TRANSITION-METAL-CATALYZED REACTIONS STARTING FROM 2,3-SUBSTITUTEDQUINOLINE DERIVATIVES

DOI: http://dx.medra.org/10.17374/targets.2021.24.1

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Abstract. *This chapter provides an overview of transition-metals catalyzed reactions involving 2,3-substitutedquinolines as starting materials.*

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1. Introduction

Quinoline derivatives are an important class of azaheterocycles found in numerous natural products and with a broad range of applications in drug discovery, materials, and catalysis.

Quinoline was first isolated from coal. In 1820, quinine, the first natural quinoline derivative, was isolated from the bark of the *Cinchona* tree as the active principle of the plant, which has been used for the treatment of malaria since pre-Colombian times. Other quinolines having various activities were subsequently isolated from different plant species. Therefore, the synthesis of quinolines and the generation of chemical libraries of these heterocycles has been the object of a great deal of research, and has led to the development of various new synthetic strategies.[1-4]

In this context, versatile starting materials that can provide rapid access to a diversity of end-products would be very useful. During the past three decades, 2-chloroquinoline-3-carboxaldehydes and their analogues, readily available by the Meth-Cohn method, have established themselves as such building blocks.[5-7]

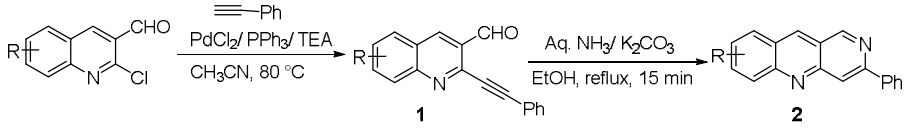
On the other hand, the past 50 years have also witnessed the emergence of transition metals as catalysts, which has enabled tremendous advances in organic chemistry, especially in the synthesis of complex molecules.[8-10]

This review focuses on the synthesis of quinoline derivatives through transition-metal catalyzed reactions that utilize 2-chloroquinoline-3-carboxaldehydes and others 2,3-substitutedquinolines as starting materials.

2. Intramolecular cyclization

The intramolecular hydroamination, hydroalkoxylation, hydroarylation, hydrothiolation and hydroselenation of 2-alkynylquinolines is a popular synthetic strategy used widely in the construction of target molecules.

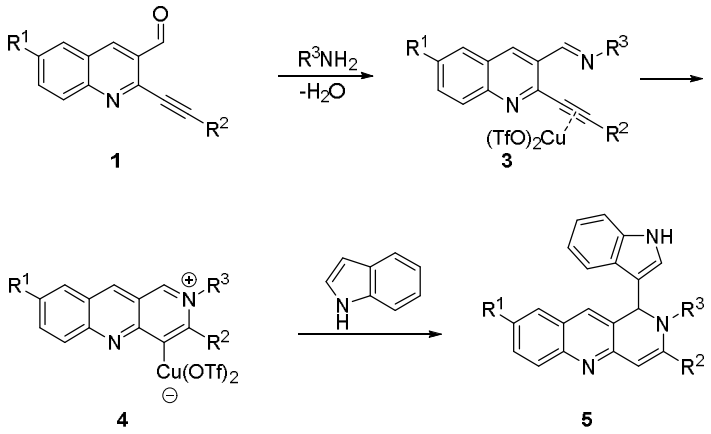
Singh and co-workers reported a route to 2-penylbenzo[*b*][1,6]naphthyridines **2** *via* the spontaneous cyclization of presumed imines arising upon treatment of 2-alkynylquinoline-3-carboxaldehydes **1** with aqueous ammonia (Scheme 1).[11] Substrates **1** were prepared by an efficient, copper-free Sonogashira coupling of 2-chloroquinolines with phenyl acetylene, and products **2** were obtained in excellent yield.



Scheme 1

The same group also described an efficient synthesis of 1-alkoxy, -amino, or -thio-benzo[*b*][1,6]naphthyridines by the annulation of 2-alkynylquinoline-3-carbonitriles in the presence of $Pd(OAc)_2$ respectively in alcohols, thiols or amines.[12,13]

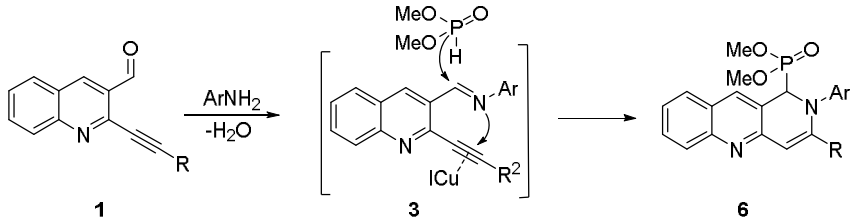
Prakash and Nagarajan described a convenient synthesis of indol-3-yl-benzo[b][1,6]naphthyridines **5** in moderate to excellent yields *via* the heteroannulation reaction shown in Scheme 2. The proposed mechanism for the overall transformation involves an initial condensation of aldehyde **1** with an amine, followed by copper(II) triflate-catalyzed cyclization of the resulting imines **3** to **4**. Finally, nucleophilic addition of indole to pyridinium **4** generated the benzonaphthyridines **5**.[14]



Scheme 2

In 2012, Čikotienė and Bukšnaitienė reported the possibility of tandem 5-exo-dig cyclization reactions of *ortho*-alkynylaryl aldehydes with dimethyl phosphite in basic media.[15]

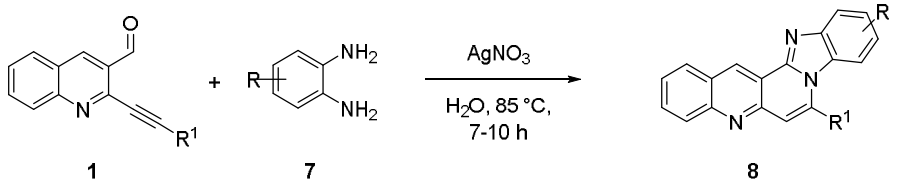
Interestingly, three-component reaction of 2-alkynylquinoline-3-carboxaldehydes, dimethylphosphite and aniline derivatives in the presence of CuI generated dimethyl 2-aryl-1,2-dihydrobenzo[*b*][1,6]naphthyridin-1-ylphosphonates **6** (Scheme 3). The proposed reaction mechanism involves an initial formation of imine **3**, followed by nucleophilic addition of dimethylphosphite to imine **3**. Finally, addition of nitrogen to the alkyne moiety activated by CuI affords the product **6**.[16]



Scheme 3

In a similar manner, Bukšnaitienė and Čikotienė achieved the synthesis of 1-trichloromethyl-1,2-dihydrobenzo[*b*][1,6]naphthyridines.[17]

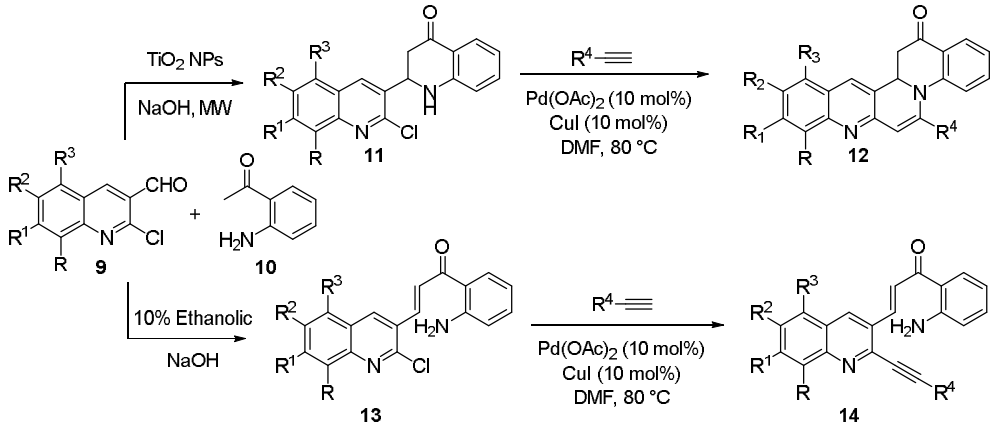
In 2012, Verma and co-workers described Ag(I)-catalyzed regioselective construction of benzimidazo[2,1-*a*]naphthyridines **8** in water (Scheme 4).[18]



1 **7** **8**

Scheme 4

Kumar and Khan reported a method for the synthesis of 2-chloroquinolinyl-4-quinolinones **11** *via* Knoevenagel condensation/aza-Michael addition between 2-chloro-3-formylquinoline **9** and 2-aminoacetophenone using NaOH in the presence of TiO_2 nanoparticles (Scheme 5). Sonogashira coupling of **11** with terminal alkynes took place with simultaneous cyclization of the product to 1,6-naphthyridines **12**. Notably, 2-chloro-3-formylquinoline **9** and 2-aminoacetophenone in basic ethanol yielded 2-aminochalcones **13**. The latter reacted with phenylacetylene in the presence of Pd to give C2-alkynylated product **14**.[19]



9 **10** **11** **12** **13** **14**

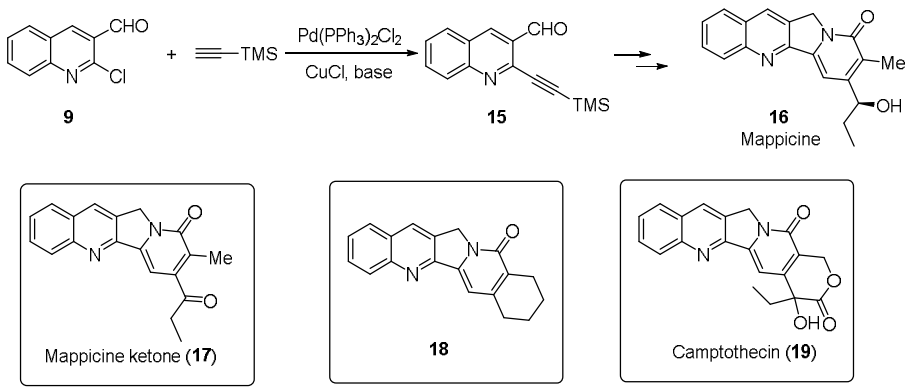
Scheme 5

In 2000, Toyota *et al.* established a six-step formal total synthesis of the natural alkaloid mappicine **16** (Scheme 6). The process was begun with Sonogashira coupling reaction of 2-chloro-3-formylquinoline and trimethylsilylacetylene in excellent yield.[20] At the same time, Greene reported the synthesis of mappicine ketone **17**, which possesses strong selective activity against the herpes viruses HSV-1 and HSV-2.[21] In 1997, a novel pathway has been described by Rigby and Danca for the synthesis of pentacyclic product **18** (camptothecin derivative) utilizing vinyl isocyanate-enamine cyclocondensation as the key synthetic step.[22]

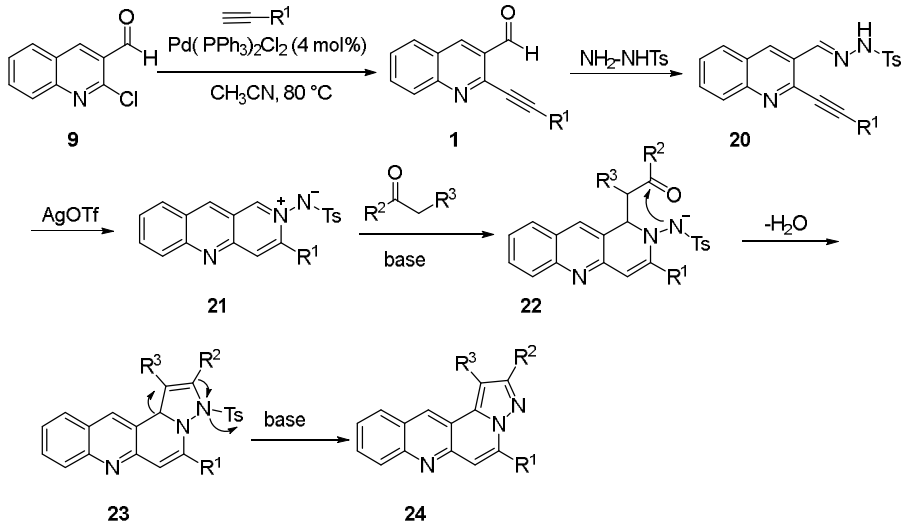
Synthesis of camptothecin **19** through three- and four-component domino Knoevenagel/hetero-Diels-Alder reactions has been reported by Tietze *et al.*[23] In addition, 2-chloroquinoline derivatives are widely used in the synthesis of camptothecin and its derivatives.[24-28]

2-Alkynyl-3-formylquinolines **1**, available from Sonogashira reaction of 2-chloro-3-formylquinoline **9** and alkynes, reacted with tosylhydrazine and carbonyl compounds in the presence of silver triflate to form benzo[*b*]pyrazolo[5,1-*f*][1,6]naphthyridines **24** in moderate to good yield (Scheme 7). The reaction begins

with the formation of hydrazone **20**, followed by generation of zwitterionic intermediate **21** in the presence of AgOTf. This intermediate give rise to the final product **24** in three steps.[29]



Scheme 6



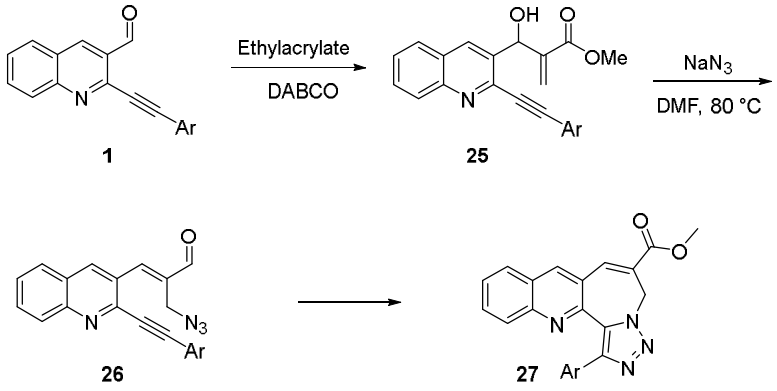
Scheme 7

The formation of 1,2,3-triazoloquinolines **27** using intramolecular Huisgen azide-alkyne [3+2]-cycloaddition was disclosed by Saravanan *et al.* (Scheme 8).[30] Baylis-Hillman reaction of **1** with ethyl acrylate leading to **25** is the key step in this process. Subsequent reaction of **25** reacted with NaN_3 in DMF at 80 °C yielded triazoloquinolines **27**. This group also investigated antifungal activity of latter compounds.

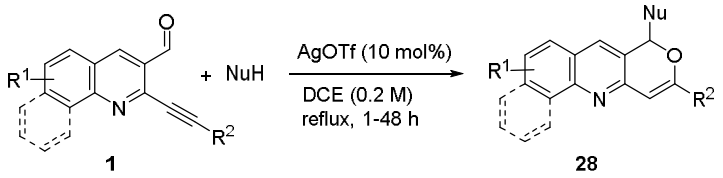
Application of silver catalysis in the construction of (hetero)arylpyranoquinolines **28** was developed by Michelet *et al.* (Scheme 9).[31] AgOTf catalyzed domino hydroarylation/cycloisomerization reactions of 2-alkynylquinoline-3-carbaldehydes **1** with heteroarenes such as *N*-methylindole, indole, and 2-methylindole afforded pyranoquinolines **28** in moderate to good yields. The reaction also worked well with other nucleophiles such as pyrroles, 1,3,5-trimethoxybenzene and 3-methylbenzofuran.

An efficient method for the synthesis of 1-alkoxy-4-iodopyrano[4,3-*b*]quinolones **29** through intramolecular electrophilic cyclization of 2-alkynylquinoline-3-carboxaldehydes in the presence of NIS

reagent has been described by Singh *et al.* (Scheme 10).[32] This method features wide substrate scope, high yields, and short reaction time. Notably, when the reaction was performed using NBS as electrophile, the products **30** and **31** were obtained.



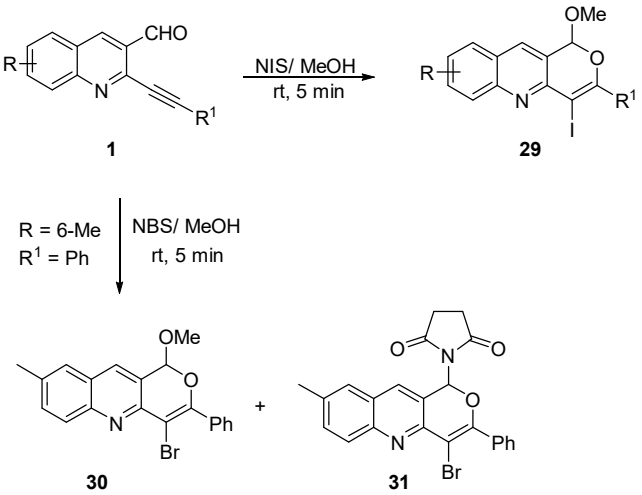
Scheme 8



R^1= H, OMe, Cl R^2= aryl, alkyl

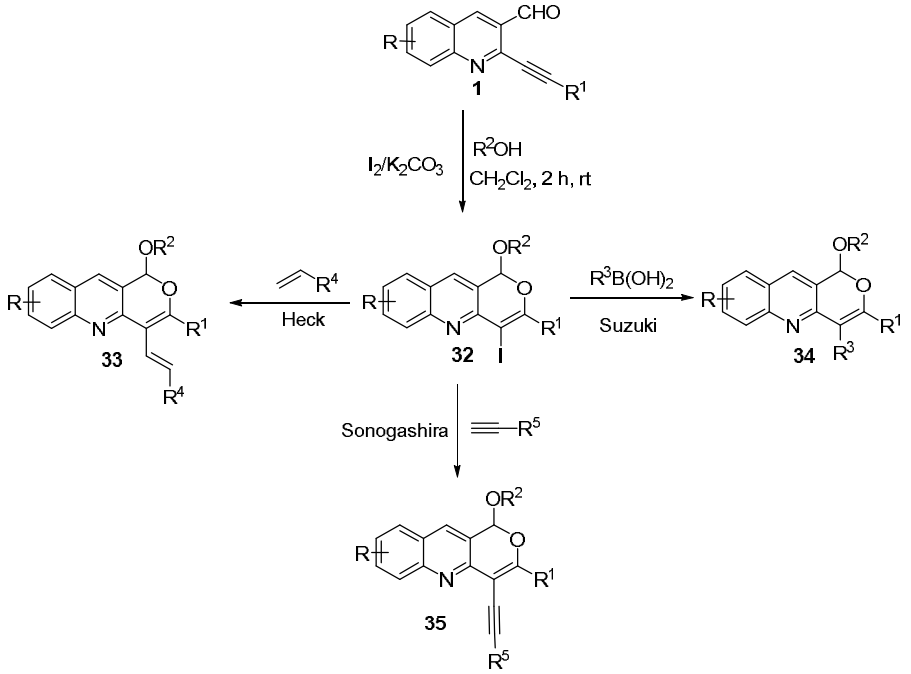
NuH = *N*-methylindole, indole, 2-methylindole, pyrroles, benzofuran,1,3,5-trimethoxybenzene

Scheme 9



Scheme 10

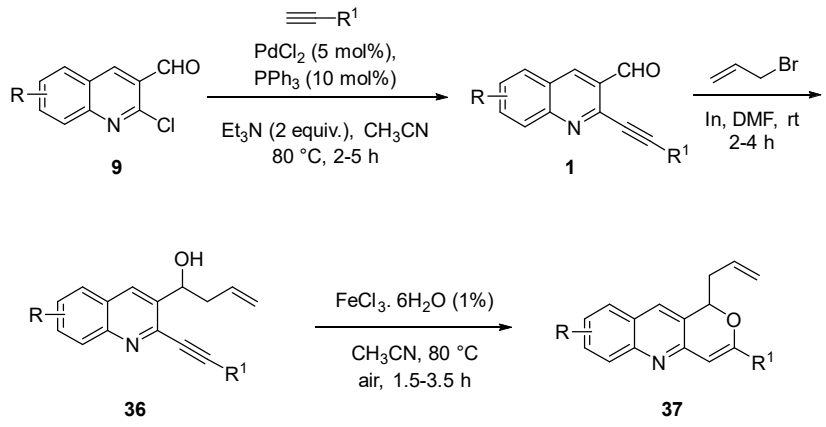
In 2011, Verma and co-workers reported the synthesis of 4-iodopyrano[4,3-*b*]quinolines **32** under mild conditions by electrophilic iodocyclization of 2-alkynylquinoline-3-carboxaldehydes **1** using I_2 and alcohols (Scheme 11).[13,33] Iodo compounds **32** extended efficiently to more complex molecules **33-35** using Heck, Sonogashira and Suzuki reactions.



Scheme 11

Silver(I) salt-dependent reaction of 2-alkynylquinoline-3-carbaldehydes and alcohols selectively leading to furoquinoline or pyranoquinoline has been reported by Godet *et al*.[34]

Singh *et al.* described the synthesis of pyrano[4,3-*b*]quinoline derivatives **37** (Scheme 12).

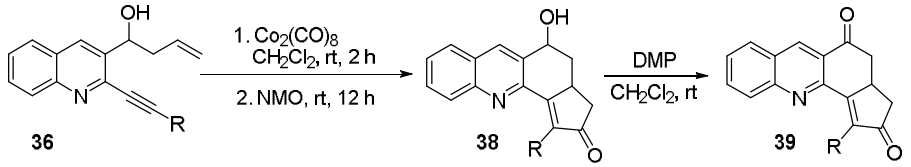


Scheme 12

Allyl-3-(2-arylalkynylquinolinyl)methanol **36** was prepared in two steps by copper-free Sonogashira coupling of 2-chloroquinoline-3-carbaldehydes with terminal alkynes followed by Barbier reaction with allylbromide in the presence of indium. The action of $FeCl_3{\cdot}6H_2O$ upon **36** triggered 6-*endo-dig* addition of the -OH onto the alkyne, leading to product **37**.[35] Primary and tertiary alcohols of general type **37** also afforded the corresponding pyrano[4,3-*b*]quinolines in good to high yields (Scheme 12).

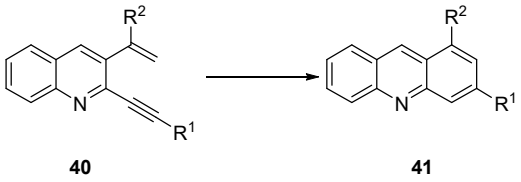
A series of pyrano[4,3-*b*]quinolin-1-ones have been synthesized in excellent yields *via* intramolecular cyclization of methyl 2-arylethynylquinoline-3-carboxylates in basic methanol.[36]

The synthesis of tetrahydrocyclopenta[*c*]acridine **38** derivatives through Pauson-Khand reaction (PKR) of quinolines of the type **36** has been reported by Belmont and Patin. Oxidation of **38** with Dess-Martin periodinane (DMP) afforded tetrahydro-2*H*-cyclopenta[*c*]acridine-2,5-dione **39** in 43-98% yields (Scheme 13).[37]



Scheme 13

Substituted acridines **41**, R^2=OTBS, were obtained *via* a 6-*endo-dig* cyclization (benzannulation) of silyl enol ethers **40**, R^2=OTBS, catalyzed by a rhodium(I) complex.[38] Similarly, 1-amino-acridines **41**, R^2=NR_2, emerged upon $PtCl_2$-promoted aminobenzannulation of enamines **40**, R^2=NR_2, prepared *in situ* by condensation of 2-alkenyl-3-acetylquinolines with secondary amine (Scheme 14).[39]



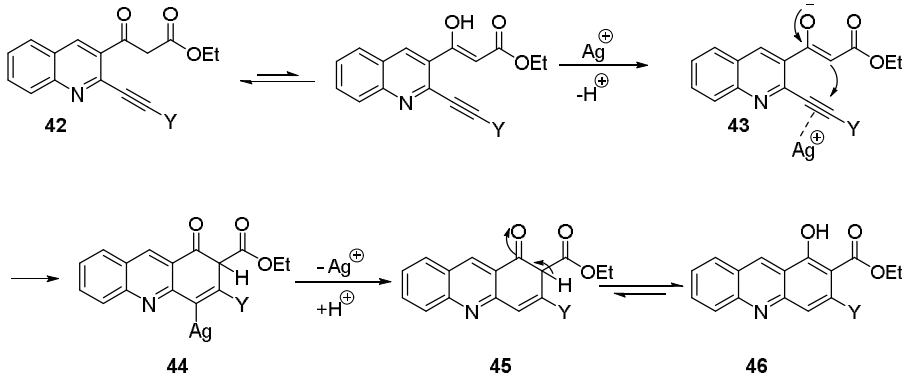
R^2 = OTBS, cat = $[Rh(CO)Cl]_2$
R^2 = NR_2, cat = $PtCl_2$

Scheme 14

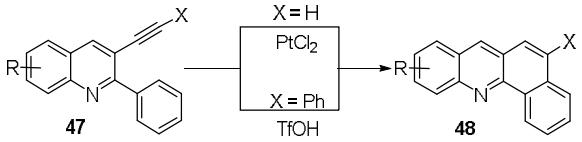
An efficient cyclization of ethyl 3-oxo-3-(2-arylethynyl)quinolin-3-yl)propanoate **42** to 3-aryl/alkylacridinol-2-carboxylates derivatives **46**, in the presence of Ag(OTf) as a catalyst at room temperature has been reported by Verma and co-workers (Scheme 15).[40] Deuterium labeling experiments led the authors to suggest the mechanism outlined in Scheme 15 for this transformation.

Kuznetsov and co-workers described a method for the preparation of benzo[*c*]acridines **48** *via* cycloisomerization of 3-alkynyl-2-arylquinolines **47** in 58-96% yields (Scheme 16).[41] Notably, cyclization of the starting **47**, X=H, took place at 120 °C when $PtCl_2$ was employed as the catalyst, but the cyclization of **47**, X=Ph, occurred at room temperature in the presence of trifluoromethansulfonic acid (TfOH).

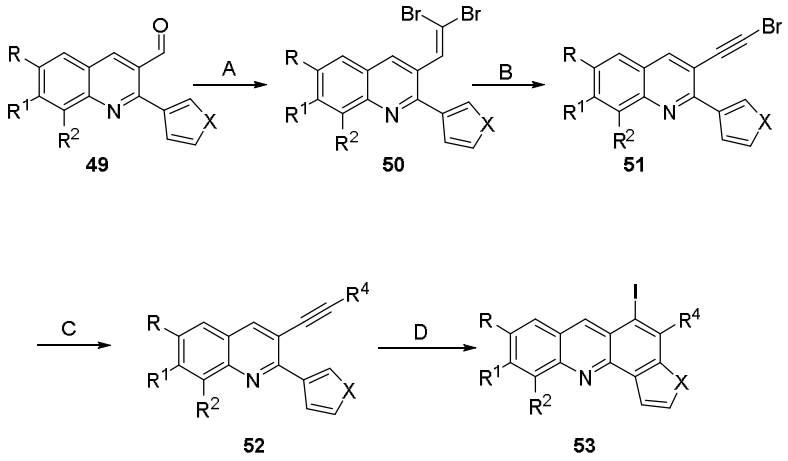
2-(Thiophen-3-yl)/(furan-3-yl)-3-carbaldehydes **49** were converted into dibromo olefins **50** using Corey-Fuchs reaction. Basic treatment of **50** followed by cross coupling reaction with arylbornic acids in the presence of $Pd(PPh_3)_2Cl_2$ generated **52**.[42] Finally, thieno[2,3-*c*]acridine and furo[2,3-c]acridine derivatives **53** were obtained *via* intramolecular cyclization reaction of the triple bond (Scheme 17).



Scheme 15



Scheme 16

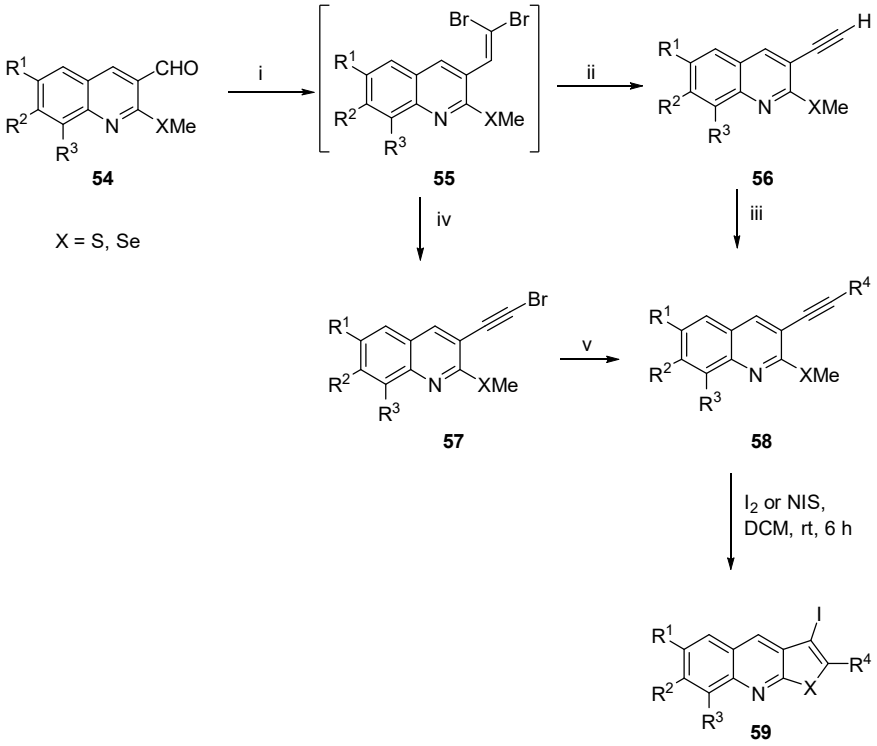


Scheme 17. Reaction conditions: (A) CBr_4, PPh_3, DCM, 0 °C, 1 h (B) DBU, DMSO, rt, 1 h (C) Phenylboronic acid, Na_2CO_3, $Pd(PPh_3)_2Cl_2$, DME, 90 °C; (D) I_2 (6 eq.), $NaHCO_3$, rt, ACN, 18 h.

Iodocyclization reaction of 3-alkynyl-2-(methylthio or seleno)quinolines **56**, **57** and **58** afforded thieno- or selenopheno[2,3-*b*]quinoline derivatives **59**, which are good substrates for Suzuki, Sonogashira and Heck reactions (Scheme 18).[43] The mechanism of the reaction has been studied by DFT methods.

Pyrrolo[3,4-*c*]quinolines **63** have been prepared in moderate yields by reaction of 2-phenylquinoline-3-carbaldehyde derivatives and sarcosine (Scheme 19). The reaction is likely to proceed *via* 1,5-dipolar electrocyclization of azomethine ylides **61**. Indeed, the reaction in the presence of

N-phenylmaleimide afforded two isomeric cycloadducts **64** and **65** (ratio 1:5) in good yield. Also, this approach was successfully employed in the synthesis of 2-methyl-2,4,5,9*b*-tetrahydro-1*H*-pyrrolo[3,4-*c*]-quinolin-4-ones from 2-chloro-3-formylquinolines.[44,45]



Scheme 18. (i) CBr_4, PPh_3, DCM, 0 °C, 1 h; (ii) *n*-BuLi, -78 °C, Et_2O, 1 h; (iii) aryl iodide, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, THF, rt, 12 h; or phenylboronic acid, Na_2CO_3, $Pd(PPh_3)_2Cl_2$, DME, 90 °C; (iv) DBU, DMSO, 1 h; (v) phenylacetylene, CuI, $Pd(PPh_3)_2Cl_2$, Et_3N, PPh_3, 70 °C, 5 h.

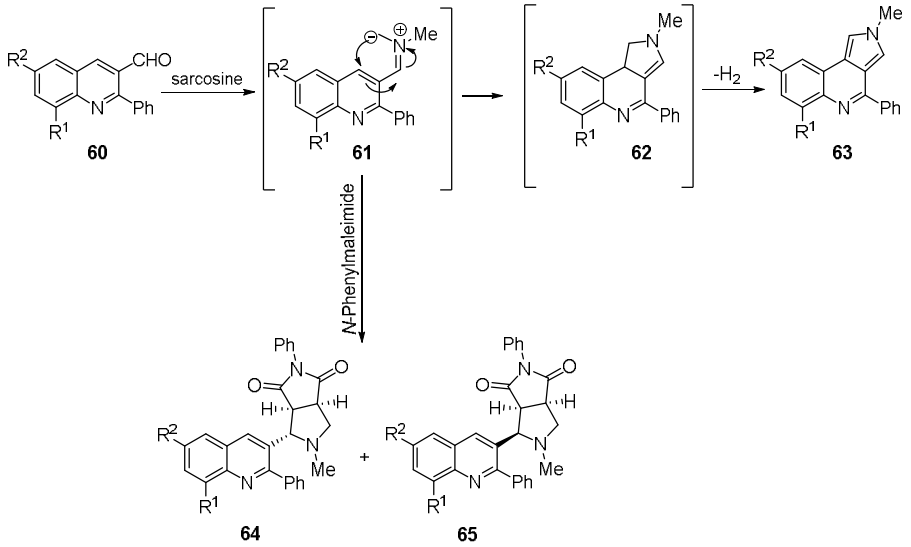
3. Arylation

Three-component domino reaction of 2-chloro-3-formylquinolines, acetophenones and boronic acid derivatives in the presence of $PdCl_2(PPh_3)_2$ led to the highly functionalized quinolines **66** (Scheme 20).[46] The proposed mechanism involves three steps: aldol condensation between 2-chloro-3-formylquinolines and acetophenones, Michael addition of a second molecule of acetophenone to the aldol product, and Suzuki coupling reaction with the boronic acid in the presence of Pd to give the desired product **66**.

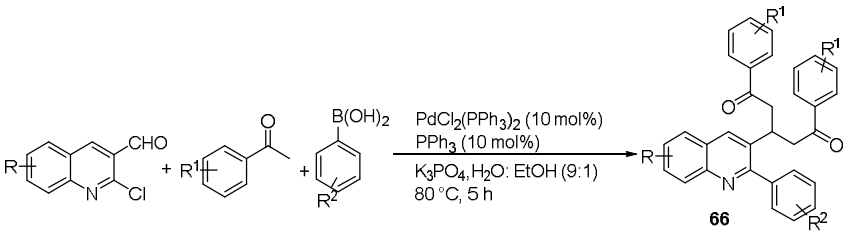
Plenio and his group found that Suzuki-Miyaura arylation of 2-chloroquinolines with arylboronic acids may also be achieved by the use of water tolerant catalytic systems such as $NaPdCl_4$ in the presence of ligand **67**,[47,48] as well as **68**[49] (Figure 1).

Arylation of methyl 2-chloroquinoline-3-carboxylate may be achieved with aryl metal reagents (Mg, Li) in the presence of $CoCl_2/Ti(OEt)_4$.[50] Haloquinoline carbaldehyde derivatives **69** undergo reductive dimerization by treatment with $NiCl_2.6H_2O/Zn/PPh_3$ (Scheme 21). The catalytic active species is $Ni[(PPh_3)]_4$, which is generated *in situ* by reaction of $NiCl_2.6H_2O$ with zinc dust and PPh_3.[51]

Polycyclic compound **76** has been efficiently obtained in three steps: Suzuki arylation of 2-cholorquinolin-3-ol with 5-chloro-2-fluorophenylboronic acid, cyclization of the emrging **73** to **74**, and further Suzuki coupling of the latter with **75** to afford **76** (Scheme 22).[52] Benzofuroquinoline **76** is of interest as organic light emitting diode.



Scheme 19



Scheme 20

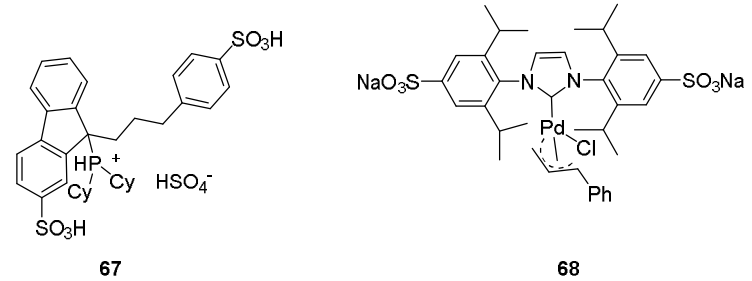
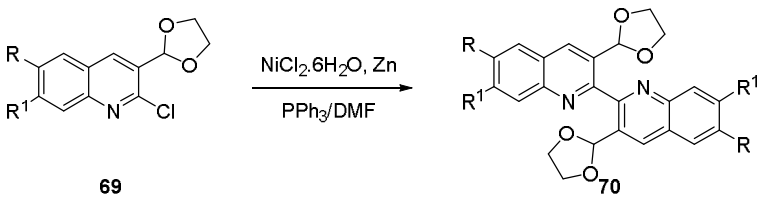
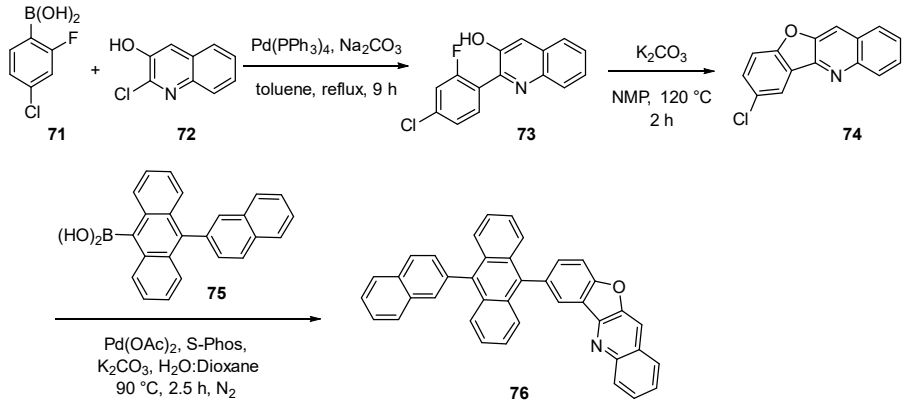


Figure 1

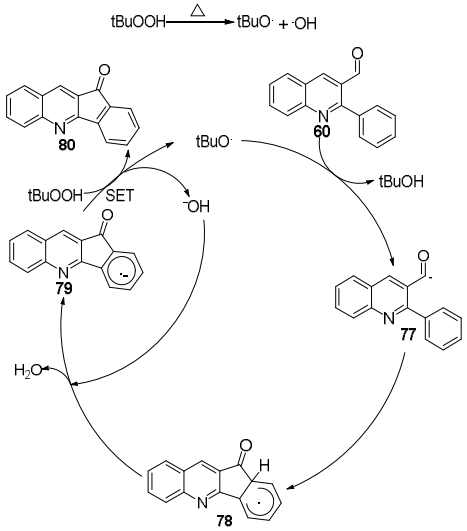


Scheme 21



Scheme 22

tert-Butyl hydroperoxide (TBHP) promoted the intramolecular cross-dehydrogenative coupling (CDC) reaction of 2-arylquinolinyl-3-carboxaldehyde **60** to indenoquinolinones **80** in good to excellent yield (Scheme 23).[53] In addition, 11*H*-indeno[1,2-*b*]quinolin-11-one showed good antibacterial activity. Since none of product **80** was detected in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as radical scavenger, the authors proposed a radical mechanism outlined in Scheme 23. First, aryl carbonyl radical **77** is generated *via* hydrogen atom transfer from the aldeyde to *t*-BuO$^{\bullet}$. Next, radical **77** adds underwent to the *ortho*-position of the phenyl ring to give radical **78**. Subsequently, deprotonation of **78** yields radical anion **79**, which undergoes single-electron transfer (SET) to intact TBHP gave **80**.

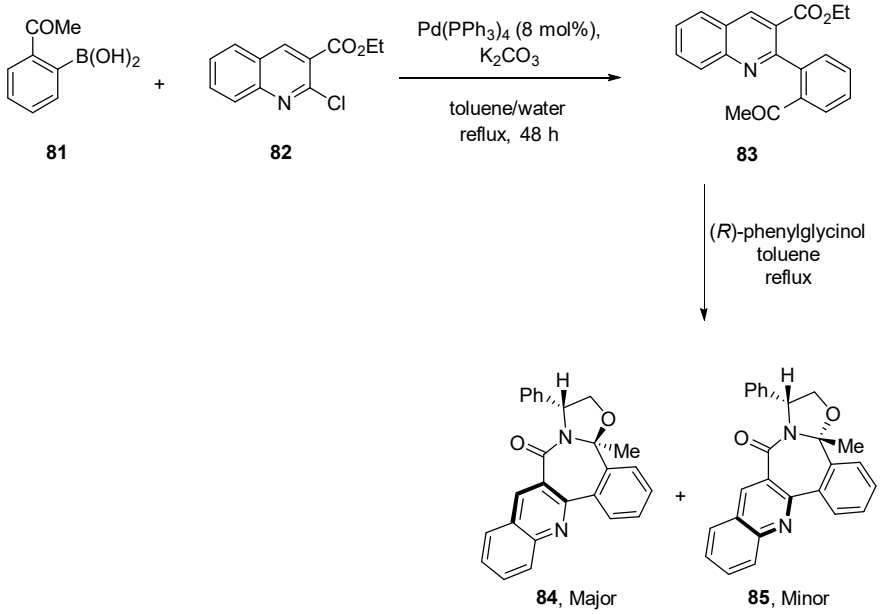


Scheme 23

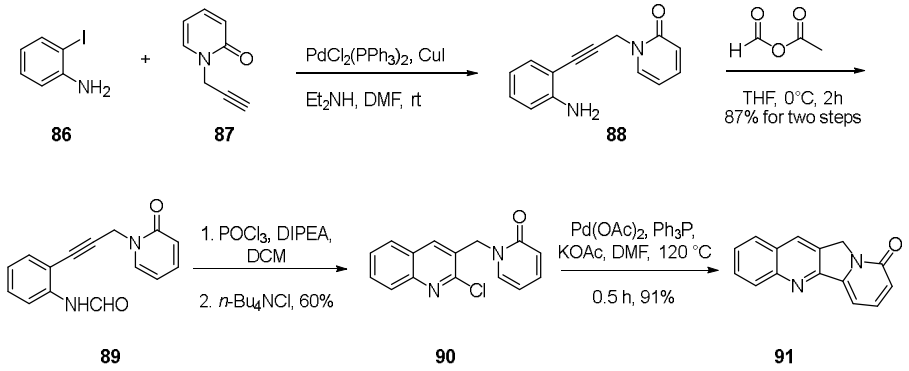
Levacher's group reported the Suzuki cross-coupling reaction of (2-acetylphenyl)boronic acid **81** and ethyl 2-chloroquinoline-3-carboxylate **82** for the preparation of biaryls **83** that employed as precursor in the construction of axially chiral 7,5-fused bicyclic lactams **84** and **85** (Scheme 24).[54]

Sonogashira coupling of *o*-iodoaniline **86** with *N*-propargylated-2-pyridinone **87** yielded **88**, which was advanced to formamide **89** in high yield.[55] Dehydration of **89** with $POCl_3$ produced the corresponding

isonitrile, which is unstable in high concentration, but that in the presence of tetrabutylammonium chloride was converted into 1-((2-chloroquinolin3-yl)methyl)pyridinone **90**. Intramolecular Heck reaction of **90** efficiently afforded quinoline **91**, the core structure of camptothecin (Scheme 25).



Scheme 24



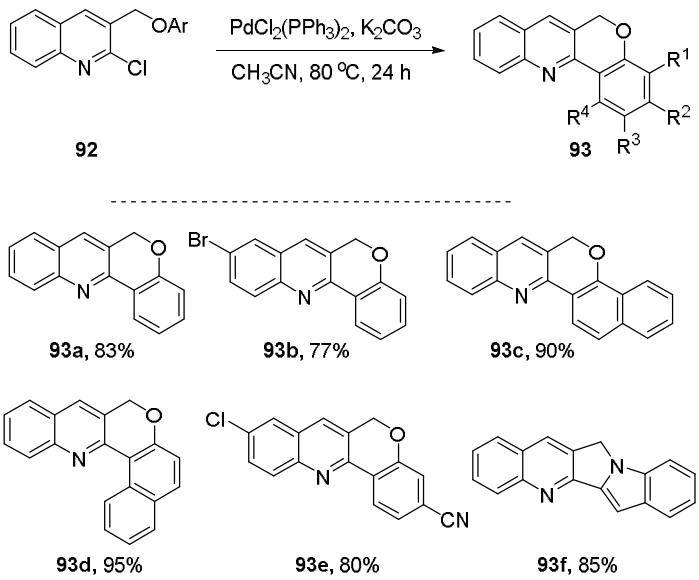
Scheme 25

Shiri *et al.* described a method for the synthesis of 6*H*-chromeno[4,3-*b*]quinolines **93** by intramolecular Heck reaction of 2-chloro-3-(phenoxymethyl) quinolines **92** (Scheme 26). A similar reaction of 2-chloro-3-(1-indolylmethyl) quinolines afforded products such as **93f**.[56]

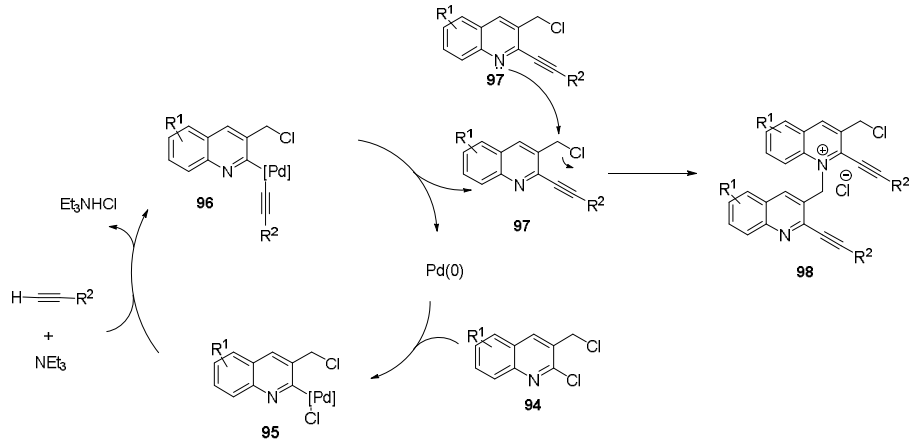
4. Alkynylation, alkenylation and carbonylation

2-Chloro-3-(chloromethyl)quinolines **94** reacted with terminal acetylenes in the presence of $PdCl_2/Ph_3P$ to form quinilnium salts **98** in good to high yield (Scheme 27).[57] Empirical evidence indicates

that compounds **98** arise *via* S_N2 dimerization of products **97**, resulting from an ordinary Sonogashira reaction of **94** with terminal alkyne.



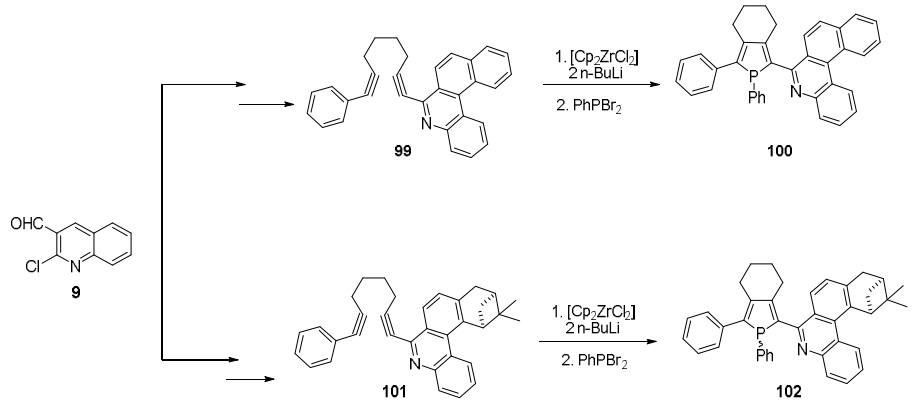
Scheme 26



Scheme 27

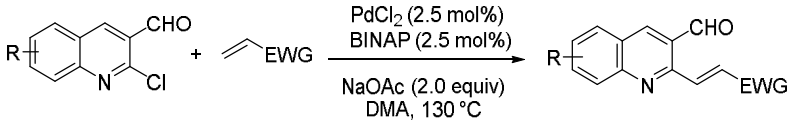
A series of novel biaryltriazoles was synthesizd and their inhibitory activities against tautomerase activity of human macrophage migration inhibitory factor (MIF) were evaluated.[58]

Aza[n]helicene phosphole derivatives **100** and **102** have been constructed respectively from aza[n]helicene diynes **99** and **101** by the Fagan-Nugent route (Scheme 28).[59] Their UV/Vis absorption and emission behaviour as well as their behaviour as P,N chelates towards coordination to Pd(II) and Cu(I) have been investigated.



Scheme 28

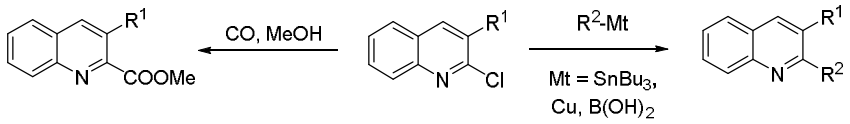
Singh and co-workers developed an efficient synthesis of methyl 3-(3-formylquinolin-2-yl) acrylates **103** through Heck reaction of 3-formylquinolin-2-yl chlorides and methyl acrylate in DMA and in presence of *rac*-BINAP-$PdCl_2$ catalytic system (Scheme 29).[60]



103

Scheme 29

Substitution of chlorine in 2-chloroquinolines *via* Castro-Stephens, Stille, Suzuki and carbonylation reactions in the presence of Pd was reported by Ciufolini *et al.* (Scheme 30).[61]



R^1 = H, Me, CH_2OMe
R^2 = Ph, alkeneyl, alkynyl

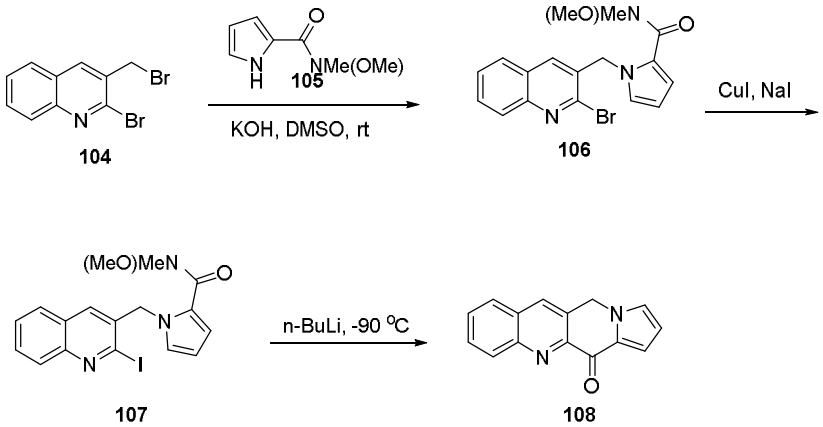
Scheme 30

Weinreb-type pyrrole-2-carboxamide **105** was subjected to *N*-alkylation with 2-bromo-3-bromomethylquinoline **104**, and the resultant *N*-(2-bromoquinolylmethyl)pyrrole-2-carboxamide **106** was converted into the corresponding iodo derivative **107** upon exposure to NaI and CuI (Scheme 31).[62] Iodine-lithium exchange with *n*-BuLi triggered intramolecular nucleophilic addition to the amide, resulting in the formation of pyrrolo[1,2-*b*]acridinone **108**.

5. Carbon-heteroatom bond formation

Hartwig and his group described the Pd-catalyzed C-N bond formation of heteroaryl and aryl chlorides with primary nitrogen nucleophiles in the presence of $Pd(OAc)_2$ and Josiphos ligand.[63] The catalyst is highly

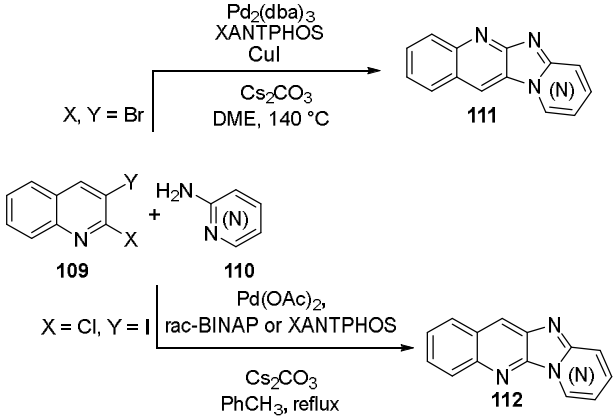
reactive, practical and with high turnover number. The reaction possesses an impressive scope (over 60 examples) and proceeds in good to excellent yield.



Scheme 31

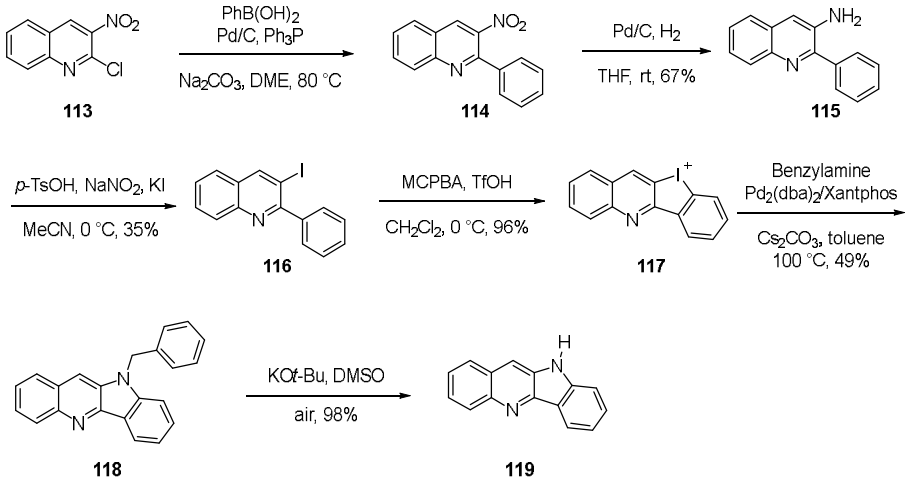
Pavlovic *et al.* used $Pd_2(dba)_3$/Xantphos system for the amination of 2-chloro-3-arylquinolines with amines.[64]

Maes' group reported a regioselective, metal-catalyzed cyclocondensation of 2-chloro-3-iodoquinoline and 2,3-dibromoquinoline **109** with amino(benzo)(di)azines **110** (Scheme 32). By controlling conditions, a selective C-2 intermolecular Pd-catalyzed amination of 2,3-dibromoquinoline with aminopyridines gave pyrido[1′,2′:1,2]imidazo[4,5-*b*]quinoline **111**. Whereas, 2-chloro-3-iodoquinoline reacted with 2-aminopyridines in the presence of $Pd(OAc)_2$/XANTHPHOS or rac-BINAP system provided pyrido[2′,1′:2,3]imidazo[4,5-*b*]quinolone **112**.[65]



Scheme 32

Detert and Letessier reported the synthesis of the quindoline **119** *via* twofold Buchwald-Hartwig amination of benzopyridoiodolium salts **117** with benzylamine, followed by oxidative debenzylation in basic medium (Scheme 33).[66] The synthesis started with Suzuki coupling of 2-chloro-3-nitroquinoline **113** with phenylboronic acid, followed by reduction of the nitro group to yield **115**. Diazotation/Sandmeyer reaction of **115** lead to **116**, which upon oxidation with 3-chloroperoxybenzoic acid gave **117**.



Scheme 33

Michel *et al*. synthesized 6-methoxy-3,3,14-trimethyl-3,14-dihydro-7*H*-benzo[*b*]chromeno[6,5-*g*][1,8]naphthyridin-7-one **120** and 5-methoxy-2,2,13-trimethyl-2,13-dihydro-6*H*-benzo[*b*]chromeno[7,6-*g*][1,8]-naphthyridin-6-one **121** in several steps starting from 2-chloro-3-quinolinecarbaldehyde (Figure 2).[67] The authors also evaluated the antitumor activity of such products,

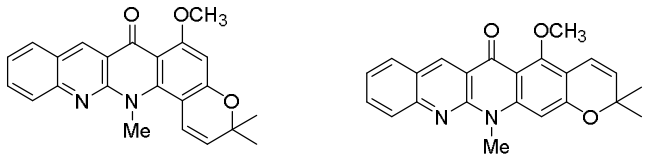
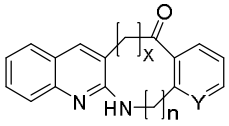


Figure 2

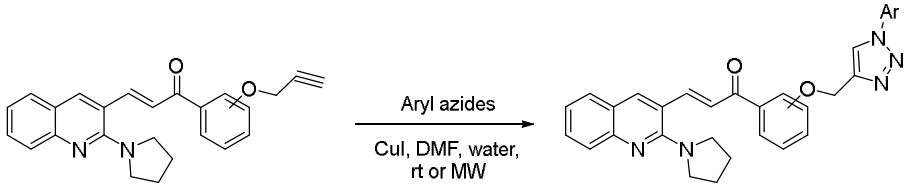
El-Aal described the construction of a novel series of quinoline heteropolycycles (tetracyclic keto-analogues of [1,8]naphthyridinones, azepino-, azocino- and azonino[2,3-*b*]quinolinones systems) **122** (Figure 3).[68]



X = 0, 1
n = 0, 1
Y = CH, N

Figure 3

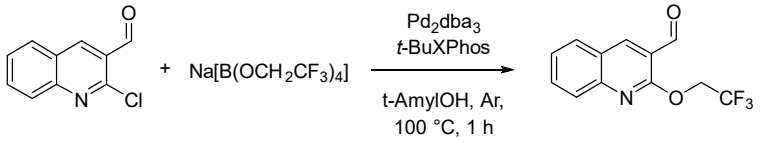
Raju and co-workers prepared 1,2,3-triazolyl-pyrrolidinyl-quinolinolines **124** through CuI-catalyzed click reaction of alkynes **123** and aromatic azides, and investigated antimicrobial activity of target molecules (Scheme 34).[69]



123 **124**

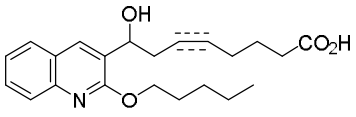
Scheme 34

In 2019, Bao *et al.* described a route to 2-sulfonylquinolines through cross coupling reaction of 2-haloquinolines with sulfonyl chlorides using zinc powder as reductant in water.[70] Phenoxylation of 2-chloroquinoline-3-carboxylic acids in the presence of anhydrous copper sulphate under microwave conditions has been demonstrated.[71] Novák *et al.* disclosed a Pd-catalyzed 2,2,2-trifluoroethoxylation of aryl and heteroaryl chlorides with tetrakis(2,2,2-trifluoroethoxy)borate salt (Scheme 35).[72]



Scheme 35

Caijo *et al.* prepared the quinoline derivatives **125** and evaluated their activity towards peroxisome proliferator activated receptors (PPARs) (Figure 4).[73]



125

Figure 4

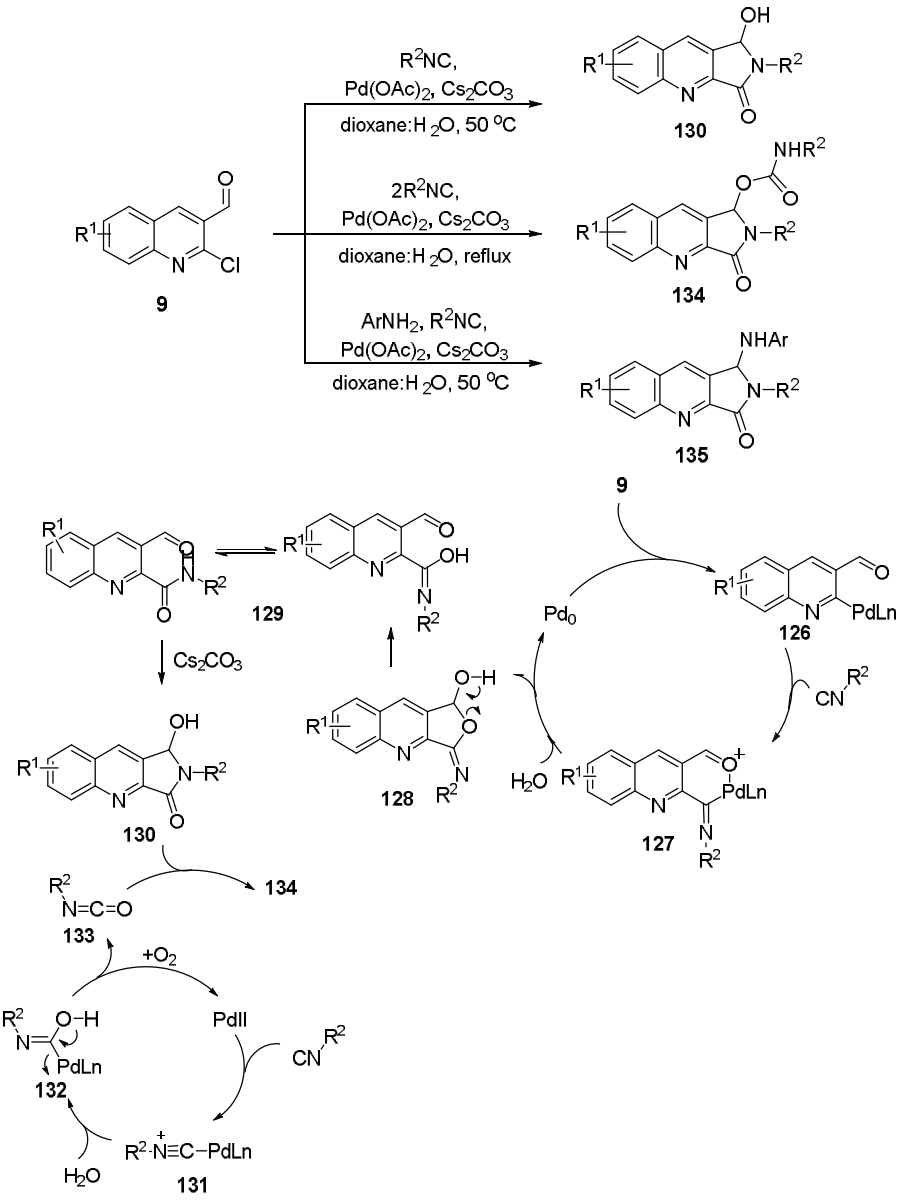
6. Amidation

Pd-catalyzed domino reaction of 2-chloroquinoline-3-carbaldehydes **9**, an isocyanide, and water at 50 °C afforded 2-alkyl-l-hydroxy-1,2-dihydro-3*H*-pyrrolo[3,4-*b*]quinolin-3-one **130** (Scheme 36).[74] The reaction at higher temperatures and in the presence of 2 equivalents of isocyanide gave 2-alkyl-3-oxo-2,3-dihydro-1*H*-pyrrolo[3,4-b]quinolin-1-yl alkylcarbamates **134** *via* carbamoylation of the primary product **130**. Interestingly, four-component reactions of 2-chloroquinoline-3-carbaldehydes, isocyanides, amines and water produced pyrrolo[3,4-b]quinolin-3(2*H*)-ones **135**. The catalytic cycle is proposed to start with the activation of **9** by Pd(0) to form intermediate **126**. Insertion of isocyanide into the C-Pd bond leads to intermediate **127**, which undergoes water addition and reductive elimination Pd(0). The emerging **128** then isomerize to the final **130**. Running the reaction in the presence of excess isocyanide and water results in palladium-mediated formation of isocyanate **133**. The latter can react with alcohol **130** to afford the carbamate **134**.

Very recently, Shiri *et al.* described a palladium-catalyzed three-component reaction of 5-(2-chloroquinolin-3-yl) oxazoles, isocyanides, and water to form 3-(oxazol-5-yl)quinoline-2-carboxamides.[75]

The same group, reported that the reaction of 2-chloroquinoline-3-carbonitriles with isocyanides is sensitive to the steric demand of the later. Thus, less hindered aliphatic and aromatic isocyanides produced

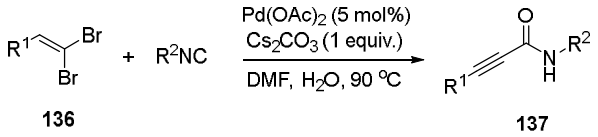
2-alkyl(aryl)-1-imino-1*H*-pyrrolo[3,4-b]quinolin-3(2*H*)-ones, while and more hindered ones, such as *tert*-butyl isocyanide gave the corresponding 3-cyanoquinoline-2-carboxamides.[76]



Scheme 36

Salehi and Shiri demonstrated an alternative method for the synthesis of 3-(hetero)arylpropynamides **137** by coupling of isocyanides with 1,1-dibromo-1-alkenes **136** in the presence of $Pd(OAc)_2/Cs_2CO_3$

(Scheme 37).[77] Probably, the transformation entails oxidative addition of Pd(0) into a CBr bond, followed by isocyanide insertion and finally HBr elimination promoted by the base present in the mediums.



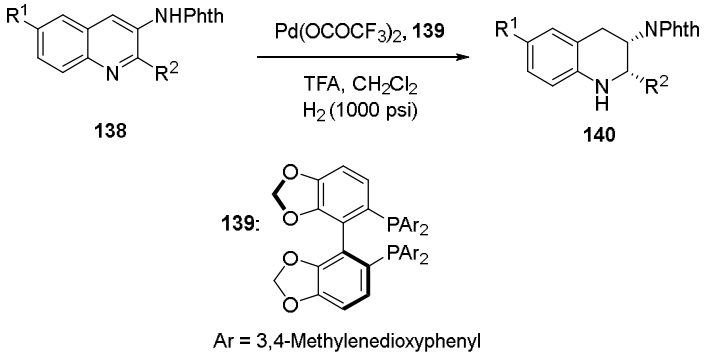
136 137

Scheme 37

7. Reduction

Asymmetric reduction of 2-aryl-3-(trifluoromethyl)quinolines with dihydropyridines in the presence of chiral phosphoric has been accomplished by Zhou and co-workers.[78] Zhou *et al*. similarly described reduction of 2-chloro-3-trifluoromethylthioquinolines[79] and 2-aryl substituted quinolin-3-amines[80] to chiral 2,3-disubstituted 1,2,3,4-tetrahydroquinoline with up to 99% of enantioselectivity.

Hydrogenation of 3-phthalimido substituted quinolines **138** to substituted tetrahydroquinolines **140** of up to 90% ee has been reported by Zhou group (Scheme 38).[81] The reaction employed as a catalyst a Pd complex of biphosphine ligand **139**.



138 140

Scheme 38

8. Conclusion

In this contribution, we have summarized important types of transition-metal-catalyzed reactions leading to 2,3-substitutedquinolines. These transformations involve various types of reactions including: cyclization, arylation, alkynylation, vinylation, carbonylation, carbon-heteroatom bond formation, amidation as well as reduction. In many cases, the above sequences evolve from 2-chloroquinoline-3-carbaldehydes derivatives that revealed to be powerful starting materials in organic synthesis. These efforts have demonstrated valuable new methodology that enable the rapid and cost-effective synthesis of diverse natural products, pharmaceuticals, and functional materials.

Acknowledgments

Alzahra University and INSF (Iran National Science Foundation) are gratefully acknowledged for support.

References

1. Prajapati, S. M.; Patel, K. D.; Vekariya, R. H.; Panchal, S. N.; Patel, H. D. *RSC Adv.* **2014**, *4*, 24463.
2. Kouznetsov, V. V.; Mendez, L. Y.; Gomez, C. M. *Curr. Org. Chem.* **2005**, *9*, 141.
3. Latha, D. S.; Yaragorla, S. C. *Eur. J. Org. Chem.* **2020**, *2020*, 2155.

4. Shiri, M.; Zolfigol, M. A.; Kruger, H. G.; Tanbakouchian, Z. *Adv. Heterocycl. Chem.* **2011,** *185*, 139.
5. Meth-Cohn, O.; Narine, B.; Tarnowski, B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1537. Meth-Cohn, O., Narine, B., Tarnowski, B., Hayes, R., Keyzad, A., Rhouati, S., Robinson, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2509. Hamama, W. S.; Ibrahim, M. E.; Gooda, A. A.; Zoorob, H. H. *RSC Adv.* **2018**, *8*, 8484.
6. Abdel-Wahab, B. F.; Khidre, R. E.; Farahat, A. A.; Sayed El-Ahl, A. A. *Arkivoc* **2012**, 211.
7. Abdel-Wahab, B. F.; Khidre, R. E. *J. Chem.* **2013**, *10*, 851297.
8. Trowbridge, A.; Walton, S. M.; Gaunt, M. J. *Chem. Rev.* **2020**, *120*, 2613.
9. Obligacion, J. V.; Chirik, P. J. *Nat. Rev. Chem.* **2018**, *2*, 15.
10. Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. *Chem. Rev.* **2019**, *119*, 2192.
11. Chandra, A.; Singh, B.; Upadhyay, S.; Singh, R. M. *Tetrahedron* **2008**, *64*, 11680.
12. Singh, R. M.; Kumar, R.; Sharma, N.; Asthana, M. *Tetrahedron* **2013**, *69*, 9443.
13. Verma, A. K.; Rustagi, V.; Aggarwal, T.; Singh, A. P. *J. Org. Chem.* **2010**, *75*, 7691.
14. Prakash, K.; Nagarajan, R. J. T. L. *Tetrahedron Lett.* **2013**, *54*, 3635.
15. Čikotienė, I.; Bukšnaitienė, R. *Adv. Synth. Catal.* **2012**, *354*, 2719.
16. Bukšnaitienė, R.; Urbanaitė, A.; Čikotienė, I. *J. Org. Chem.* **2014**, *79*, 6532.
17. Bukšnaitienė, R.; Čikotienė, I. *Heterocycl. Commun.* **2012**, *18*, 87.
18. Rustagi, V.; Tiwari, R.; Verma, A. K. *Eur. J. Org. Chem.* **2012**, *2012*, 4590.
19. Kumar, Y. S.; Khan, F. N. *Catal. Lett.* **2017**, *147*, 919.
20. Toyota, M.; Komori, C.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 7110.
21. Mekouar, K.; Génisson, Y.; Leue, S.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 5212.
22. Rigby, J. H.; Danca, D. M. J. T. l. *Tetrahedron Lett.* **1997**, *38*, 4969.
23. Tietze, L. F.; Bischoff, M.; Khan, T. A.; Liu, D. *Chem. Heterocycl. Comp.* **2017**, *53*, 434.
24. Liu, Q.; Liu, M.; Huang, G.; Chen, F.-E. *Tetrahedron* **2019**, *75*, 2647.
25. Ciufolini, M. A.; Roschangar, F. *Angew. Chem.* **1996**, *108*, 1789.
26. Ciufolini, M. A.; Roschangar, F. *Tetrahedron* **1997**, *53*, 11049.
27. Song, L.; Tian, G.; He, Y.; Van der Eycken, E. V. *Chem. Commun.* **2017**, *53*, 12394.
28. Murata, N.; Sugihara, T.; Kondo, Y.; Sakamoto, T. *Synlett* **1997**, *1997*, 298.
29. Zahid, M.; Iaroshenko, V. O.; Saghyan, A. S.; Fischer, C.; Langer, P. J. T. *Tetrahedron* **2013**, *69*, 3451.
30. Saravanan, N.; Arthanareeswari, M.; Kamaraj, P.; Sivakumar, B. *Res. Chem. Intermed.* **2015**, *41*, 5379.
31. Bontemps, A.; Mariaule, G.; Desbène-Finck, S.; Helissey, P.; Giorgi-Renault, S.; Michelet, V.; Belmont, P. *Synthesis* **2016**, *48*, 2178.
32. Singh, B.; Chandra, A.; Singh, S.; Singh, R. M. *Tetrahedron* **2011**, *67*, 505.
33. Aggarwal, T.; Imam, M.; Kaushik, N. K.; Chauhan, V. S.; Verma, A. K. *ACS Comb. Sci.* **2011**, *13*, 530.
34. Godet, T.; Vaxelaire, C.; Michel, C.; Milet, A.; Belmont, P. *Chem. Eur. J.* **2007**, *13*, 5632.
35. Asthana, M.; Singh, J. B.; Singh, R. M. *Tetrahedron Lett.* **2016**, *57*, 615.
36. Sharma, N.; Asthana, M.; Nandini, D.; Singh, R.; Singh, R. M. *Tetrahedron* **2013**, *69*, 1822.
37. Patin, A.; Belmont, P. *Synthesis* **2005**, *2005*, 2400.
38. Belmont, P.; Andrez, J.-C.; Allan, C. S. *Tetrahedron Lett.* **2004**, *45*, 2783.
39. Belmont, P.; Belhadj, T. J. O. l. *Org. Lett.* **2005**, *7*, 1793.
40. Shukla, S. P.; Tiwari, R.; Verma, A. K. *Tetrahedron* **2012**, *68*, 9035.
41. Shestakov, A. N.; Pankova, A. S.; Kuznetsov, M. A. *Chem. Heterocycl. Comp.* **2017**, *53*, 1103.
42. Sonawane, A. D.; Garud, D. R.; Udagawa, T.; Kubota, Y.; Koketsu, M. *New J. Chem.* **2018**, *42*, 15315.
43. Sonawane, A. D.; Garud, D. R.; Udagawa, T.; Koketsu, M. *Org. Biomol. Chem.* **2018**, *16*, 245.
44. Pintér, Á.; Nyerges, M.; Virányi, A.; Tőke, L. J. T. *Tetrahedron Lett.* **2003**, *44*, 2343.
45. Nyerges, M.; Pintér, Á.; Virányi, A.; Blaskó, G.; Tőke, L. J. T. *Tetrahedron* **2005**, *61*, 8199.
46. Ubba, E.; Kumar, Y. S.; Dasaradhan, C.; Khan, F.-R. N.; Jeong, E. D.; Chung, E. H. *Tetrahedron Lett.* **2015**, *56*, 4744.
47. Fleckenstein, C. A.; Plenio, H. *Chem. Eur. J.* **2008**, *14*, 4267.
48. Fleckenstein, C. A.; Plenio, H. *J. Org. Chem.* **2008**, *73*, 3236.
49. Roy, S.; Plenio, H. *Adv. Synth. Catal.* **2010**, *352*, 1014.
50. Zeng, J.; Liu, K. M.; Duan, X. F. *Org. Lett.* **2013**, *15*, 5342.

51. Benameur, A.; Boumoud, T.; Boumoud, B.; Rhouati, S. *J. Chem.* **2010**, *7*, 782913.
52. Nishimae, Y.; Groarke, M.; Wolleb, H.; Wolleb, A.; Nakano, Y.; Nagashima, H.; Haketa, T.; Kawamura, M.; Shiomi, T.; Google Patents, WO2017/221999.
53. Mishra, K.; Pandey, A. K.; Singh, J. B.; Singh, R. M. *Org. Biomol. Chem.* **2016**, *14*, 6328.
54. Penhoat, M.; Levacher, V.; Dupas, G. *J. Org. Chem.* **2003**, *68*, 9517.
55. Liu, L.; Wang, Y.; Wang, H.; Peng, C.; Zhao, J.; Zhu, Q. J. T. L. *Tetrahedron Lett.* **2009**, *50*, 6715.
56. Shiri, M.; Fathollahi-Lahroud, M.; Yasaei, Z. *Tetrahedron* **2017**, *73*, 2501.
57. Gholami-Koupaei, Z.; Shiri, M.; Kaffash, S.; Yasaei, Z. *Polycycl. Arom. Comp*. doi: 10.1080/10406638.2019.1695216.
58. Dziedzic, P.; Cisneros, J. A.; Robertson, M. J.; Hare, A. A.; Danford, N. E.; Baxter, R. H.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2015**, *137*, 2996.
59. Graule, S.; Rudolph, M.; Shen, W.; Williams, J. G.; Lescop, C.; Autschbach, J.; Crassous, J.; Réau, R. *Chem. Eur. J.* **2010**, *16*, 5976.
60. Sharma, N.; Asthana, M.; Kumar, R.; Mishra, K.; Singh, R. M. *Tetrahedron Lett.* **2014**, *55*, 2348.
61. Ciufolini, M. A.; Mitchell, J. W.; Roschangar, F. *Tetrahedron Lett.* **1996**, *37*, 8281.
62. Ruiz, J.; Lete, E.; Sotomayor, N. *Tetrahedron* **2006**, *62*, 6182.
63. Shen, Q.; Shekhar, S.; Stambuli, J. P.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2005**, *44*, 1371.
64. Pavlovic, V.; Petkovic, M.; Popovic, S.; Savic, V. *Synth. Commun.* **2009**, *39*, 4249.
65. Loones, K. T.; Maes, B. U.; Dommisse, R. A. *Tetrahedron* **2007**, *63*, 8954.
66. Letessier, J.; Detert, H. *Synthesis* **2012**, *44*, 290.
67. Tian, W.; Yougnia, R.; Depauw, S.; Lansiaux, A.; David-Cordonnier, M.-H.; Pfeiffer, B.; Kraus-Berthier, L.; Leonce, S.; Pierre, A.; Dufat, H. *J. Med. Chem.* **2014**, *57*, 10329.
68. El-Aal, H. A. A. *Aust. J. Chem.* **2017**, *70*, 1082.
69. Pradeep, M.; Vishnuvardhan, M.; Krishna, V. B.; Raju, R. M. *Russ. J. Gen. Chem.* **2019**, *89* (2), 313.
70. Bao, P.; Wang, L.; Liu, Q.; Yang, D.; Wang, H.; Zhao, X.; Yue, H.; Wei, W. *Tetrahedron Lett.* **2019**, *60*, 214.
71. Saravanan, U. T.; Vijayalakshmi, S. *Asian J. Chem.* **2012**, *24*, 3524.
72. Pethő, B.; Zwillinger, M.; Csenki, J. T.; Káncz, A. E.; Krámos, B.; Müller, J.; Balogh, G. T.; Novák, Z. *Chem. Eur. J.* **2017**, *23*, 15628.
73. Caijo, F.; Mosset, P.; Grée, R.; Audinot-Bouchez, V.; Boutin, J.; Renard, P.; Caignard, D.-H.; Dacquet, C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4421.
74. Shiri, M.; Ranjbar, M.; Yasaei, Z.; Zamanian, F.; Notash, B. *Org. Biomol. Chem.* **2017**, *15*, 10073.
75. Yasaei, Z.; Mohammadpour, Z.; Shiri, M.; Tanbakouchian, Z.; Fazelzadeh, S. *Front. Chem.* **2019**, 433.
76. Tanbakouchian, Z.; Zolfigol, M. A.; Notash, B.; Ranjbar, M.; Shiri, M. *Appl. Organometal. Chem.* **2019**, *33*, 5024.
77. Salehi, P.; Shiri, M. *Adv. Synth. Catal.* **2019**, *361*, 118.
78. Guo, R.-N.; Chen, Z.-P.; Cai, X.-F.; Zhou, Y.-G.. *Synthesis* **2014**, *46*, 2751.
79. Zhou, J.; Zhang, Q.-F.; Zhao, W.-H.; Jiang, G.-F. *Org. Biomol. Chem.* **2016**, *14* (29), 6937.
80. Cai, X.-F.; Guo, R.-N.; Feng, G.-S.; Wu, B.; Zhou, Y.-G. *Org. Lett.* **2014**, *16*, 2680.
81. Cai, X.-F.; Huang, W.-X.; Chen, Z.-P.; Zhou, Y.-G. *Chem. Commun.* **2014**, *50*, 9588.