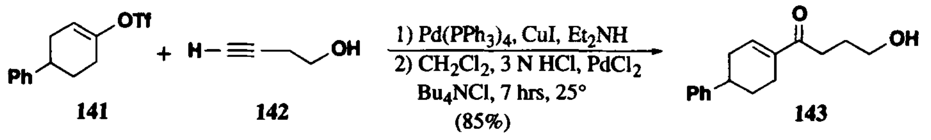
139



140

Remarkably, although the use of amines as bases fails to afford any conjugated enyne, when ethyl propynoate is employed as the 1-alkyne, good results can be obtained by substituting sodium acetate for the amine.[136]

It is also worthwhile mentioning that conjugated enynes prepared according to one of the above mentioned procedures can be efficiently converted to α,β-enones by reaction with an acidic CH_2Cl_2/3N HCl two-phase system, in the presence of the *n*-Bu_4NCl-$PdCl_2$ combination.[159] The synthesis of the γ'-hydroxy-α,β-enone **143** from cycloalkenyltriflate **141** and 3-butyn-1-ol (**142**) according to this protocol is illustrated in Eq. 37.[159]

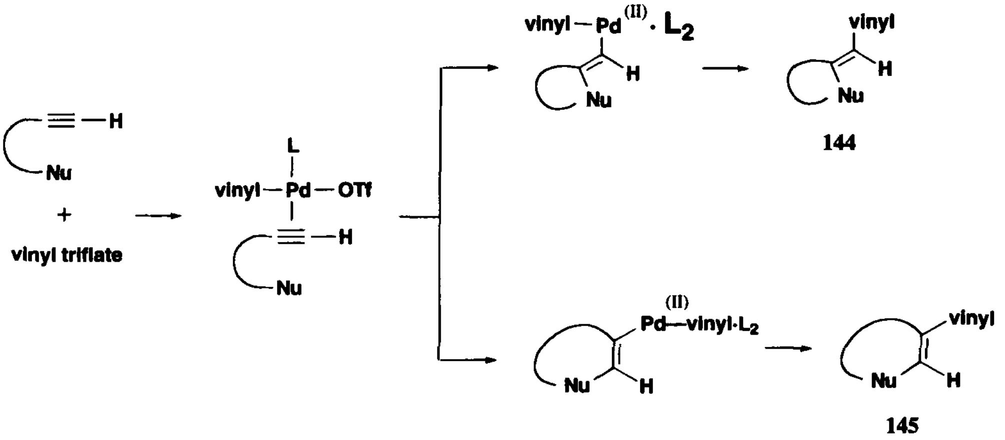


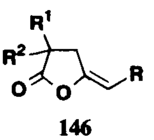
(37)

The scope of the reaction between 1-alkynes and vinyl triflates has been considerably widened by the observation that nucleophiles near the triple carbon-carbon bond can participate to this palladium-mediated reaction through an intramolecular attack on the triple carbon-carbon bond activated by coordination to the σ-vinylpalladium(II) complex generated *in situ* by oxidative addition of the vinyl triflate to the catalytically active palladium(0) complex. This attack, in principle, may lead to cyclic derivatives **144** or **145** (Scheme 7).[160]

Cyclic compounds such as (*E*)-δ-vinyl-γ-methylene-γ-butyrolactones of general formula **146**,[141,161] 2,3,5-trisubstituted furans of general formula **147**[114] as well as 2-substituted 3-acylindoles **80b**[107] have been synthesized according to this strategy.

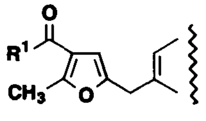
SCHEME 7





146

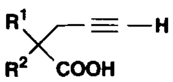
[R = alkenyl; R^1 = H, COOMe; R^2 = H, alkyl]



147

[R^1 = Me, EtO]

Interestingly, compounds **146** were obtained when vinyl triflates were reacted with 4-pentynoic acids **148** in acetonitrile in the presence of Et_3N and n-Bu_4NCl as well as a catalytic amount of $Pd(OAc)_2(PPh_3)_2$.[141,161]



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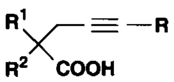
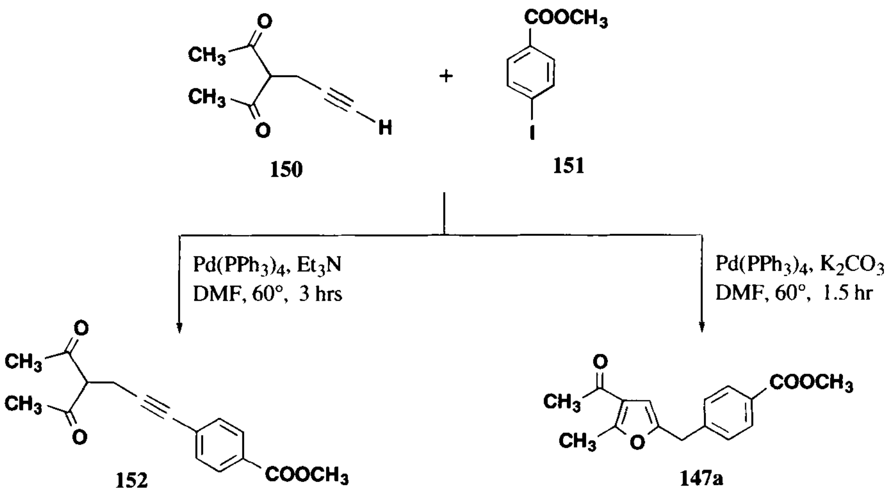


149 [$R^1 = R^2 = H$; R = alkenyl]

On the other hand, conjugated enynes **149** could selectively be synthesized starting from **148** and vinyl triflates when the catalyst was a mixture of $Pd(OAc)_2(PPh_3)_2$ and CuI and the reaction was carried out in DMSO in the presence of Et_2NH or i-Pr_2NH.[138]

It has also been reported that the cyclization/coupling balance is strongly dependent on the nature of the added base.[114] Thus, compound **150** is able to react with iodoarene **151** in the presence of $Pd(PPh_3)_4$ and Et_3N to give the cross-coupled product **152** in 77% yield (Scheme 8). Conversely, when K_2CO_3 is used as the base, this reaction affords the furane derivative **147a** in 56% yield (Scheme 8).[114]

SCHEME 8



Finally, 1-alkynes have been shown to be able to react with aryl perfluoro-alkanesulfonates **153** in DMF solution in the presence of a palladium complex (*e. g.* $PdCl_2(PPh_3)_2$) and an amine as the base (*e. g.* Et_3N) to give arylacetylenes of general formula **154** (Eq. 38).[78,138,162-168]

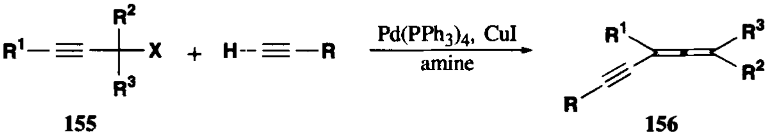
$$\underset{}{R-\!\equiv\!-H} + \underset{\mathbf{153}}{Ar-OSO_2R_F} \xrightarrow[\text{DMF}]{\text{Pd cat, amine}} \underset{\mathbf{154}}{R-\!\equiv\!-Ar} \tag{38}$$

[R_F = CF_3, $H(CF_2)O(CF_2)_2$, $Br(CF_2)O(CF_2)_2$, $CF_2HCF_2O(CF_2)_2$, $CF_2H(CF_2)_5O(CF_2)_2$]

This reaction, which can also be used to prepare substituted polyfluorophenylalkynes which are intermediates in the synthesis of potential optical materials,[168] represents a useful alternative to the previously discussed palladium-copper-mediated reaction between 1-alkynes and aryl bromides or iodides. In fact, compounds **153** can be easily prepared from the corresponding phenols,[169] which sometimes represent reagents more easily available than the corresponding aryl halides. Nevertheless, taking into account the high cost of the perfluoroalkanesulfonyl derivatives used for the synthesis of compounds **153**, the procedure involving the use of these esters does not appear suitable for large scale preparations.

V. PALLADIUM-MEDIATED REACTIONS BETWEEN 1-ALKYNES AND PROPARGYL DERIVATIVES, ALLENYL BROMIDES OR 1-HALO-1- ALKYNES

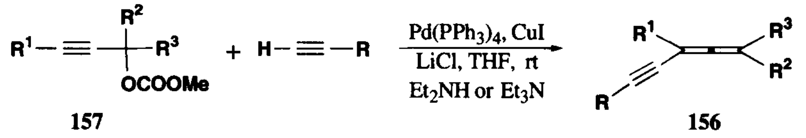
1,2-Dien-4-ynes **156** have been conveniently synthesized by coupling of substituted propargylic halides or tosylates **155** with 1-alkynes in the presence of an amine (i-Pr_2NH for primary halides, i-Pr_2NH or Et_3N for secondary and tertiary halides) and catalytic amounts of $Pd(PPh_3)_4$ and CuI (Eq. 39).[170]



(39)

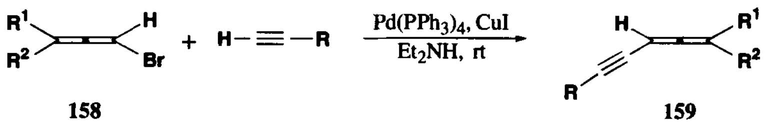
The best results have been obtained when chlorides rather than bromides or iodides were used. Although under these conditions propargylic acetates were found to be unreactive, they could be activated by addition of LiCl or $ZnCl_2$ in refluxing THF.[170]

Compounds **156** have also been synthesized in 31-83% yield by reaction of substituted propargylic carbonates **157** with 1-alkynes in THF solution, in the presence of $Pd(PPh_3)_4$ (5 mol %), CuI (10 mol %) and LiCl (2 equiv) (Eq. 40).[171]



(40)

On the other hand, dienynes **159** have been obtained in high yields when 1-alkynes were allowed to react with allenyl bromides **158** in Et_2NH at room temperature, in the presence of $Pd(PPh_3)_4$ (1 mol %) and CuI (2 mol %) (Eq. 41).[172]

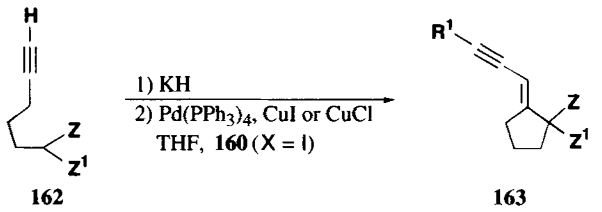


(41)

1-Alkynes are also suitable for coupling with 1-iodo-1-alkynes **160** (X = I) in THF in the presence of $PdCl_2(PPh_3)_2$ and CuI as well as i-Pr_2NH as the base, to give 1,3-diynes **161** in 45-100% yield (Eq. 42).[173]

$$\underset{\mathbf{160}\ (X = I)}{R^1-\equiv-X} + H-\equiv-R \xrightarrow[\text{THF, } i\text{-}Pr_2NH\text{, rt}]{PdCl_2(PPh_3)_2\text{, CuI}} \underset{\mathbf{161}}{R^1-\equiv-\equiv-R} \qquad (42)$$

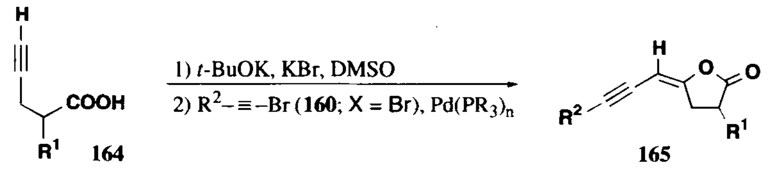
Nevertheless, it has been proved that (*E*)-ethenylidenecyclopentanes **163** are obtained (35-71% yield) on treatment of compounds **160** (X = I) with enolates of δ-acetylenic β-ketoesters, β-diesters or β-sulfonylesters of general formula **162**, in the presence of $Pd(PPh_3)_4$ (3 mol %) and CuCl or CuI (6 mol %) (Eq. 43).[174]



(43)

[Z = COOMe; Z' = COOMe, COMe, SO_2Ph, CN]

Finally, 5-(*E*)-alkynylidene tetrahydro-2-furanones **165**, which display interesting biological properties mainly as suicide inhibitors of serine proteases, have been synthesized in 55-84% yield by reaction of potassium carboxylates of acetylenic acids **164** with 1-bromo-1-alkynes **160** (X = Br) in DMSO in the presence of a palladium(0) complex prepared *in situ* from $Pd(OAc)_2$ and 4 equiv of tri-(*o*-tolyl)phosphine or tri-(2-furyl)phosphine (Eq. 44).[175]

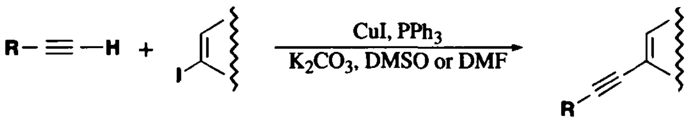


(44)

VI. COPPER MEDIATED REACTIONS BETWEEN 1-ALKYNES AND ARYL IODIDES, VINYL IODIDES, ALLYL HALIDES OR PROPARGYL DERIVATIVES

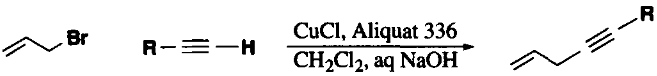
The coupling reaction between 1-alkynes and aryl or vinyl halides can also be promoted by copper (I) compounds without using palladium complexes as catalysts.[176-181] However, in some procedures a stoichiometric amount of a copper salt is needed.[176-178,181] By contrast, quite recently it has been found that aryl or vinyl iodides can react smoothly with 1-alkynes, in the presence of K_2CO_3

as the base and catalytic amounts of CuI and PPh_3, to give the corresponding disubstituted acetylenes in excellent yields (Eq. 45).[179,180] The method provides a less expensive alternative to the standard palladium-copper mediated variants.



(45)

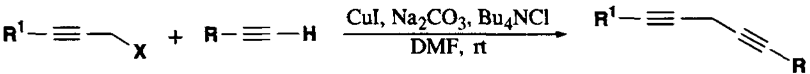
A copper(I) salt also mediates the reaction between allyl bromides and 1-alkynes, which affords 1,4-enynes.[182] In particular, such compounds can be prepared in 38-93% yield by reaction of an 1-alkyne with 1.25 equiv of an allyl bromide in CH_2Cl_2 solution, in the presence of 0.25 equiv of CuCl and a small quantity of Aliquat-336, and using 30% aqueous NaOH as the base (Eq. 46).[182] Under these experimental conditions arylacetylenes appear to be more reactive than alkylacetylenes.



(46)

It must also be noted that 1-bromo-3-methyl-2-butene, which is slightly less reactive than allyl bromide, reacts with terminal alkynes to give mixtures of two isomeric products in a *ca.* 9:1 ratio.[182] The main component of these mixtures is the *normal* cross-coupled product and the minor component is the 1,4-enyne characterized by a terminal double bond.

It is also worthy of mention that, in the presence of concentrated (30-50%) alkali solutions, some types of 1,4-enynes, *e. g.* 5-aryl-1-penten-4-ynes, react further under the PTC conditions used for the coupling reactions. For example, reactions between arylacetylenes and allyl bromide lead to the corresponding 1,4-enynes, along with allenes and 2,4-enynes.[182] Thus, this copper(I) mediated reactions does not seem to be of very broad scope. On the other hand, skipped diynes of general formula **167**, which can contain sensitive functional groups, have been selectively prepared in high yields (70-84%) by treatment of propargylic halides or tosylates **166** with 1-alkynes in the presence of 1 equiv of CuI, 1 equiv of n-Bu_4NCl and 1.5 equiv of K_2CO_3 in DMF at room temperature (Eq. 47).[183]



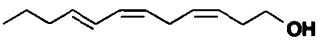
166 (X =Br, I, OTs)

167

(47)

Alternatively, compounds **167** have been synthesized in 66-92% yield by reaction between 1-alkynes and propargylic tosylates or chlorides in DMF at room temperature, in the presence of 1 equiv of CuI, 2 equiv of NaI and 2 equiv of K_2CO_3, each finely ground and anhydrous.[184]

A similar procedure has been recently used in a key step of the synthesis of (3Z,6Z,8E)-3,6,8-dodecatrien-1-ol (**168**) a natural trail pheromone component of *Reticulitermes* termites.[185]



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REFERENCES

1. K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 4467 (**1975**).
2. K. Sonogashira, in *Comprehensive Organic Synthesis*, B. M. Trost and I. Fleming, Eds., Pergamon Press, Oxford, Vol 3, 521-549 (1991).
3. K. Sonogashira and S. Takahashi, *J. Syn. Org. Chem. Jpn.*, **51**, 1053 (1993).
4. L. Cassar, *J. Organomet. Chem.* **93**, 253 (1975).
5. H. A. Dieck and F. R. Heck, *ibid.*, **93**, 259 (1975).
6. K. Ishizu, U. D. G. Prabhu, D. Draney, B. H. Lee and C. S. Marvel, *Polym. Sci. Polym. Chem. Ed.*, **20**, 2851 (1982).
7. H. Yamanaka, M. Shiraiwa, K. Edo and T. Sakamoto, *Chem. Pharm. Bull. Jpn.*, **27**, 270 (1979).
8. K. Edo, H. Yamanaka and T. Sakamoto, *Heterocycles*, **9**, 271 (1978).
9. H. Yamanaka, M. Shiraiwa, E. Yamamoto and T. Sakamoto, *Chem. Pharm. Bull. Jpn.*, **29**, 3543 (1981).
10. P. E. Eaton and D. Stössel, *J. Org. Chem.*, **56**, 5138 (1991).
11. R. Rossi, A. Carpita and C. Bigelli, *Tetrahedron Lett.*, **26**, 523 (1985).
12. T. Hiyama, N. Wakasa, T. Ueda and T. Kusumoto, *Bull. Chem. Soc. Jpn.*, **63**, 640 (1990).
13. Q-Y. Chen and Z-Y. Yang, *Tetrahedron Lett.*, **27**, 1171 (1986).
14. D. E. Ames, D. Bull and C. Takundwa, *Synthesis*, 364 (**1981**).
15. J. A. Marshall and W. J. DuBay, *J. Org. Chem.*, **58**, 3602 (1993).
16. M. Alami, F. Ferri and G. Linstrumelle, *Tetrahedron Lett.*, **34**, 6403 (1993).
17. W. B. Austin, N. Bilov, W. J. Kelleghan and K. S. Y. Lau, *J. Org. Chem.*, **46**, 2280 (1981).
18. N. G. Kundu and M. Pal, *Chem. Commun.*, 86 (**1993**).
19. D. A. Evans and T. Bach, *Angew. Chem. Int. Ed. Engl.*, **32**, 1326 (1993).
20. G. A. Tolstikov, A. G. Mustafin, R. R. Gataullin, L. V. Spirikhin and I. B. Abdrakhmanov, *Izv. Akad. Nauk Ser. Khim.*, 1449 (**1992**).

21. S. Torii, L. H. Xu and H. Okumoto, *Synlett*, 515 (**1992**).

22. Y. Huang and H. Alper, *J. Org. Chem.*, **56**, 4534 (1991).

23. Q-Y. Chen and Z-T. Li, *J. Chem. Soc. Perkin Trans. I*, 2931 (**1992**).

24. T. Sakamoto, Y. Kondo, S. Iwashita, T. Nagano and H. Yamanaka, *Chem. Pharm. Bull. Jpn.*, **36**, 1305 (1988).

25. N. G. Kundu and S. K. Dasgupta, *J. Chem. Soc. Perkin Trans. I*, 2657 (1993).

26. G. Galambos, C. Szántay Jr., J. Tamás and C. Szántay, *Heterocycles*, **36**, 2241 (1993).

27. A. Carpita, D. Neri and R. Rossi, *Gazz. Chim. Ital.*, **117**, 481 (1987).

28. T. Sakamoto, F. Shiga, A. Yasuhara, D. Uchiyama, Y. Kondo and H. Yamanaka, *Synthesis*, 746 (1992).

29. S. Takahashi, Y. Kuroyama, K. Sonogashira and N. Hagihara, *ibid.*, 627 (1980).

30. T. R. Hoye, P. R. Hanson, A. C. Kovelesky and T. D. Ocain, Z. Zhuang, *J. Am. Chem. Soc.*, **113**, 9369 (1991).

31. A. Padwa, K. E. Krumpe, Y. Gareau and U. Chiacchio, *J. Org. Chem.*, **56**, 2523 (1991).

32. J. Bussenius, N. Laber, T. Mü ller and W. Eberbach, *Chem. Ber.*, **127**, 247 (1994).

33. R. Boese, J. R. Green, J. Mittendorf, D. L. Mohler and K. P. C. Vollhardt, *Angew. Chem. Int. Ed. Engl.*, **31**, 1643 (1992).

34. P. T. De Sousa Jr. and R. J. K. Taylor, *Synlett*, 755 (1990).

35. B. V. Nguyen, Z-Y. Yang and D. J. Burton, *J. Org. Chem.*, **58**, 7368 (1993).

36. S. Tsuboi, H. Kuroda, S. Takatsuka, T. Fukawa, T. Sakai and M. Utaka, *ibid..*, **58**, 5952 (1993).

37. J. Wityak and J. B. Chan, *Synth. Commun.*, **21**, 977 (1991).

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

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

40. P. A. Wender and C. K. Zercher, *J. Am. Chem. Soc.*, **113**, 2311 (1991).

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

42. V. Ratovelomanana and G. Linstrumelle, *ibid..*, **25**, 6001 (1984).

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

44. G. P. Roth, D. R. Marshall, J. F. Kadow, S. W. Mamber, W. C. Rose, W. Solomon and N. Zein, *Biorganic Med. Chem. Lett.*, **4**, 711 (1994).

45. P. Magnus and M. Davies, *Chem. Commun.*, 1522 (**1991**).

46. K. Kanematsu, M. Tsuruoka, Y. Takaoka and T. Sasaki, *Heterocycles*, **32**, 859 (1991).

47. Y. Sakai, E. Nishiwaki, K. Shishido, M. Shibuya and M. Kido, *Tetrahedron Lett.*, **32**, 4363 (1991).

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

49. P. A. Magriotis, M. E. Scott and K. D. Kim, *ibid.*, **32**, 6085 (1991).

50. V. Ratovelomanana and G. Linstrumelle, *Synth. Commun.*, **11**, 917 (1981).

51. T. Nishikawa, A. Ino, M. Isobe and T. Goto, *Chemistry Lett.*, 1271 (**1991**).

52. D. L. Clive, A. Khodabocus, P. G. Vernon, A. G. Angoh, L. Bordeleau, D. S. Middleton, C. Lowe and D. Kellner, *J. Chem. Soc. Perkin Trans. I*, 1433 (**1991**).

53. A. M. Boldi and F. Diederich, *Angew. Chem. Int. Ed. Engl.*, **33**, 468 (1994).

54. K. C. Nicolaou, T. Ladduwahetty, I. M. Taffer and R. E. Zipkin, *Synthesis*, 344 (**1986**).

55. M. A. Ciufolini and T. J. Weiss, *Tetrahedron Lett.*, **35**, 1127 (1994).

56. R. S. Paley, J. A. Lafontaine and M. P. Ventura, *ibid.*, **34**, 3663 (1993).

57. R. Rossi, A. Carpita, M. G. Quirici and M. L. Gaudenzi, *Tetrahedron*, **38**, 631 (1982).

58. M. Alami and G. Linstrumelle, *Tetrahedron Lett.*, **32**, 6109 (1991).

59. N. Sato, A. Hayakawa and R. Takeuchi, *J. Heterocyclic Chem.*, **27**, 503 (1990).

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

61. E. C. Taylor and S. Goswami, *Tetrahedron Lett.*, **32**, 7357 (1991).

62. R. Diercks, J. C. Armstrong, R. Boese and K. P. C. Vollhardt, *Angew. Chem. Int. Ed. Engl.*, **25**, 268 (1986).

63. D. Guillerm and G. Linstrumelle, *Tetrahedron Lett.*, **27**, 5857 (1986).

64. K. Feldman and C. J. Burns, *J. Org. Chem.*, **56**, 4601 (1991).

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

66. K. Fujiwara, H. Sakai and M. Hirama, *J. Org. Chem.*, **56**, 1688 (1991).

67. I. R. Butler and C. Soucy-Breau, *Can. J. Chem.*, **69**, 1117 (1991).

68. B. P. Andreini, A. Carpita, R. Rossi and B. Scamuzzi, *Tetrahedron*, **45**, 5621 (1989).

69. K. C. Nicolaou, T. Ladduwahetty and E. M. Elisseou, *Chem. Commun.*, 1580 (**1985**).

70. R. Rossi, A. Carpita, V. Lippolis and M. Benetti, *Gazz. Chim. Ital.*, **120**, 783 (1990).

71. M. A. De la Rosa, E. Velarde and A. Guzmán, *Synth. Commun.*, **20**, 2059 (1990).

72. N. A. Bumagin, A. B. Ponomaryov and I. P. Beletskaya, *Synthesis*, 728 (1984).

73. K. Kikukawa, A. Abe, F. Wada and T. Matsuda, *Bull. Chem. Soc. Jpn.*, **56**, 961 (1983).

74. J. Reisch and P. Nordhaus, *J. Heterocyclic Chem.*, **28**, 167 (1991).

75. Z-Y. Yang and D. J. Burton, *Tetrahedron Lett.*, **31**, 1369 (1990).

76. S. Eddario, H. Mestdagh and C. Rolando, *ibid.*, **32**, 69 (1991).

77. A. Arcadi, S. Cacchi and F. Marinelli, *ibid.*, **30**, 2581 (1989).

78. P. D. Beer, O. Kocian, R. J. Mortimer and C. Ridgway, *Chem. Commun.*, 1460 (**1991**).

79. M. J. Robin and P. J. Barr, *J. Org. Chem.*, **48**, 1854 (1983).

80. J. R. Weir, B. A. Patel and R. F. Heck, *ibid.*, **45**, 4926 (1980).

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

82. D. R. Haubrich, S. J. Ward, E. Baizman, M. R. Bell, J. Bradford, R. Ferrari, M. Miller, M. Perrone, A. K. Pierson, J. K. Saelens and D. Luttinger, *J. Pharmacol. Exp. Ther.*, **255**, 511 (1990).

83. K. P. C. Vollhardt and L. S. Winn, *Tetrahedron Lett.*, **22**, 315 (1981).

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

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

86. T. K. Dougherty, K. S. Y. Lau and F. L. Hedberg, *J. Org. Chem.*, **48**, 5273 (1983).

87. G. Fournet, G. Balme, B. Van Hemelryck and J. Gore, *Tetrahedron Lett.*, **31**, 5147 (1990).

88. E. Brocato, C. Castagnoli, M. Catellani and G. P. Chiusoli, *ibid.*, **33**, 7433 (1992).

89. S. Torii, H . Okumoto, T. Kotani, S. Nakayasu and H. Ozaki, *ibid.*, **33**, 3503 (1992).

90. L. Cassar, *Ann. N. Y. Acad. Sci.*, **333**, 208 (1980).

91. H. Alper, *Adv. Organomet. Chem.*, **19**, 183 (1981).

92. R. Rossi, A. Carpita and P. Piccardi, in *Pesticide Chemistry: Human Welfare and the Environment,* J. Miyamoto and P. C. Kearney, Eds.; Pergamon Press, Oxford, vol 1, pp 129-134 (1983).

93. R. Rossi and A. Carpita, *Tetrahedron,* **39**, 287 (1983).

94. R. Rossi, A. Carpita and A. Lezzi, *ibid.*, **40**, 2773 (1984).

95. A. Carpita, A. Lezzi and R. Rossi, *Synthesis,* 571 (**1984**).

96. M. D'Auria, *Synth. Commun.*, **22**, 2393 (1992).

97. S. Kotani, M. Ono, H. Yamaguchi, K. Shiina and K. Sonogashira, in *Abstracts of 35th Symposium in Organometallic Chemistry,* Osaka, Japan, 1988, p 190.

98. A. Osahwa, Y. Abe and H. Igeta, *Chemistry Lett.*, 241 (**1979**).

99 T. Sakamoto, Y. Kondo and H. Yamanaka, *Chem. Pharm. Bull. Jpn.*, **30**, 2410 (1982).

100. T. Sakamoto, Y. Kondo and H. Yamanaka, *ibid.*, 30, 2417 (1982).

101. T. Sakamoto, Y. Kondo and H. Yamanaka, *ibid.*, **34**, 2362 (1986).

102. Y. Kondo, R. Watanabe, T. Sakamoto and H. Yamanaka, *ibid.*, **37**, 2933 (1989).

103. T. Sakamoto, Y. Kondo and H. Yamanaka, *Heterocycles,* **24**, 31 (1986).

104. A. Tischler and T. J. Lanza, *ibid.*, **27**, 1653 (1986).

105. K. Iritani, S. Matsubara and K. Utimoto, *Tetrahedron Lett.*, **29**, 1799 (1988).

106. T. Sakamoto, Y. Kondo, S. Iwashita, T. Nagano and H. Yamanaka, *Chem. Pharm. Bull. Jpn.*, **36**, 1305 (1988).

107. A. Arcadi, S. Cacchi, V. Carnicelli and F. Marinelli, *Tetrahedron,* **50**, 437 (1994).

108. A. Arcadi, S. Cacchi and F. Marinelli, *Tetrahedron Lett.*, **33**, 3915 (1992).

109. F-T. Luo and R-T. Wang, *ibid.*, **33**, 6835 (1992).

110. T. Sakamoto, M. An-naka, Y. Kondo and H. Yamanaka, *Chem. Pharm. Bull. Jpn.*, **34**, 2754 (1986).

111. T. Sakamoto, Y. Kondo, R. Watanabe and H. Yamanaka, *ibid.*, **34**, 2719 (1986).

112. T. Sakamoto, M. Miura, Y. Kondo and H. Yamanaka, *ibid.*, **34**, 2760 (1986).

113. X. Lu, X. Huang and S. Ma, *Tetrahedron Lett.*, **34**, 5963 (1993).

114. A. Arcadi, S. Cacchi, R. C. Larock and F. Marinelli, *ibid.*, **34**, 2813 (1993).

115. a) V. N. Kalinin, M. V. Shostakovsky and A. B. Ponomaryov, *ibid.*, **31**, 4073 (1990); b) S. Torii, H. Okumoto, L. H. Xu, M. Sadakane, M. V. Shostakovsky, A.B.Ponomayov and V. N. Kalinin, *Tetrahedron*, **49**, 6773 (1993).

116. V. N. Kalinin, M. V. Shostakovsky and A. B. Ponomaryov, *Dokl. Akad. Nauk SSSR*, **312**, 1142 (1990).

117. S. Torii, L. H. Xu, M. Sadakane and H. Okumoto, *Synlett*, 513 (**1992**).

118. S. Torii, L. H. Xu and H. Okumoto, *ibid.*, 695 (1991).

119. S. Torii, H. Okumoto and L. H. Xu, *Tetrahedron Lett.*, **32**, 237 (1991).

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

121. B. P. Andreini, A. Carpita and R. Rossi, *Tetrahedron Lett.*, **27**, 5533 (1986).

122. R. F. Jackson and R. A. Raphael, *ibid.*, **24**, 2117 (1983).

123. T. R. Hoye, P. R. Hanson, A. C. Kovelesky, T. D. Ocain and Z. Zhuang, *J. Am. Chem. Soc.*, **113**, 9369 (1991).

124. E. C. Taylor and S. Goswami, *Tetrahedron Lett.*, **32**, 7357 (1991).

125. B. Das and N. G. Kundu, *J. Chem. Res. (S)*, 364 (**1992**).

126. K. C. Nicolaou and W.-M. Dai, *Angew. Chem. Int. Ed. Engl.*, **30**, 1387 (1991).

127. A. S. Kende and C. A. Smith, *Tetrahedron Lett.*, **29**, 4217 (1988).

128. A. G. Myers, P. M. Harrington and E. Y. Kuo, *J. Am. Chem. Soc.*, **113**, 694 (1991).

129. P. A. Wender and M. J. Tebbe, *Tetrahedron,* **50**, 1419 (1994).

130. K. C. Nicolaou, J. Y. Ramphal, N. A. Petasis and C. N. Serhan, *Angew. Chem. Int. Ed. Engl.,* **30**, 1100 (1991).

131. K. C. Nicolaou and S. E. Webber, *J. Am. Chem. Soc.*, **106**, 5374 (1984).

132. K. C. Nicolaou, R. E. Zipkin, R. E. Dolle and B. D. Harris, *ibid.,* **106**, 3548 (1984).

133. D. Chemin and G. Linstrumelle, *Tetrahedron,* **48**, 1943 (1992).

134. A. S. Craig, A. W. Norman and W. H. Okamura, *J. Org. Chem.*, **57**, 4374 (1992).

135. J. Suffert, A. Eggers, S. W. Scheuplein and R. Brückner, *Tetrahedron Lett.,* **34**, 4177 (1993).

136. S. Cacchi, E. Morera and G. Ortar, *Synthesis,* 320 (**1986**).

137. W. J. Scott, M. R. Peñ a, K. Swä rd, S. J. Stoessel and J. K. Stille, *J. Org. Chem.,* **50**, 2302 (1985).

138. A. Arcadi, S. Cacchi, M. Delmastro and F. Marinelli, *Synlett.,* 409 (**1991**).

139. R. Brückner, S. W. Scheuplein and J. Suffert, *Tetrahedron Lett.,* **32**, 1449 (1991).

140. J. Mascareñ as, L. A. Sarandeses, L. Castedo and A. Mouriño, *Tetrahedron,* **47**, 3485 (1991).

141. A. Arcadi, A. Burini, S. Cacchi, M. Delmastro, F. Marinelli and B. R. Pietroni, *J. Org. Chem.,* **57**, 976 (1992).

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

143. K. Nakatani, K. Arai, N. Hirayama, F. Matsuda and S. Terashima, *ibid.,* **48**, 633 (1992).

144. K. Nakatani, K. Arai, K. Yamada and S. Terashima, *Tetrahedron Lett.,* **32**, 3405 (1991).

145. L. A. Sarandeses, M. J. Vallé s, L. Castedo and A. Mouriño, *ibid.,* **49**, 731 (1993).

146. K. Nakatani, K. Arai and S. Terashima, *Chem. Commun.,* 289 (**1992**).

147. J. Suffert and R. Brückner, *Tetrahedron Lett.,* **32**, 1453 (1991).

148. K. Nakatani, K. Arai, N. Hirayama, F. Matsuda and S. Terashima, *ibid.,* **31**, 2323 (1990).

149. R. Brückner, S. W. Scheuplein and J. Suffert, *ibid.,* **32**, 1449 (1991).

150. J. P. Sestelo, J. Mascareñ as, L. Castedo and A. Mouriño, *J. Org. Chem.,* **58**, 118 (1993).

151. S. W. Scheuplein, K. Harms and R. Brückner, J. Suffert, *Chem. Ber.*, **125**, 271 (1992).

152. J. R. Granja, L. Castedo and A. Mouriño, *J. Org. Chem.*, **58**, 124 (1993).

153. E. J. Corey, M. Klang, M. C. Desai, A. K. Gosh and I. N. Houpis, *J. Am. Chem. Soc.*, **110**, 649 (1988).

154. B. Figadè re, A. W. Norman, H. L. Henry, H. P. Koeffler, J-Y. Zhou and W. H. Okamura, *J. Med. Chem.*, **34**, 2452 (1991).

155. A. S. Lee, A. W. Norman and W. H. Okamura, *J. Org. Chem.*, **57**, 3846 (1992).

156. E. J. Corey and A. V. Gavai, *Tetrahedron Lett.*, **29**, 3201 (1988).

157. M. Moniatte, M. Eckhardt, K. Brickmann, R. Brückner and J. Suffert, *ibid.*, **35**, 1965 (1994).

158. K. Nakatani, K. Arai, K. Yamada and S. Terashima, *Tetrahedron*, **48**, 3045 (1992).

159. A. Arcadi, S. Cacchi and F. Marinelli, *ibid.*, **49**, 4955 (1993).

160. S. Cacchi, in *Seminars in Organic Synthesis*, XVIII Summer School *A. Corbella*, June 14-18, 1993, Società Chimica Italiana, pp 217-242.

161. S. Cacchi, M. Delmastro, S. Iannelli and M. Nardelli, *Gazz. Chim. Ital.*, **122**, 11 (1992).

162. Q-Y. Chen and Z-Y. Yang, *Tetrahedron Lett.*, **27**, 1171 (1986).

163. J. W. Tilley and S. Zawoisky, *J. Org. Chem.*, **53**, 386 (1988).

164. R. W. Guthrie, G. L. Kaplan, F. A. Mennona, J. W. Tilley, R. W. Kirstead, J. G. Mullin, R. A. Le Mahieu, S. Zawoiski, M. O' Donnel, H. Growley, B. Yaremko and A. F. Welton, *J. Med. Chem.*, **32**, 1820 (1989).

165. G. T. Crisp and S. Papadopoulos, *Aust. J. Chem.*, **42**, 279 (1989).

166. K-L. Evans, P. Prince, E. T. Huang, K. R. Boss and R. D. Gandour, *Tetrahedron Lett.*, **31**, 6753 (1990).

167. R. G. Dushin and S. J. Danishefsky, *J. Am. Chem. Soc.*, **114**, 655 (1992).

168. Q-Y. Chen and Z-Y. Li, *J. Chem. Soc. Perkin Trans. I*, 2931 (1992).

169. a) P. J. Stang, M. Hanack and L. R. Subramanian, *Synthesis*, 85 (1982); b) J. K. Stille, *Pure Appl. Chem.*, **57**, 1771 (1985); c) W. J. Scott and J. E. McMurry, *Acc. Chem. Res.*, **21**, 47 (1988); d) K. Ritter, *Synthesis*, 735 (1993).

170. S. Gueugnot and G. Linstrumelle, *Tetrahedron Lett.*, **34**, 3853 (1993).

171. T. Mandai, T. Nakata, H. Murayama, H. Yamaoki, M. Ogawa, M. Kawada and J. Tsuji, *Tetrahedron Lett.*, **31**, 7179 (1990).

172. T. Jeffery-Luong and G. Linstrumelle, *Synthesis*, 32 (**1983**).

173. J. Wityak and J. B. Chan, *Synth. Commun.*, **21**, 977 (1991).

174. D. Boussy, G. Balme and J. Gore, *Tetrahedron Lett.*, **32**, 6541 (1991).

175. D. Boussy, J. Gore and G. Balme, *ibid.*, **33**, 2811 (1992).

176. R. D. Stephens and C. E. Castro, *J. Org. Chem.*, **28**, 2163 (1963).

177. R. D. Stephens and C. E. Castro, *ibid.*, **28**, 3313 (1963).

178. C. E. Castro, E. Gaughan and D. C. Owsley, *ibid.*, **31**, 4071 (1966).

179. K. Okuro, M. Furuune, M.Miura and M. Nomura, *Tetrahedron Lett.*, **33**, 5363 (1992).

180. K. Okuro, M. Furuune, M. Enna, M. Miura and M. Nomura, *J. Org. Chem.*, **58**, 4716 (1993).

181. T. Ogawa, K. Kusume, M. Tanaka, K. Hayami and H. Suzuki, *Synth. Commun.*, **19**, 2199 (1989).

182. V. V. Grushin and H. Alper, *J. Org. Chem.*, **57**, 2188 (1992).

183. T. Jeffery, S. Gueugnot and G. Linstrumelle, *Tetrahedron Lett.*, **33**, 5757 (1992).

184. M. A. Lapitskaya, L. L. Vasiljeva and K. K. Pivnitsky, *Synthesis*, 65 (**1993**).

185. L. Argenti, F. Bellina, A. Carpita, E. Rossi and R. Rossi, *Synth. Commun.*, **24**, 2281 (1994).

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