Halogenated Quinolines as Substrates for the Palladium-Catalyzed Cross-Coupling Reactions to Afford Substituted Quinolines

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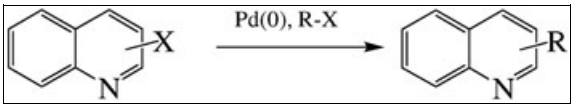

The use of palladium complexes in catalyzing the cross-coupling of halogenated quinolines with various organometalic reagents has led to the development of radically new methods of synthesizing novel substituted quinoline derivatives. The focus of this review is on the application of the following palladium-catalyzed reactions of halogenated quinolines with organometalic reagents to afford substituted quinoline derivatives: Kumada, Stille, Negishi, Sonogashira, Suzuki, Heck, and Hiyama cross-coupling reactions.

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Contents

1. INTRODUCTION AND SCOPE

Halogenated quinolines have become important intermediates in metal-catalyzed carbon–carbon bond formation to afford novel substituted quinoline derivatives with potential application in natural products, pharmaceuticals, and materials. The aryl, alkynyl, or alkenyl moieties, for example, are widely distributed in quinoline derivatives that serve as potent inhibitors of tyrosine kinase (platelet-derived growth factor receptor tyrosine kinase [PDGF-RTK]) [1], antiretroviral agents [2], or LTD_4 receptor antagonists [3], respectively. The 6,7-dimethoxyquinoline derivatives **1** substituted at the 3-position with lipophilic groups such as 4-methoxyphenyl, 4-hydroxyphenyl, 3-fluorophenyl, 3-fluoro-4-methoxyphenyl, 6-methoxypyridin-3-yl, cyclopentyl, *trans*-β-styryl, or thiophene-3-yl group were found to exhibit increased potency as PDGF-RTK inhibitors [1]. Polyhydroxylated styrylquinolines exemplified by **2** are potent HIV-1 integrase inhibitors in *in vitro* experiments; they block the replication of HIV-1 in cell cultures and are devoid of cytotoxicity [2]. The 2-arylquinolines **3** bearing a vinyl, alkynyl, or phenyl substituent on the C-4 position were found to display high affinity (3–5 n*M*) and significant selectivity (up to 83-fold) for estrogen receptor β (ERβ) [4].

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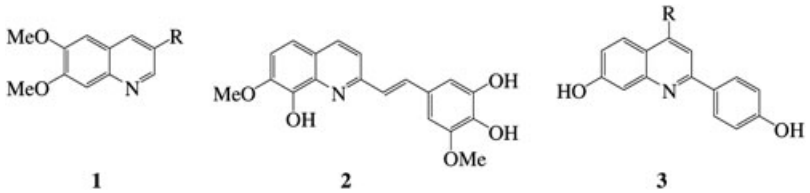
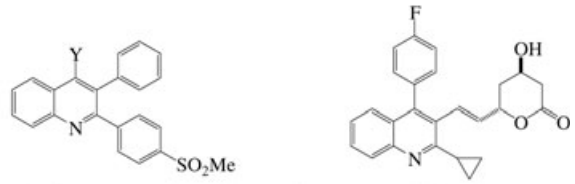


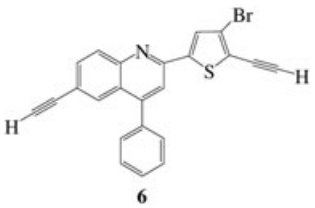
1 **2** **3**

The 2,3-diarylquinolines **4** substituted at the C-4 position with H, CH_3, NH_2, CO_2H, or Ph have been found to serve as selective cyclooxygenase-1/-2 (COX-1 or COX-2) inhibitors [5]. Conversely, the 2,3,4-trisubstituted derivative, NK-104 **5** {calcium salt of 7-[2-cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-3,5-dihydroxy-6-heptenoic acid}, is a highly potent HMG-CoA reductase inhibitor [6].



4(**a**)Y=Ph; (**b**) NH_2; (**c**) CO_2H; (**d**) H; (**e**) CH_3 **5** (NK-104)

Aluminum complexes derived from 4-chloro-, 4-amino-, and 4-aryl-8-hydroxyquinolines exhibit photoluminescence and electroluminescence properties [7,8]. Similarly, the analogous 2,4-diarylquinolines show intense blue emission on UV excitation [9]. Polyarylquinoline moiety, on the other hand, constitutes a π-conjugated bridge in nonlinear optical polymers [10] and also serves as electron-acceptor unit in carbazole–quinoline and phenothiazine–quinoline copolymers and oligomers found to exhibit intramolecular charge transfer [11]. Polyalkynyl- or polyarylquinoline-based compounds also constitute an important component in optoelectronic materials [12–14]. The 2-, 3-, and 4-(*p*-substituted phenyl)ethynylquinolines, and the analogous 1- and 4-(*p*-substituted phenyl) ethynylisoquinolines also exhibit photophysical and electrogenerated chemiluminescence (ECL) properties [15]. 2-(4-Bromo-5-ethylnylthiophen-2-yl)-6-ethynyl-4-phenylquinoline **6** has been applied in sensors and light emitting diodes [16].



6

Despite the popularity and efficiency of metal-catalyzed cross-coupling reactions of halogenated quinolines to afford novel substituted quinoline derivatives, there is no comprehensive review that focuses on this important subdomain of heterocyclic chemistry. Instead, comprehensive review articles continue to appear in literature describing the synthesis of substituted quinolines *via* the classical methods [17] with few examples of their preparation *via* metal-catalyzed cross-coupling reactions of halogenated quinolines described in review articles and monographs [18,19]. This anomaly prompted us to review available published data on the applications of the following palladium-catalyzed cross-coupling of halogenated quinolines with various organometalic reagents to afford substituted quinolines: Kumada, Stille, Negishi, Sonogashira, Suzuki, Heck, and Hiyama cross-coupling reactions.

2. REACTIVITY OF HALOGENATED QUINOLINE DERIVATIVES IN CROSS-COUPLING REACTIONS

The use of halogenated quinolines as intermediates in palladium-catalyzed cross-coupling reactions to form Csp^2–Csp^2 or Csp^2–Csp bond(s) takes advantage of the ease of displacement of iodine, bromine, or chlorine atom (s) on the aryl or heteroaryl moiety by nucleophiles or metal catalysts. This approach has led to variously substituted quinoline derivatives that are difficult to prepare *via* the known classical methods for the synthesis of polysubstituted quinolines. Although the known order of reactivity in transition metal–mediated cross-coupling of aryl halides (I > Br >> Cl) allows selective coupling with iodides or bromides in the presence of chlorides, several activated heteroaryl chlorides such as 4-chloropyridine and 4-chloroquinoline derivatives have since been found to undergo metal-catalyzed cross-coupling with ease. Moreover, highly efficient sources for palladium(0) catalysts and ligands have been developed to promote carbon–carbon bond formation using the relatively less reactive arylchlorides. The Ar-X bond strength which increases as follows: I < Br < Cl < F ($D_{Ph\text{-}X}$ values 65, 81, 96, and 126 kcal/mol, respectively) has been found to allow successive substitution of the halogen atoms (I > Br > Cl >> F) in dihaloquinolines [20]. Among the cross-coupling reactions with organometallic reagents that involve halogenoquinolines or their triflate or tosylate derivatives, the Suzuki and Sonogashira coupling reactions and to some extent the

Stille and Negishi reactions are more prevalent. Only limited examples exist for the Kumada and Hiyama cross-coupling reactions of halogenated quinolines to afford substituted quinolines.

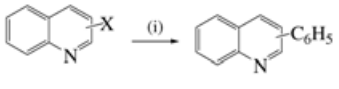
3. APPLICATION OF CROSS-COUPLING REACTIONS IN THE SYNTHESIS OF SUBSTITUTED QUINOLINES

3.1. Kumada cross-coupling reaction. The palladium-catalyzed coupling of Grignard reagents with aryl/vinyl halides and triflates is most commonly called the Kumada reaction [21]. Palladium-catalyzed Kumada cross-coupling reaction between phenylmagnesium chloride and haloquinolines **7a** (X = 2-Cl) or **b** (X = 3-Br) in tetrahydrofuran (THF) at −5 or 25°C afforded the corresponding phenylquinolines **8a** (X = 2-Ph) or **b** (X = 3-Ph) in 80 and 75% yield, respectively (Scheme 1) [22].

3-Bromoquinoline **9** was converted to the corresponding lithium tri(quinolyl)magnesates at −10°C on treatment with Bu_3MgLi in THF and the resulting organomagnesium derivatives **10** was reacted with heteroaryl bromides (Br-HetAr) in the presence of bis(dibenzylideneacetone) palladium(0)/1,1′-bis(diphenylphosphino)ferrocene ($Pd(dba)_2$/dppf) catalyst mixture to afford 3-heteroaryl substituted quinolines **11** in low to moderate yields (Scheme 2) [23]. This procedure avoids a preliminary synthesis of the organometallic substrate *via* the lithio derivative.

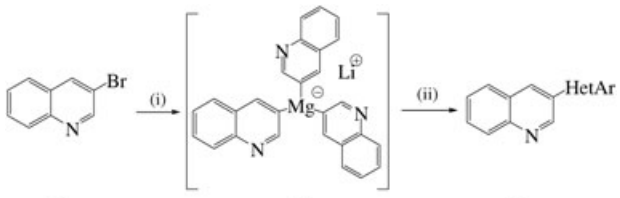
Organ *et al.* used PEPPSI (pyridinium, enhanced, precatalyst, preparation, stabilization and initiation) precatalysts to promote Kumada reaction of several heterocycles including the cross-coupling of 2-chloro-4-methylquinoline with 1,1′-biphenylmagnesium bromide to afford the 2,3-disubstituted quinoline derivative in 90% yield [24]. As palladium is a soft metal, Kumada reaction with palladium catalysts has been found to work well and to proceed at room temperature with quinoline derivatives bearing the soft bromo and iodo substituents. The activation of the hard C-F/Cl bond for the chloro- and fluoroquinoline derivatives, on the other hand, occurs at higher temperature in the presence of nickel catalyst [Ni acetylacetonate $(acac)_2$/1,2-bis(diphenylphosphine)ethane (dppe)] [25]. The use of iron acetylacetonate [$Fe(acac)_3$] as catalyst has been found to provide advantages over the more expensive palladium or nickel catalysts in terms of short reaction times and the low temperatures used [26,27]. Despite its relatively early discovery, the application of the Kumada reaction is somewhat limited compared with the other cross-coupling reactions largely due to the incompatibility of Grignard reagents with many functional groups. The reducing ability of Grignard reagents also causes the precipitation of palladium black and arrest the catalytic turnover. Consequently, the use of organozinc (Negishi reaction), organoboron (Suzuki reaction), and organotin (Stille reaction) reagents has, to a large extent, replaced the use of Grignard reagents in cross-coupling reactions. However, in cases where a Grignard reagent-sensitive functionality is not present, the Kumada reaction represents an efficient method for the C-C bond formation to afford biaryl systems.

Scheme 1. Palladium-catalyzed reaction of 2/3-halogenoquinolines with phenylmagnesium chloride. Reagents and conditions: (i) PhMgCl, $Pd(dba)_2$/dppf, THF, temperature (°C), 5 h.



7 **8**

Scheme 2. Cross-coupling of lithium tri(quinolyl)magnesate with halopyridines and haloquinolines. Reagents and conditions: (i) Bu_3MgLi, THF, −10°C, 2.5 h; (ii) Br-HetAr, THF, $Pd(dba)_2$/dppf, room temperature, 18 h then H_2O.



9 **10** **11**

	Br-HetAr	% Yield
11a	2-Bromopyridine	56
11b	3-Bromopyridine	35
11c	2,4-Dibromopyridine	53
11d	2-Bromoquinoline	51
11e	3-Bromoquinoline	45
11f	2-Bromothiophene	24
11g	3-Bromothiophene	15

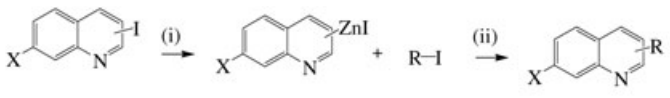
3.2. Negishi cross-coupling reaction. The Negishi cross-coupling reaction of aryl or vinyl halides/triflates with organozinc reagents in the presence of palladium [Pd^0, Pd^{2+}] or nickel source [Ni^0, Ni^{2+}] as catalyst and a phosphine ligand is a versatile and efficient method for the synthesis of a variety of quinolinyl motif [28]. The organozinc reagent can be prepared either from the corresponding organohalide (RX) by reductive metalation [29] or from other organometalic compounds, often RLi, by transmetalation [30]. Dichlorobis(triphenylphosphine) palladium(II) [$PdCl_2(PPh_3)_2$] or dichlorobis[1,2-bis (diphenylphosphino)ferrocene]palladium(II) [$PdCl_2$(dppf)] are commonly used as catalysts to promote the Negishi

cross-coupling reaction [31]. 2-Chloro- and 3-bromoquinolines and their 8-triflate analog were coupled with 1-ethoxyvinylzinc chloride in the presence of either $PdCl_2(PPh_3)_2$ or $Pd(dba)_2/PPh_3$ mixture in THF to afford the corresponding acetylquinoline derivatives [31]. 3-Quinolinylzinc bromide derived from 3-bromoquinoline with Rieke zinc in the presence of lithium chloride was coupled with 2-iodopyridine, 3-iodothiophene, and 3-iodobenzenecyanide using $Pd(PPh_3)_4$ in THF at room temperature to afford the corresponding 3-substituted quinolines in 65, 53, and 70% yield, respectively [32]. Iodoquinolines **12** were reacted with zinc dust in *N*,*N*-dimethylacetamide (DMA) and the resulting quinolyl zinc iodides **13** were subjected to $Pd(dba)_2$-catalyzed Negishi reaction with organoiodides **14** in the presence of tris(*o*-furyl)phosphine [P(*o*-furyl)$_3$] to afford the corresponding substituted quinoline derivatives **15** (Scheme 3) [33].

Palladium-mediated coupling reaction of the 4-bromoquinoline derivatives **16** with zinc cyanide [$Zn(CN)_2$] in dimethylformamide (DMF) followed by demethylation with pyridinium bromide afforded the 4-cyanoquinolines **17** in high yield (Scheme 4) [4]. Cyanation of 7-chloroquinoline with $Zn(CN)_2$ using the catalyst system composed of allylpalladium(II) chloride dimer [(η^3-$C_3H_5PdCl)_2$] and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) afforded 7-cyanoquinoline in 79% yield [34].

A series of 3-substituted 6,7-dimethoxyquinoline derivatives with PDGF-RTK inhibitory activity were prepared from the corresponding 3-bromoquinoline or quinoline-3-triflates *via* palladium-catalyzed reaction with organozinc chlorides [1]. 2,4-Dichloroquinoline **18** has been found to react with benzylic zinc **19** or phenylzinc reagents in the presence of palladium complexes as catalyst to afford the 2-substituted quinoline derivatives **20** (Scheme 5) [35]. This α-selective coupling is controlled by coordination of the quinoline nitrogen with palladium, which activates the α-position relative to the γ-carbon. The 4-substituted quinoline isomers **21**, on the other hand, were isolated as major or sole products in the presence of lithium chloride (4 equiv) in DMF at room temperature [35]. This reverse selectivity is attributed to

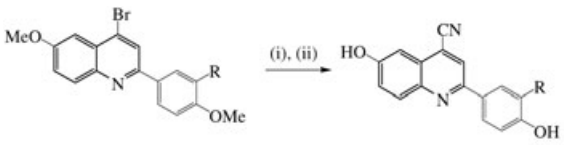
Scheme 3. Palladium-catalyzed Negishi cross-coupling of quinolyl zinc iodides with organoiodides. Reagents and conditions: (i) Zn, DMA; (ii) $Pd(dba)_2$, P(*o*-furyl)$_3$, THF, room temperature or heat (for **13c**, **e**, and **f**).



12 **13** **14** **15**

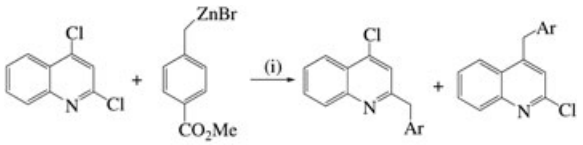
	X	I	R-I	R	% Yield
15a	H	2-I	(*E*)-1-iodo-1-octene	-CH=CH-$(CH_2)_5$Me	61
15b	Cl	4-I	(*E*)-1-iodo-1-octene	-CH=CH-$(CH_2)_5$Me	72
15c	Cl	4-I	4-iodonitrobenzene	-$C_6H_4NO_2$	86
15d	Cl	4-I	1-iodo-6-methyl-1-hexyne	-C≡C-$(CH_2)_3$CH(Me)$_2$	55
15e	Cl	4-I	3-iodo-2-methyl-2-cyclopenten-1-one		71
15f	Cl	4-I	5-iodo-*N*,*N*-dimethyluracil		61

Scheme 4. Palladium-catalyzed coupling of the 4-bromoquinoline derivatives with zinc cyanide. Reagents and conditions: (i) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 80°C; (ii) Pyr·HBr, 200°C.



16 **17**(**a**) R=H (78%); (**b**) R=F (87%)

Scheme 5. Negishi cross-coupling of 2,4-dichloroquinoline with benzylzinc reagent. Reagents and conditions: (i) $Pd(PPh_3)_4$, DMF or THF, room temperature, 2–18 h for **20** or $Pd(PPh_3)_4$, LiCl (2–4 equiv), DMF, room temperature, 4–24 h for **21.**



18 **19** **20** **21**

the strong coordination of halide ions with zinc ion which polarizes the Zn-C bond to lead to possible metal exchange with lithium ion to activate **19**. Ionization and metal exchange are facilitated in the more polar DMF, which is known to stabilize partially ionized transition states and intermediates than THF. The more nucleophilic lithium derivative of **19** attacks the γ-carbon to afford **21**.

(2-Methoxyquinolin-6-yl)zinc(II) chloride derived from 6-bromo-2-methoxyquinoline **22** through halogen–metal exchange with two equivalents of *t*-butylithium and $ZnCl_2$ in THF was reacted with 4-bromobenzamides **23** in the presence of $Pd(PPh_3)_4$ under reflux to afford 6-[4-(*N*,*N*-dialkylcarbomoyl)phenyl]-2-methoxyquinolines **24** (R = isopropyl, isobutyl, or cyclohexyl) in 52–83% yield (Scheme 6) [36,37]. The 6-substituted 2-methoxyquinolines were found to inhibit human and rat steroid 5α reductases [37].

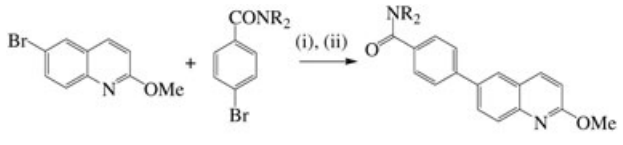
A Negishi reaction sequence involving halogen–metal exchange on 2-chloropyridine derivative **25** using lithium naphthalenide complex afforded a lithiopyridine which was, in turn, treated with $ZnCl_2$ to yield pyridylzinc reagent **26** [38]. The latter was then coupled with methyl 2-chloro-3-quinolinecarboxylate to afford quinoline derivative **27** (80%), which is a precursor for the synthesis of camptothecin (Scheme 7).

Negishi cross-coupling of 2,6-dibromoquinoline **28** with zinc reagent using $Pd(OAc)_2/P(o\text{-furyl})_3$ catalyst mixture in toluene/DMA afforded a 2-substituted quinoline derivative **29** (Scheme 8) [39]. The latter was, in turn, subjected to nickel-catalyzed cross-coupling with ^{14}C-labeled methylzinc iodide to afford the radiolabeled *N*-methyl-D-aspartate (NMDA) antagonist, 3-(diethoxyphosphonomethyl)quinoline derivative **30**, in 37% yield.

Palladium-catalyzed Negishi cross-coupling reaction represents a powerful tool for the formation of carbon–carbon bonds because of the ready availability of organozinc compounds and their high compatibility with various functional groups. The cross-coupling reaction normally occurs at or slightly above room temperature to avoid the degradation of the zinc compound at high temperature. Moreover, the quinolinyl motif can be used in the Negishi coupling reactions as either electrophilic or nucleophilic coupling partner.

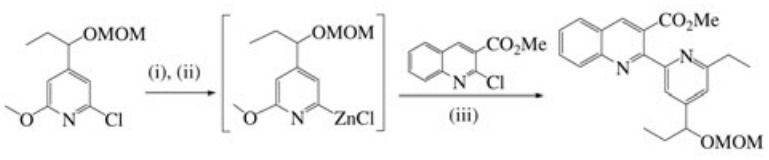
3.3. Sonogashira cross-coupling reaction. Among the variety of transition metal–catalyzed coupling reactions, Sonogashira reaction of halogenoquinolines with terminal acetylenes has become an important tool for the construction of Csp^2–Csp bonds to afford alkynylated quinoline systems. Series of 2-, 3- and 4-(*p*-substituted phenyl)ethynylquinolines, which exhibit chemiluminescence properties were previously prepared in good yields by Sonogashira coupling of the corresponding phenylacetylene derivative with the respective haloquinolines [15]. 3-Formyl-2-iodoquinoline was coupled with trimethylsilylacetylene in THF using $PdCl_2(PPh_3)_2$/CuI catalyst mixture and triethylamine as a base [40]. A series of substituted 2-chloroquinolines bearing cyano or carbaldehyde group at the 3-position were coupled with phenylacetylene using a $PdCl_2/PPh_3$ catalyst mixture and triethylamine as a base in acetonitrile at 80°C to afford the corresponding 2-ethynylquinoline derivatives in high yield (78–88%) [41]. $Pd(PPh_3)_4$/CuI-catalyzed Sonogashira cross-coupling of the 2-iodo-, 3-bromo-, and 4-iodoquinolines with phenylacetylene,

Scheme 6. Negishi coupling of 6-bromoquinoline with 4-bromobenzamide. Reagents and conditions: (i) *t*-BuLi, THF, $ZnCl_2$, −75°C; (ii) $Pd(PPh_3)_4$, reflux, 2 h.



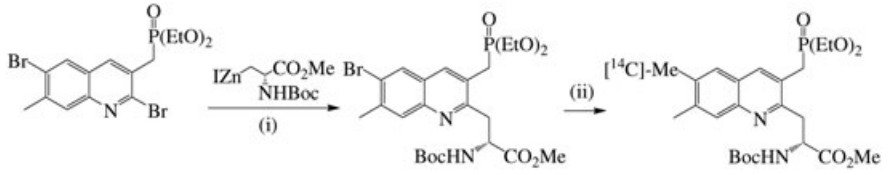
22 **23** **24**

Scheme 7. Negishi reaction of pyridylzinc chloride with methyl 2-chloro-3-quinolinecarboxylate. Reagents and conditions: (i) lithium naphthalide, THF, −90 to −70°C; (ii) $ZnCl_2$, THF, −78 to 25°C; (iii) $Pd(PPh_3)_4$, THF, reflux.



25 **26** **27**

Scheme 8. Successive Negishi cross-coupling of 2,6-dibromoquinoline with organozinc reagents. Reagents and conditions: (i) $Pd(OAc)_2$, P(*o*-furyl)$_3$, PhMe/DMA; (ii) [^{14}C]-MeZnI; $NiCl_2$(dppp); THF.



28 **29** **30**

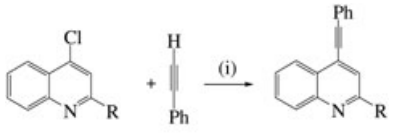
1-hexyne, or propagylalcohol in water in the presence of diisopropylethylamine (DIEA) previously afforded the corresponding alkynylquinolines [42]. The *p*-substituted phenyl-2-quinolinylethylenes prepared *via* $PdCl_2(PPh_3)_2$/CuI-catalyzed Sonogashira reaction of 2-chloroquinoline with *p*-substituted phenylacetylene derivatives in THF in the presence of triethylamine were found to exhibit ECL properties [43]. Sonogashira cross-coupling of 3-bromoquinoline with 1-decyne or 1,5-hexadiyne in the presence of $Pd(PPh_3)_4$–CuI catalyst mixture in pyrrolidine afforded (3-quinolyl)decyne and 1,6-bis(3-quinolyl)hexa-1,5-diyne in 99% and 70% yield, respectively [27]. The 1,6-bis(3-quinolyl)hexa-1,5-diyne was found to exhibit significant activity against HTLV-1 transformed cells [44]. The 4-chloroquinoline **31** (R = H) and its 2-methyl derivative **31** (R = Me) were coupled with phenylacetylene **32** in the presence of palladium–phosphinous acid catalyst $[(t\text{-Bu})_2P(OH)]_2PdCl_2$ [dihydrogen dichlorobis(di-*tert*-butylphosphinito-*k*P) palladate(2-) (POPd)], tetrabutylammonium bromide (TBAB) and NaOH in deionized water under reflux to afford the 4-phenylethynylquinoline **33** (R = H) and 2-methyl-4-phenylethylenylquinoline **33** (R = Me) in 71% and 73% yield, respectively (Scheme 9) [45].

2,4-Dibromoquinoline was coupled with various terminal acetylenes to afford monosubstituted compounds believed to be the 4-alkynylated quinoline derivatives [46]. This reaction was however reinvestigated by Nolan and Comins who, on the basis of heteronuclear multiple bond correlation (HMBC) and some chemical transformations, established the structure of the resulting products to be that of the 2-substituted derivatives [47]. A similar regioselectivity was also observed for the Pd/C–CuI–PPh_3-catalyzed Sonogashira coupling of 2,4-dichloroquinoline with terminal alkynes in water [48]. In contrast to the reactivity of 2,4-dibromoquinoline, the analogous 2-bromo-4-iodoquinoline afforded the 4-alkynylated 2-bromoquinoline derivative, exclusively [49]. The observed result can be attributed to the Ar-X bond strength which increases as follows: I < Br < Cl < F and allows successive substitution of the halogen atoms (I > Br > Cl >> F) in dihaloquinolines [20]. Palladium–CuI-catalyzed Sonogashira cross-coupling of 2,4-dichloroquinoline **34** with excess terminal alkynes afforded the corresponding 2,4-dialkynylquinolines **35** in a single-pot operation (Scheme 10) [50]. A Pd/C–CuI-mediated dual carbon–carbon bond formation reaction of 2,4-diiodoquinoline with terminal alkynes including propagyl alcohols was achieved in water to afford series of 2,4-(dialkynyl)quinoline derivatives [51].

The reaction of 4-chloro-6-(bromo/iodo)quinoline **36** with phenylacetylene **32** in dioxane–water in the presence of 2 equiv of triethylamine and $Pd(PPh_3)_4$–CuI catalyst mixture afforded 4-chloro-6-phenylethynylquinoline **37** in 93% yield (Scheme 11) [52]. The use of an excess of phenylacetylene (2.2 equiv), on the other hand, led to a mixture of the monoalkynylated derivative **37** (15%) and dialkynylated quinoline **38** (83%). The latter was isolated as sole product and in high yield in the presence of an excess of phenylacetylene (3 equiv) in triethylamine.

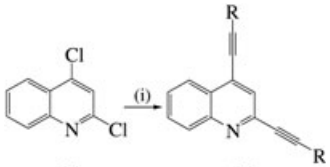
$PdCl_2(PPh_3)_3$/CuI-catalyzed Sonogashira cross-coupling of 3,6-diiodoquinoline with trimethylsilylacetylene in the presence of K_2CO_3 in piperidine afforded 3,

Scheme 9. Palladium–phosphinous acid–catalyzed alkynylation of 4-chloroquinoline. Reagents and conditions: (i) POPd, TBAB, NaOH, CuI, H_2O, 5 h.



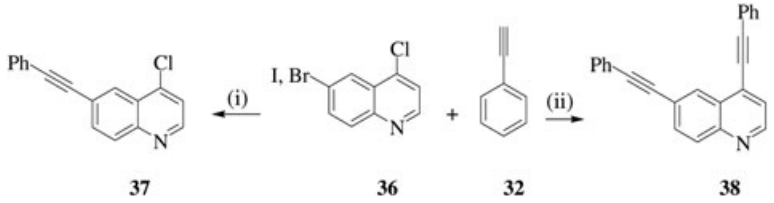
31 **32** **33**

Scheme 10. One-pot palladium/CuI-catalyzed dialkynylation of 2,4-dichloroquinoline. Reagents and conditions: (i) Pd/C, PPh_3, CuI, NEt_3, water, 80–85°C.



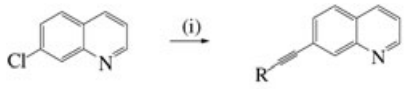
34 **35**

Scheme 11. Palladium/CuI-catalyzed mono- and dialkynylation of 4,6-dihaloquinoline. Reagents and conditions: (i) $Pd(PPh_3)_4$, CuI, NEt_3 (2 equiv), dioxane–H_2O; (ii) $Pd(PPh_3)_4$, CuI, NEt_3 (4 equiv).



37 **36** **32** **38**

Scheme 12. Palladium/ligand-mediated C-7 alkynylation of 7-chloroquinoline. Reagents and conditions: (i) HC CR, $Pd(MeCN)_2Cl_2$. Xphos, 0.2*M* Cs_2CO_3, MeCN, 75°C, 16–22 h.

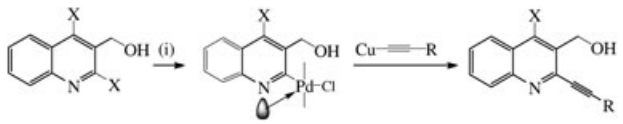


39 **40 (a)** R=Ph (57%); **(b)** -$(CH_2)_3$NHBoc (68%)

6-diethynylquinoline [53]. Polymers formed *via* $PdCl_2(PPh_3)_2$/CuI-catalyzed cross-coupling of 3,6-diiodoquinoline with 1,4-diethynyl-2,5-bis(2-ethynylhexyl)benzene and 3,6-diethynylquinoline with 1,4-diiodo-2,5-bis(2-ethylhexyloxy) benzene in piperidine were found to exhibit fluorescence properties [53]. The Sonogashira reaction of the inactivated 7-chloroquinoline **39** with terminal alkynes [phenylacetylene, ethyl-5-hexynoate, and *N*-(Boc)-5-pentyneamine], on the other hand, proved more challenging and the desired 7-alkynylated quinoline derivatives **40** were only isolated in moderate yield when dichlorobis(acetonitrile)palladium(II) [$PdCl_2(MeCN)_2$]-XPhos was used a catalyst mixture and 0.2*M* Cs_2CO_3 as a base in acetonitrile (Scheme 12) [34].

The (2,4-dihaloquinolin-3-yl)methanol **41** was reacted with terminal alkynes in dioxane in the presence of diisopropylamine or triethylamine and $PdCl_2(PPh_3)_2$/CuI catalyst mixture to afford [4-halo-2-(alkynyl)quinolin-3-yl] methanol **42** in 74% yield (Scheme 13) [47]. The high reactivity at C-2 versus C-4 when X = Cl is attributed to the increased positive character of the α-carbon of the α,β-unsaturated framework due to the electron-withdrawing effect of the adjacent nitrogen of the quinoline ring. The observed regioselectivity in alkynylation of 2,4-dihaloquinolines (X = I, Br, and Cl) is also attributed to the activation of the C-2 position through the coordination of nitrogen of quinoline ring with palladium [48, 50, 51].

Scheme 13. Regioselective C-2 alkynylation of 2,4-dihaloquinoline. Reagents and conditions: (i) HC CR, $PdCl_2(PPh_3)_2$, CuI, 1,4-dioxane, 23°C, H-N(*i*-Pr)$_2$.

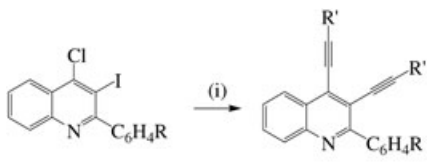


Sonogashira reaction was used before on 2-(4-chlorophenyl)-4-iodoquinoline with phenylacetylene in triethylamine at reflux in the presence of a $Pd(PPh_3)_4$/CuI mixture to afford 2-(4-chlorophenyl)-4-(phenylethynyl)quinoline in 72% yield [54]. $PdCl_2(PPh_3)_2$/CuI-catalyzed Sonogashira coupling of 2-aryl-4-chloro-3-iodoquinolines **43** with terminal acetylenes (1.5 equiv) in triethylamine afforded the 2-aryl-3-(alkynyl)-4-chloroquinolines **44** as sole products (Scheme 14) [55, 56].

The 2-aryl-3,4-bis(alkynyl)quinoline derivatives **45** were prepared in a single-pot operation from **43** using 2.5 equiv of terminal acetylenes in dioxane–water under reflux (Scheme 15) [56].

Palladium-catalyzed polycondensation of the monomers **46** with 2,5-dibromo-3-alkylthiophene **47** in THF in the

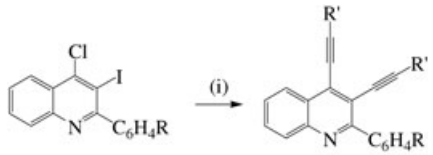
Scheme 14. Regioselective Sonogashira cross-coupling on 2-aryl-4-chloro-3-iodoquinolines. Reagents and conditions: (i) HC CR′ (1.5 equiv); $PdCl_2(PPh_3)_2$, CuI, NEt_3, heat, 2 h.



43 **45a-d**

	R	R'	% Yield
45a	H	-C_6H_5	72
45b	F	-C_6H_5	67
45c	Cl	-C_6H_5	84
45d	OMe	-C_6H_5	79
45e	Cl	-CH(OH)CH_3	97

Scheme 15. One-pot Pd(0)–CuI-catalyzed dialkynylation of 2-aryl-4-chloro-3-iodoquinolines. Reagents and conditions: (i) HC CR′ (2.5 equiv), $PdCl_2(PPh_3)_2$, CuI, NEt_3, dioxane–water (3:1, v/v), heat.



43 **45a-d**

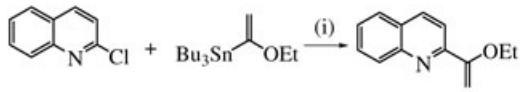
	R	R'	% Yield
45a	H	$-C_6H_5$	72
45b	F	$-C_6H_5$	67
45c	Cl	$-C_6H_5$	84
45d	OMe	$-C_6H_5$	79
45e	Cl	$-CH(OH)CH_3$	97

presence of diisopropylamine afforded the polymers **48**(**a**) **PQEPDT** and (**b**) **PQEPOT** in high yields (78–83%; Scheme 16) [16]. These polymers combine very high fluorescence efficiency in the solid state with enhanced electrochemical redox properties compared with those of known polyquinolines and prior poly(arylene ethynylene)s.

3.4. Stille cross-coupling reaction. The Stille cross-coupling of aryl and vinyl halides/triflates with organostannanes is a powerful and widely used method for the formation of carbon–carbon bonds. Substituted 3-bromoquinolines and their quinoline-3-triflate derivatives were also subjected to palladium-catalyzed Stille reaction with arylstannanes to afford the corresponding substituted quinolines with PDGF receptor tyrosine kinase inhibitory activity [1]. 2-Chloroquinoline **49** was reacted with (1-ethoxyvinyl)tri(*n*-butyl)stannane **50** in the presence of Pd $(dba)_2/PPh_4$ catalyst mixture in toluene under reflux to afford 2-(1-ethoxyvinyl)quinoline **51** (Scheme 17) [20].

2-(Chloro/bromo)quinoline **52** (R′ = H) and its 8-acetoxy/methoxy-2-bromoquinoline derivatives (R′ = OAc, OMe)

Scheme 17. Stille cross-coupling of 2-chloroquinoline with (1-ethoxyvinyl) tri(*n*-butyl)stannane. Reagents and conditions: (i) toluene, 4% $Pd(dba)_2$, 8% PPh_3, reflux, 12 h.



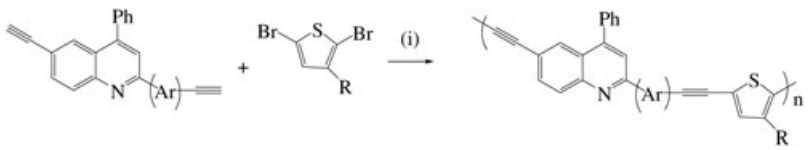
49 **50** **51**

were coupled with 2-stannylated pyridines **53** using $PdCl_2(PPh_3)_2$ as catalyst in DMF to afford the corresponding 2-substituted quinoline derivatives **54** in 46–82% yield (Scheme 18) [57]. The reaction also afforded the cross-coupled products in high yield when 2-stannylquinolines were reacted with 2-bromoquinoline, 2-bromo-4-methylpyridine, 2-bromoisolquinoline, and 9-benzyl-1-chloro-4-methyl-9*H*-β-carboline.

Choppin *et al.* coupled 3-bromoquinoline with (2-chloropyridyl)-2-tributyltin in the presence of $Pd(PPh_3)_4$ to afford the corresponding 3-substituted quinoline derivative in 65% yield [58]. $Pd(PPh_3)_4$-catalyzed Stille coupling of 4-bromoquinolines **55** with tributyl(vinyl)tin or (trimethylsilylethynyl)tributyltin afforded the corresponding vinyl **56** or alkynyl analogs **57**, respectively (Scheme 19) [4]. The coupling of **55a** or **55b** with (1-ethoxyvinyl)tributyltin followed by acid hydrolysis (1*N* HCl) afforded the 4-acetylquinoline analogs. The analogous 4-acetyl, 4-vinyl, and 4-alkynyl quinoline derivatives were found to display high affinity (3–5 n*M*) and significant selectivity (up to 83-fold) for ERβ [4]. Palladium-catalyzed Stille coupling of 2-chloro-, 3-bromo-, or 4-chloroquinoline with (1-ethoxyvinyl)tri(*n*-butyl)stannane in refluxing toluene afforded the corresponding acetylquinolines in 68%, 88%, or 60% yield, respectively [30]. Under similar reaction conditions, the 4,7-dichloroquinoline or 2,4-dichloroquinoline afforded the 4-acetyl-7-chloroquinoline (40%) or 2-acetyl-4-chloroquinoline (44%), exclusively.

Maguire *et al.* used organostannanes on 3-bromoquinoline and quinoline-3-triflates to prepare a series of 3-substituted 6,7-dimethoxyquinoline derivatives with PDGF-RTK inhibitory activity [1]. Wolf and Lerebours also reported an

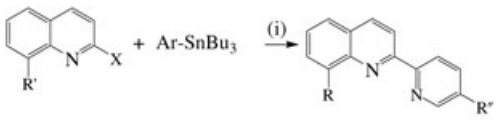
Scheme 16. Palladium-catalyzed polycondensation of **46** with 2,5-dibromo-3-alkylthiophene. Reagents and conditions: (i) $PdCl_2(PPh_3)_2$, CuI, NH^iPr_2, THF, 60°C, 72 h.



46 **47** **48(a)** Ar=-C_6H_4-, R=-$C_{12}H_{25}$: **PQEPDT**

(b) Ar= ; R=-C_8H_{17}: **PQEPOT**

Scheme 18. Palladium-catalyzed Stille reaction of 2-haloquinolines with 2-stannylpyridines. Reagents and conditions: (i) $PdCl_2(PPh_3)_2$, DMF.

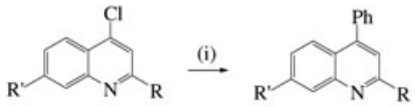


52 **53** **54**

	X	R'	R''	% Yield
54a	Br	H	H	71
	Cl	H	H	51
54b	Br	H	Me	59
	Cl	H	Me	46
54c	Br	OAc	H	57
54d	Br	OAc	Me	49
54e	Br	OMe	H	78
54f	Br	OMe	Me	82

efficient Stille cross-coupling reaction of 4-chloroquinoline and its 2-chloro or 2-methyl derivatives with phenyltrimethylstannane under aqueous conditions using commercially available and water-soluble palladium–phosphinous acid complexes $[(t\text{-Bu})_2P(OH)]_2PdCl_2$ (POPd), $([(t\text{-Bu})_2P(OH)(t\text{-Bu})_2PO]\text{–}PdCl)_2$ [dihydrogen di-μ-chlorotetrakis (di-*tert*-butylphosphinito-*k*P)dipalladate(2-) (POPd1)], and $[(t\text{-Bu})_2P(OH)PdCl_2]_2$ [dihydrogen di-μ-chlorodichlorobis (di-*tert*-butylphosphinito-*k*P)dipalladate(2-) (POPd2)] as catalysts [59]. The 4-chloroquinoline derivatives **58** were coupled with phenyltrimethylstannane in the presence palladium–phosphinous acid complexes and *N*,*N*-dicyclohexylmethylamine (Cy_2NMe) in water at 135–140°C to afford the 4-phenylquinolines **59** (Scheme 20). In the 4,7-dichloroquinoline **58c** (R′ = Cl), no product resulting from C-C bond formation at the C-7 was observed.

Scheme 20. Palladium–phosphinous acid–catalyzed arylation of 4-chloroquinoline derivatives. Reagents and conditions: (i) $PhSnMe_3$, POPd, Cy_2NMe, H_2O, 135–140°C, 24 h.



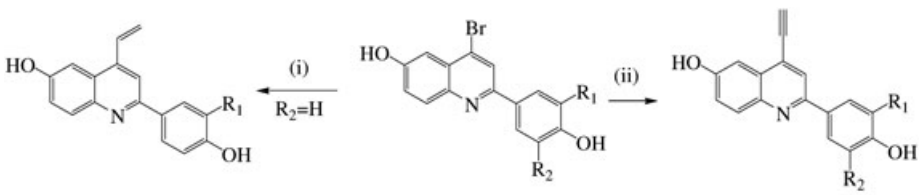
58 **59**

	R	R'	% Yield
59a	H	H	80
59b	Me	H	91
59c	H	Cl	76

In a subsequent POPd-catalyzed Stille couplings, Cy_2NMe was replaced with an inorganic base cesium fluoride (CsF) and this led to improved yields due to the ease of chromatographic separation of the product, which proved to be difficult when the aliphatic amine was used as a base [60]. CsF was also found to enhance the reactivity of arylstannanes due to the high affinity of organotin compounds for fluorine. The introduction of palladium–phosphinous acids to aqueous organic catalysis using inexpensive aryl chlorides and bromides provides another entry for the development of coupling procedures utilizing water as the solvent. Moreover, the stability of palladium–phosphinous acid complexes (POPd, POPd1, and POPd2) to air greatly facilitates catalyst handling and operation of the Stille reaction without the need for inert conditions. Despite these improvements, the high toxicity of the tin reagents [61] and the difficulty in removing the tin byproducts still constitute the major drawback for Stille cross-coupling.

3.5. Suzuki cross-coupling reaction. Palladium-catalyzed Suzuki cross-coupling reactions of boranes, boronic esters, or boronic acids with aryl halides or triflates in the presence of palladium catalyst and a base to form biaryl derivatives has emerged over many years as an

Scheme 19. Stille coupling of **55** with tributyl(vinyl)tin or (trimethylsilylethynyl)tributyltin. Reagents and conditions: (i) $CH_2{=}CHSnBu_3$, $Pd(PPh_3)_4$, PhMe, heat; (ii) $Bu_3SnC\text{-}Si(Me)_3$, $Pd(PPh_3)_4$, PhMe, reflux, then K_2CO_3, MeOH.



56(a) R_1=H (69%)

(b) R_1=F (81%)

55(a), (b)

57(a) R_1, R_2=H (80%)

(b) R_1=F, R_2=H (86%)

(c) R_1, R_2=F (87%)

extremely powerful tool in organic synthesis. This method has found a wide application in the synthesis of aryl- and vinyl-substituted quinoline derivatives with potential application in natural products, pharmaceuticals, and materials. Mitchell and coworkers subjected 2-chloro-, 3-chloro-, and 4-chloroquinolines to $Pd(PPh_3)_4$-catalyzed cross-coupling with arylboronic acids in the presence of 2*M* Na_2CO_3 in benzene to afford a series of substituted quinolines in high yields (76–97%) [62]. Benzimidazole–oxime palladium(II) complex was also used as precatalyst to promote Suzuki cross-coupling of 3-bromoquinoline with arylboronic acids in water in the presence of TBAB under microwave conditions to afford the corresponding 3-arylquinolines in 80–94% yield within 8–11 min [63]. 4-Chloroquinoline was coupled with {2-[(2,2-dimethylpropanoyl)amino]phenyl}boronic acid in dimethoxyethane in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 (aq) to afford 2,2-dimethyl-*N*-(2-quinolin-4-ylphenyl)propanamide in 96% yield [64]. The Suzuki–Miyaura cross-coupling of 4-chloro-8-tosyloxyquinoline **60** with various aryl boronic acids under anhydrous conditions afforded the corresponding 4-aryl-8-tosyloxyquinolines **61** (Scheme 21) [65]. Aluminum complexes (Alq3) derived from the 4-amino- or 4-aryl-8-hydroxy quinoline derivatives were found to exhibit photoluminescence and electroluminescence properties [7, 8].

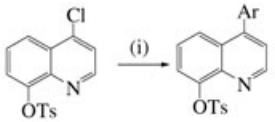
4-Haloquinoline **62** was coupled with various boronic acid derivatives in the presence of ligand-free $Pd(OAc)_2$ in DMF to afford 4-arylated quinoline derivatives **63** (Scheme 22) [66]. 4-Bromo-6-hydroxy-2-(5-fluoro-4-hydroxyphenyl)quinoline was coupled with phenylboronic acid using $Pd(PPh_3)_4$ as catalyst and sodium carbonate in aqueous dimethoxyethane to afford 6-hydroxy-2-(5-fluoro-4-hydroxyphenyl)4-phenylquinoline, which was found to exhibit affinity and selectivity for ERβ [4].

7-Chloroquinoline **64**, which exhibits reactivity pattern typical of aromatic chlorides was previously coupled with arylboronic acids using palladium acetate as catalyst in the presence of a ligand [PPh_3, Sphos (2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl) or XPhos] to afford the 7-arylquinoline derivatives **65** in moderate to high yield depending on the nature of the ligand used (Scheme 23) [34].

An *m*,*p*-methylenedioxyphenyl group was introduced at the 2-position of **66** by Suzuki cross-coupling reaction of the corresponding boronic acid at 75°C to afford the 2,3,4-trisubstituted derivatives **67a** (7-MeO; R = CO_2Et), **b** (5-MeO; R = CO_2Et) and **c** (7-MeO; R = COMe; Scheme 24) [67].

6-Bromo-4,7-dichloro-3-iodoquinoline **68** was found to undergo successive palladium-catalyzed cross-coupling with phenylboronic acid derivatives under conventional and microwave conditions to afford the 3-arylsubstituted quinoline **69** and 3,6-diaryl-4,7-dichloroquinoline derivative **70**, respectively (Scheme 25) [68].

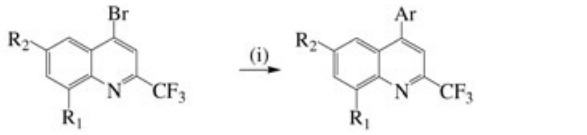
Scheme 21. Suzuki cross-coupling of **60** with arylboronic acids under anhydrous conditions. Reagents and conditions: (i) arylboronic acid, $Pd(PPh_3)_4$, DMF, K_2CO_3.



60 **61**

	Ar	% Yield
61a	-C_6H_5	78
61b	4-MeC_6H_4-	79
61c	4-MeC_6H_4-	89
61d	4-$MeOC_6H_4$-	76
61e	4-NCC_6H_4-	65

Scheme 22. Palladium acetate–catalyzed Suzuki coupling of **62** with arylboronic acids. Reagents and conditions: (i) $ArB(OH)_2$, PPh_3, $Pd(OCOCH_3)_2$, DMF.



62 (R_1=H, Br; R_2=H, CH_3, F, Cl) **63** (Ar=Ph, C_4H_5-, C_7H_9-)

Scheme 23. $Pd(OAc)_2$/ligand-catalyzed cross-coupling of 7-chloroquinoline. Reagents and conditions: (i) condition **A**: $ArB(OH)_2$, 3*N* Na_2CO_3 (aq), PhMe/isopropanol, 80°C; condition **B**: $ArB(OH)_2$, 2*N* K_3PO_4 (aq), PhMe, 70°C.

64 **65**

	Ligand	Ar	% Yield
65a	PPh_3	-C_6H_5	44[A]
65b	SPhos	3,4,5-$(MeO)_3C_6H_2$-	87[A]
65c	XPhos	*p*-$CF_3C_6H_5$-	48[A]
65d	XPhos	-C_6H_5	83[B]
65e	XPhos	*o*-MeC_6H_4-	77[B]
65f	XPhos	*p*-FC_6H_4-	94[B]

Scheme 24. Chemoselective C-2 arylation of 2-bromo-4-chloroquinoline derivatives. Reagents and conditions: (i) 3,4-methylenedioxyphenyl boronic acid, $Pd(PPh_3)_4$, Cs_2CO_3, 1,4-dioxane/H_2O, 75°C, 3 h.

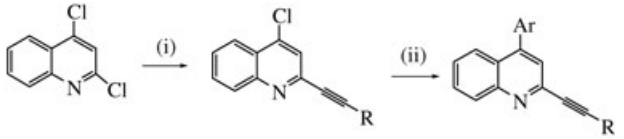
66 **67a-c**

A two-step procedure involving successive Sonogashira and Suzuki cross-coupling to afford the 2-alkynyl-4-arylquinoline has been reported by Reddy *et al.* [50]. The first step involved Pd–CuI-catalyzed Sonogashira cross-coupling of the 2,4-dichloroquinoline **34** with terminal alkynes to afford 2-alkynyl-4-chloroquinoline **71** (Scheme 26). The latter was further subjected to Suzuki cross-coupling with arylboronic acid in the presence of $PdCl_2(PPh_3)_2$, tricyclohexylphosphine (PCy_3) as a ligand and $CsCO_3$ as a base in dioxane–water to afford the 2-alkynyl-4-arylquinoline **72**.

A similar approach was used recently on systems **44** which were further subjected to $Pd(PPh_3)_4$-catalyzed Suzuki cross-coupling with *trans*-phenylvinylboronic acid or 4-fluorophenylboronic acid in the presence of K_2CO_3 and PCy_3 as ligand in aqueous dioxane at 80°C to afford the 2,3,4-trisubstituted quinolines **73a–f** in reasonable yields (Scheme 27) [56]. As the reaction failed to take place in the absence of the ligand, it was concluded that an alkylphosphine ligand counteracts the inhibitory effect of the extra PPh_3 generated from dissociation of $Pd(PPh_3)_4$ to $Pd(0)(PPh_3)_2$ to speed up the oxidative addition step.

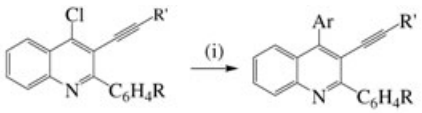
Suzuki cross-coupling of the 2-aryl-4-chloro-3-iodoquinolines **43** with arylboronic acids (1.2–2.0 equiv) using $Pd(PPh_3)_4$ as a catalyst and 2*M* K_2CO_3 in DMF under reflux afforded the 2,3-diaryl-4-chloroquinolines **74** in moderate yields (Scheme 28) [69, 70]. The corresponding 2-aryl-3-iodo-4-methoxyquinolines afforded the 2,3-diaryl-4-methoxyquinolines in moderate to high yield [69]. Under similar reaction conditions, the 2-aryl-3-iodo-4-(triphenylphosphoranylideneamino)quinolines coupled with phenylboronic acid afforded the 2,3-diaryl-4-(triphenylphosphoranylideneamino)quinolines,

Scheme 26. Successive Sonogashira and Suzuki cross-coupling of 2,4-dichloroquinoline. Reagents and conditions: (i) H-C C-R, Pd/C-PPh_3/CuI, Et_3N, H_2O, 80°C; (ii) $ArB(OH)_2$, $(PPh_3)_2PdCl_2$, PCy_3, Cs_2CO_3, dioxane–H_2O, 80°C.



34 **71** **72**

Scheme 27. $Pd(PPh_3)_4$–PCy_3-catalyzed Suzuki coupling of 2,3-disubstituted 4-chloroquinolines. Reagents and conditions: (i) $ArB(OH)_2$, $Pd(PPh_3)_4$, PCy_3, K_2CO_3, dioxane–water (4:1, v/v), heat, 18 h.



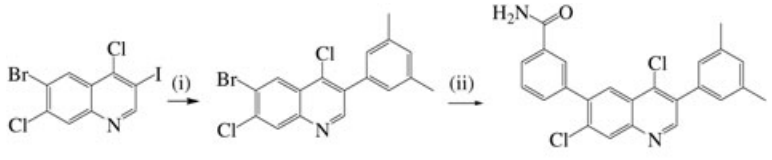
44a-d **73a-f**

	4-R	R'	R'	% Yield
73a	H	$-C_6H_5$	CH=CHPh	92
73b	F	$-C_6H_5$	-CH=CHPh	90
73c	OMe	$-C_6H_5$	-CH=CHPh	55
73d	F	-CH(OH)Me	-CH=CHPh	50
73e	H	$-C_6H_5$	4-FC_6H_4-	74
73f	OMe	$-C_6H_5$	4-FC_6H_4-	62

which were in turn, hydrolyzed with 80% acetic acid to afford the primary 4-amino-2,3-diarylquinolines [71]. $PdCl_2(PPh_3)_2$-catalyzed Suzuki cross-coupling of **43** with arylboronic acids (2.5 equiv) in the presence of tricyclohexylphosphine (PCy_3) and K_2CO_3 in dioxane–water (3:1, v/v) recently afforded the 2,3,4-triarylquinolines **75** in a single-pot operation (Scheme 28) [70].

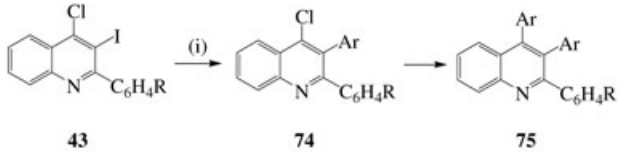
Beletskaya *et al.* investigated the reactivity 6-bromo-4-chloroquinoline toward sequential palladium-catalyzed amination with morpholine and Suzuki cross-coupling with arylboronic acids to yield the corresponding 4,6 and

Scheme 25. Successive Suzuki cross-coupling of 6-bromo-4,7-dichloro-3-iodoquinoline. Reagents and conditions: (i) $ArB(OH)_2$, $PdCl_2(dppf)$, 1*M* Cs_2CO_3, THF, 35°C, 72 h; (ii) $Ar'B(OH)_2$, $Pd(dppf)Cl_2$, 1*M* Cs_2CO_3, THF, μw, 100°C, 15 min.



68 **69** **70**

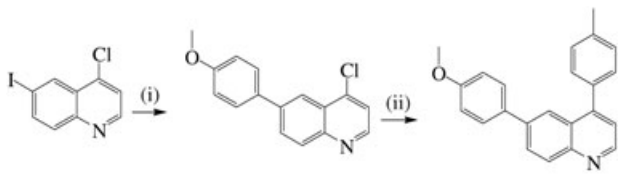
Scheme 28. Chemoselective C-3 arylation and one-pot diarylation of 2-aryl-4-chloro-iodoquinolines. Reagents and conditions: (i) $Pd(PPh_3)_4$, $ArB(OH)_2$, 2*M* K_2CO_3, DMF, reflux for **74**;[a] (i) $Ar(OH)_2$, $PdCl_2(PPh_3)_2$, PCy_3, K_2CO_3, dioxane–H_2O, reflux for **75**.[b]



43 **74** **75**

	4-R	Ar	% Yield (**74**)[a]	% Yield (**75**)[b]
a	H	C_6H_5-	60	59
b	F	C_6H_5-	55	55
c	Cl	C_6H_5-	50	61
d	OMe	C_6H_5-	53	58
e	H	*p*-FC_6H_4-	66	72
f	F	*p*-FC_6H_4-	55	75
g	Cl	*p*-FC_6H_4-	61	62
h	OMe	*p*-FC_6H_4-	79	62

Scheme 29. Successive Suzuki cross-coupling of 4-chloro-6-iodoquinoline. Reagents and conditions: (i) 4-$MeOC_6H_4B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, dioxane–H_2O, reflux; ii) 4-$MeC_6H_4B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, dioxane–H_2O, reflux.



36 **76** **77**

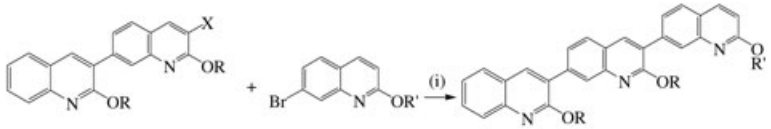
6,4-arylaminoquinolines [72]. The 4-chloro-6-(bromo/iodo) quinolines **36** were also subjected to successive replacement of the two halogen atoms *via* Suzuki cross-coupling to afford the Csp^2–Csp^2 cross-coupled products **76** and **77**, respectively (Scheme 29) [73, 74]. The second arylboronic acid was in this case added to the reaction mixture after completion of the first step (tlc monitoring) without isolating the incipient 6-substituted derivative **76**.

Quinolinylboronic acids **78** [X = $B(OH)_2$] derived from dimeric quinolines (X = H) prepared in turn, *via* palladium-catalyzed Suzuki cross-coupling reaction of 2-alkoxyquinoline-3-boronic acids with 2-alkoxy-7-bromoquinolines under microwave irradiation were subjected to further cross-coupling with 2-alkoxy-7-bromoquinolines **79** to afford the corresponding trimeric quinoline derivatives **80** (Scheme 30) [75]. The dimeric quinolines **78** (X = H) were tested for *in vitro* antiprolific activity toward a human fibroblast primary culture and two human solid cancer cell lines (MCF-7 and PA 1).

Wolf and Ekoue-Kovi extended the use of palladium–phosphinous acid complexes to Suzuki cross-coupling reaction [76]. The authors subjected 4-chloroquinolines to POPd [$(t\text{-Bu})_2P(OH)]_2PdCl_2$-catalyzed cross-coupling with arylboronic acids using Cs_2CO_3 as a base in 1,4-dioxane at 100°C to afford the corresponding aryl substituted quinolines in high yield (74–99%). The key advantage of the Suzuki reaction is the high tolerance to most functional groups, the mild conditions under which the reaction is conducted, the relative stability of boronic acids/esters to heat and water, the ease of handling and separation of boron-containing byproducts, and their abundant commercial availability.

3.6. Heck cross-coupling reaction. The Heck reaction which involves Pd-catalyzed [$Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, or $Pd(OAc)_2$] carbon–carbon bond formation through inter- or intramolecular cross-coupling reaction between organohalides or triflates with alkenes is a powerful tool for the construction of alkenyl- and aryl-substituted alkenes. Palladium-catalyzed Heck reaction of 2-chloro- or 3-bromoquinolines and their 8-triflate analog with *n*-butyl vinyl ether (CH_2=CHOBu) using a $Pd(dba)_2$–dppp mixture and thallium acetate (TlOAc) as a base in DMF at 80°C afforded the corresponding 2-acetyl- (68%), 3-acetyl- (81%), and 8-acetylquinoline (68%) in better yields than Stille reaction of the same substrates with (1-ethoxyvinyl)tri(*n*-butyl)stannane [30]. 3-Bromoquinoline was previously coupled with *n*-butyl acrylate, styrene,

Scheme 30. Suzuki cross-coupling under microwave conditions. Reagents and conditions: (i) $PdCl_2(PPh_3)_2$, 2*M* Na_2CO_3, THF, μw, 15–30 min, 65°C.



78 (X=$B(OH)_2$) **79** **80(a)** R,R'=Me (52%)

(b) R,R'=Et (82%)

(c) R=Me, R'=Bu (77%)

vinylpyridine, and vinyl ether derivatives in the presence of 0.1–0.0001% $(\eta^3\text{-}C_3H_5PdCl)_2$/tedicyp [*cis*,*cis*,*cis*-tetrakis(diphenylphosphinomethyl)cyclopentane] complex in DMF using potassium carbonate as a base to afford the 3-substituted quinoline derivatives in 32–96% yield [77]. Benzimidazole–oxime palladium(II) complex and TBAB mixture in water was also used to couple 3-bromoquinoline with styrene under microwave condition to afford (*E*)-(styryl)quinoline in 87% yield [63]. Whereas the 4-chloroquinoline afforded the corresponding 4-acetylquinoline in 60% yield, this substrate was recovered unchanged under the Heck condition using *n*-butyl vinyl ether as coupling partner. $PdCl_2/2PPh_3$-catalyzed Heck coupling of 4-bromo-8-tosyloxyquinoline **81** and arylvinyl derivatives **82** in anhydrous DMF afforded the corresponding (*E*)-4-(2-arylvinyl)-8-tosyloxyquinolines **83** in high yield (Scheme 31) [78]. The aluminum complexes derived from the corresponding (*E*)-4-(2-arylvinyl)-8-hydroxyquinolines were also found to exhibit photoluminescence properties [78].

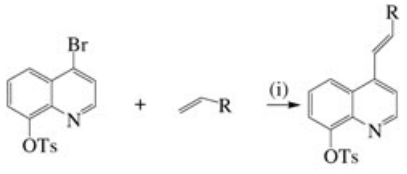
Arcardi *et al.* prepared the (*Z*)-methyl 2-acetamido-3-(2-(4-chlorophenyl)quinolin-4-yl)acrylate **86** (50%) *via* Pd-catalyzed intermolecular reaction of 4-iodo-2-(4′-chlorophenyl)quinoline **84** with α-acetamidoacrylate **85** (Scheme 32) [54].

Highly active palladium–phosphinous catalysts: POPd, POPd1, and POPd2 have also been used in Heck additions of various 2-substituted 4-chloroquinolines **87** to *tert*-butyl acrylate **88** and the reaction was found to proceed with high distereoselectivity (*E*/*Z* > 25:1) to afford quinolylacrylates **89** in high yields (Scheme 33) [60]. The use of other bases such as NaOAc, Cs_2CO_3, and *t*-BuOK/*t*-BuOH led to relatively lower yields or required prolonged reaction times. Whereas chromatographic separation of Cy_2NMe from quinolylacrylates proved to be difficult; in some cases, inorganic bases were found to facilitate product purification.

Styrylquinoline derivatives bearing a carboxyl group either directly bound to the quinoline ring or through an ethylenic space were previously prepared *via* the Heck reaction and were found to inhibit HIV-1 replication [2]. 4-(2-Methylphenylamino)-3-iodoquinoline **90** was subjected to standard Heck reaction conditions in the presence of terminal alkenes **91** to afford 3-vinylquinolines **92** which exhibit gastric H^+/K^+-ATPase inhibitory activity (Scheme 34) [79].

The Heck reaction of 8-bromoquinoline with acrolein or acrolein diethyl using $Pd(OAc)_2$, tetrabutylammonium acetate ($n\text{-}Bu_4NOAc$), K_2CO_3, and KCl in DMF at 90°C afforded the expected aldehyde derivative in 50% yield together with dehalogenated quinoline (8%) [80].

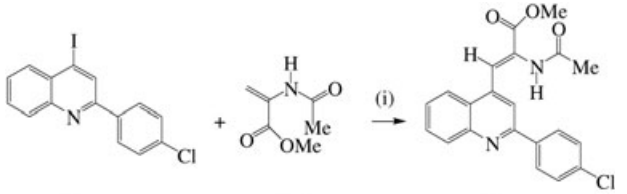
Scheme 31. Heck coupling of 4-bromo-8-tosyloxyquinoline with arylvinyl derivatives. Reagents and conditions: (i) $PdCl_2/2PPh_3$, K_2CO_3, DMF, 130°C.



81 **82** **83**

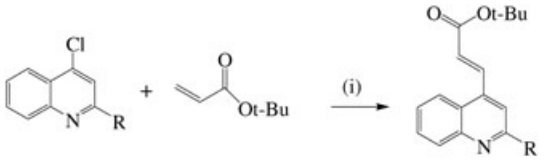
	R	% Yield
83a	-C_6H_5	70
83b	4-$MeOC_6H_4$-	69
83c	4-NCC_6H_4-	83
83d	4-MeC_6H_4-	67
83e	4-ClC_6H_4-	70
83f	4-pyridyl	98
83g	4-pyridyl	90
83h	2,4,6-$(MeO)C_6H_2$-	86

Scheme 32. Pd-catalyzed coupling of 4-iodoquinoline with α-acetamidoacrylate. Reagents and conditions: (i) AcOK, $Pd(OAc)_2$, DMF, heat, 60°C.



84 **85** **86**

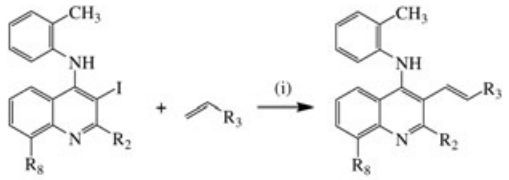
Scheme 33. Heck coupling of 2-substituted 4-chloroquinolines. Reagents and conditions: (i) POPd, *tert*-butyl acrylate, Cy_2NMe, DMF, 135°C, 24 h.



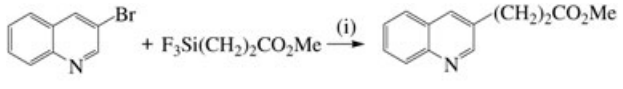
87 **88** **89**

	R	% Yield
89a	H	85
89b	Me	75
89c	*n*-Bu	70
89d	*t*-Bu	66
89e	Ph	72

Scheme 34. Heck coupling of 4-(2-methylphenylamino)-3-iodoquinoline with terminal alkenes. Reagents and conditions: (i) $Pd(OAc)_2$, $(n\text{-}Bu)_4NCl$, KOAc, DMF, 100°C, 2 h.



Scheme 35. Hiyama coupling of 3-bromoquinoline with alkyltrifluorosilane. Reagents and conditions: (i) 5% $Pd(PPh_3)_4$, $n\text{-}Bu_4NF$, THF, 100°C, 8 h.



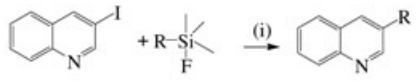
3.7. Application of Hiyama coupling in the synthesis of substituted quinolines. Palladium-catalyzed cross-coupling of organosilanes with aryl/vinyl halides or triflates, commonly referred to as the Hiyama reaction is promoted by activation of C-Si bond through formation of a pentacoordinated silicate with nucleophiles such as F^- or HO^- [81]. Transmetalation of the polarized C-Si bond becomes more facile and the cross-coupling, in turn, proceeds smoothly. Mahsuhashi *et al.* reported the coupling reaction of 3-bromoquinoline **93** with functionalized alkyltrifluorosilane **94** in the presence of $Pd(PPh_3)_4$ catalyst and tetrabutylammonium fluoride (TBAF; $n\text{-}Bu_4NF$) in THF to afford methyl 3-(quinolin-3-yl)propanoate **95** in 65% yield (Scheme 35) [82].

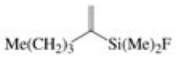
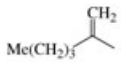
3-Iodoquinoline **96** was coupled with organofluorosilicon compounds **97** using $(\eta^3\text{-}C_3H_5PdCl)_2$ in DMF or THF in the presence of KF, TBAF or tris(diethylamino)sulfonium difluorotrimethylsilicate (TASF) to afford methyl, alkenyl, and phenyl substituted quinoline derivatives **98** (Scheme 36) [83].

Palladium-catalyzed Hiyama coupling of 2-cyclopropyl-3-iodo-4(4-fluorophenyl)quinoline **99** with vinylsilane **100** in THF in the presence of TBAF afforded a trisubstituted quinoline derivative **101** (83%), which is a HMG-CoA reductase inhibitor (Scheme 37) [84]. Deprotection and lactonization of **101** with trifluoroacetic acid (3 equiv) in dichloromethane afforded **5** (NK-104) [85], a highly potent HMG-CoA reductase inhibitor [6].

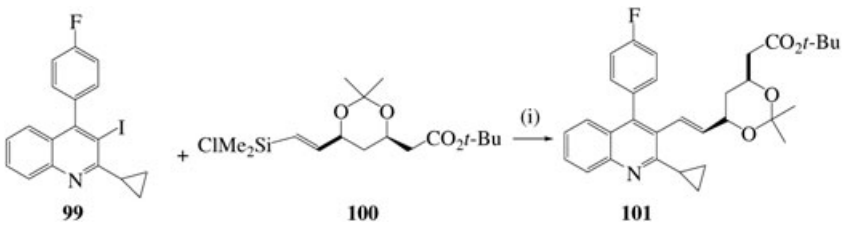
The Hiyama coupling reaction is an attractive alternative to the palladium-catalyzed cross-coupling reactions by organoboron, organotin, and organozinc, because organosilicon compounds are nontoxic and relatively easy to prepare. Moreover, the reaction conditions tolerate functional groups in comparison with strong nucleophilic Grignard

Scheme 36. Pd-catalyzed cross-coupling of organofluorosilicon compounds with 3-iodoquinoline. Reagents and conditions: (i) **97** (3 equiv), $(\eta^3\text{-}C_3H_5PdCl)_2$, fluoride salt, solvent, heat.



	Fluoride salt	Organofluorosilicon (**97**)	Solvent	R	% Yield
98a	KF (2 equiv.)	$PhSi(Et)F_2$	DMF	$-C_6H_5$	68
98b	TBAF (1.5 equiv.)	$(E)\text{-}PhCH{=}CHSi(Me)_2F$	THF	PhCH=CH-	84
98c	TASF (1 equiv.)	$(Et_2N)_3S.Me_3SiF_2$	DMF	$-CH_3$	66
98d	TASF ((1 equiv.)		DMF		64

Scheme 37. Palladium-catalyzed Hiyama coupling of **99** with vinylsilane derivative. Reagents and conditions: (i) TBAF, $[(allyl)PdCl_2]$, THF, 60°C, 30 min.



reagents. The Hiyama reaction is also effective to promote Csp^2–Csp^3 bond formation to yield alkyl substituted quinoline derivatives.

4. CONCLUSIONS AND PERSPECTIVE

The high reactivity of the aryl-iodo bond toward oxidative addition with palladium cross-coupling reactions has been found to allow successive substitution of the halogen atoms (I > Br > Cl >> F) in dihaloquinolines to afford variously substituted quinoline derivatives. The high reactivity at C-2 versus C-4 is attributed to the increased positive character of the α-carbon due to the electron-withdrawing effect of the adjacent nitrogen of the quinoline ring and its coordination to palladium. Despite the successes in sequential metal-catalyzed halogen substitution reactions, the development of versatile and efficient methods for the synthesis of polysubstituted quinolines from dihaloquinolines in a single operation remains a challenge in organic synthesis. The choice of suitable catalyst and/or catalyst/ligand mixture would enable the preparation of polysubstituted quinolines from activated dihaloquinolines in a single operation. Given the need for efficient methods for the incorporation of heterocyclic moieties in pharmaceutical compounds, it can be expected that continued growth and exciting new advances will continue in this important subdomain of metal-catalyzed cross-coupling research. The following points should be considered when preparing substituted quinoline derivatives *via* palladium-catalyzed cross-coupling reaction.

- Analysis of the substrates toward oxidative addition (nonactivated versus activated systems) and substituent effects (*viz.*, electron-donating and/or electron-withdrawing groups, steric bulk, leaving group, *etc.*).
- Selection of reaction type: Kumada (Mg), Negishi (Zn), Suzuki (B), Stille (Sn), and Hiyama (Si).
- Palladium catalyst: $Pd(PPh_3)_4$, $Pd(OAc)_2$, $PdCl_2(CH_3CN)_2$, Pd-$(dba)_2$, *etc.*
- Ligands: free, monodentate (PPh_3 and PR_3), and bidentate (dppf and binap).
- Base: strong/weak base, organic, or inorganic base.
- Solvent: solubility and solvent effects (stability and reactivity).
- Additives (cocatalyst): salt-effects (LiCl, $ZnCl_2$, and CuI).
- Reaction conditions: inert atmosphere and temperature.
- Workup: purification of the product, catalyst recycling, and waste disposal.

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