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ARTICLE TYPE

A convenient and efficient C-OH bond activation, $PdCl_2(PPh_3)_2$ catalyzed, C-C bond formation of tautomerizable quinolinones with the aid of BOP reagent and boronic acids

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An efficient, highly chemoselective $PdCl_2(PPh_3)_2$ catalyzed, C-C bond formation of tautomerizable quinolinones with various boronic acids via C-OH bond activation using benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate (BOP) reagent in the presence of K_2CO_3 /1,4-dioxane system under aqueous conditions, leads to the formation of functionalized quinolines in excellent yields which offers great utility, advantageous in the synthesis of interesting compounds.

Introduction

Natural and synthetic quinolines and their analogs (Fig. 1) possess interesting biological properties which are also useful synthetic building blocks in organic chemistry.[1-9] The quinoline structural moiety possesses wide range of biological activities including antibacterial, antifungal, analgesic properties,[10-16] antituberculosis,[17-23] antimalarial,[24-27] anti-inflammatory,[28] anticancer,[29] antibiotic,[30] antihypertensive,[31] and anti-HIV activities.[32-34] The quinolines containing alkyl, alkenyl chains at the 2-potision have shown promising activity against several *Leishmania* strains.[35-37] Halogen-containing quinolines demonstrates potential bioactivity and the chloro functionalality plays a great source in further structural mdofications.[38-44] In spite of wide range of pharmacological activities and numerous reports of their synthetic methods, [45-54] there is a need for the development of a new, simple, convenient, and environmentally benign synthetic approaches for the 2-substituted quinolines using mild conditions remains an active research area.

Quinolines substituted at the 2-position shows *in vivo* activities against *Leishmania donovani*[55-57] and are in its preclinical development.[58-61] In addition, some compounds display substantial antiviral activity in HIV-infected cells, [62-67]anticancer,[68-72] antimalarial activities.[73-78]

A number of methods have been developed for the synthesis of 2-substituted quinolines.[9-88] However, so far there is no direct report available for the synthesis of 2-substituted quinolines from its amide analog and boronic acids. The reported methods involve Suzuki coupling of 2-halo substituted quinolines with various boronic acids.[89,90] Multistep reaction sequences, harsh conditions and sometimes toxic reagents such as $POCl_3$ were involved for the preparation of chloro intermediate which gave lower or moderate yields. In order to overcome these difficulties and to ease the synthesis of 2-substituted quinolines, researchers took an effort to expedite a direct arylation**.**

It must be noted that aromatic Csp^2–OH activation is highly challenging when compated to the Csp^3–OH bond which is due to the high energy barrier and the aromatic ring stability. However Kang and his co-workers demonstrated an effective method for the activation of the Csp^2–OH bond of tautomerizable heterocycles with phosphonium salts in the formation of the C–N bond. Recently, Kang and co-workers[91] reported the Pd-catalyzed cross-coupling reactions of wide variety of tautomerizable heterocycles with aryl boronic acids via C-OH bond activation using phosphonium salts bromotripyrrolidinophosphonium hexafluoro phosphate (PyBroP) as activating reagents. This involved heterocycle-Pd(II)−phosphonium intermediate species in the mechanism.

The authors also achieved the synthesis of 6-arylpurine ribonucleoside without any protection-activation-coupling-deprotection sequence. This procedure demonstrated an excellent reactivity and chemoselectivity even with hindered boronic acids. This methodology have rendered numerous opportunities and also provided an attractive route for the direct arylation of tautomerizable heterocyclics via functionalization of activated C–OH bond. And can be used as a nucleophile substitution for potential heterocyclics (Fig 2). Abhishek et al., achieved direct cross-coupling of tautomerizable heterocycles through PyBroP-mediated, microwave assisted and Pd/Cu-catalyzed sequential C–OH/C–H activation for symmetrical 1,2-, 1,3-, and 1,4-bidiazine units (Fig 2).[92, 93] Similarly direct alkynylation of tautomerizable heterocylcles has been achieved by Kang et al via the alkyne C-H/tautomerizable heterocycles C−OH activation by PyBrOP followed by dehydrative cross coupling -Sonogashira coupling with alkyl or aryl terminal alkynes, alkenyl and also with alkynylalcohols. The alkynes bearing a hydroxyl group also reacted smoothly without any protection–deprotection step. The reactions invoved Pd/Cu-catalyst for effective Csp^2- Csp bond formations (Fig 2).[94-96]. Aldrich et al utilized $PdCl_2(CH_3CN)_2$, $(P(Cy)_2$Biphenyl 2-yl, Cs_2CO_3 system and in the absence of CuI using the modified strategy. They have also achieved 6-alkynylpurine ribonucleoside derivatives showing potential

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cytostatic activity

The PyBroP-mediated coupling of *3,4-Dihydropyrimidin-2(1H)-one* with various nucleophiles to give the multifunctionalized pyrimidines have also been reported (Fig 5 2).[97]

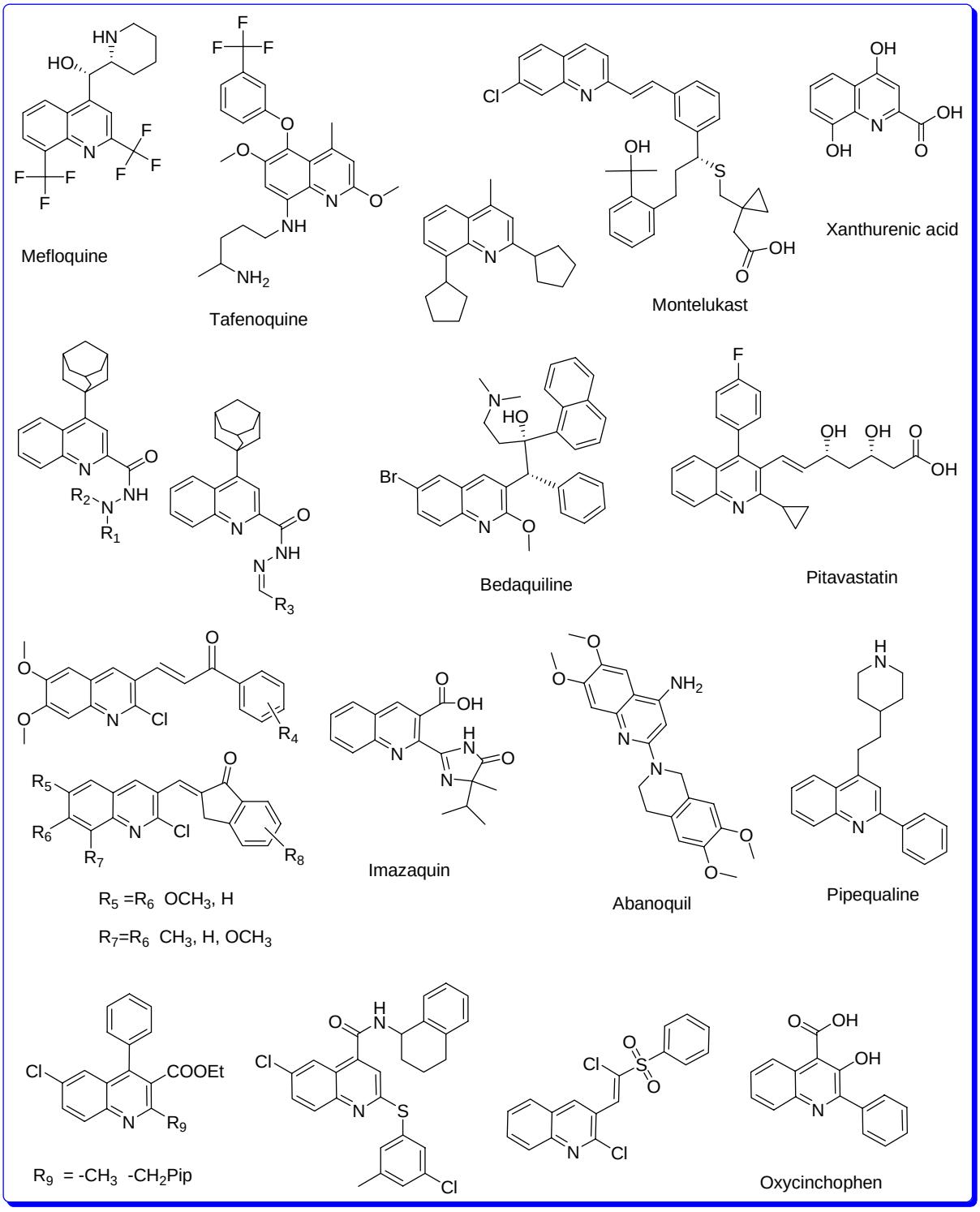

Fig 1 Biologically important 2- or 2,4-substituted quinolines

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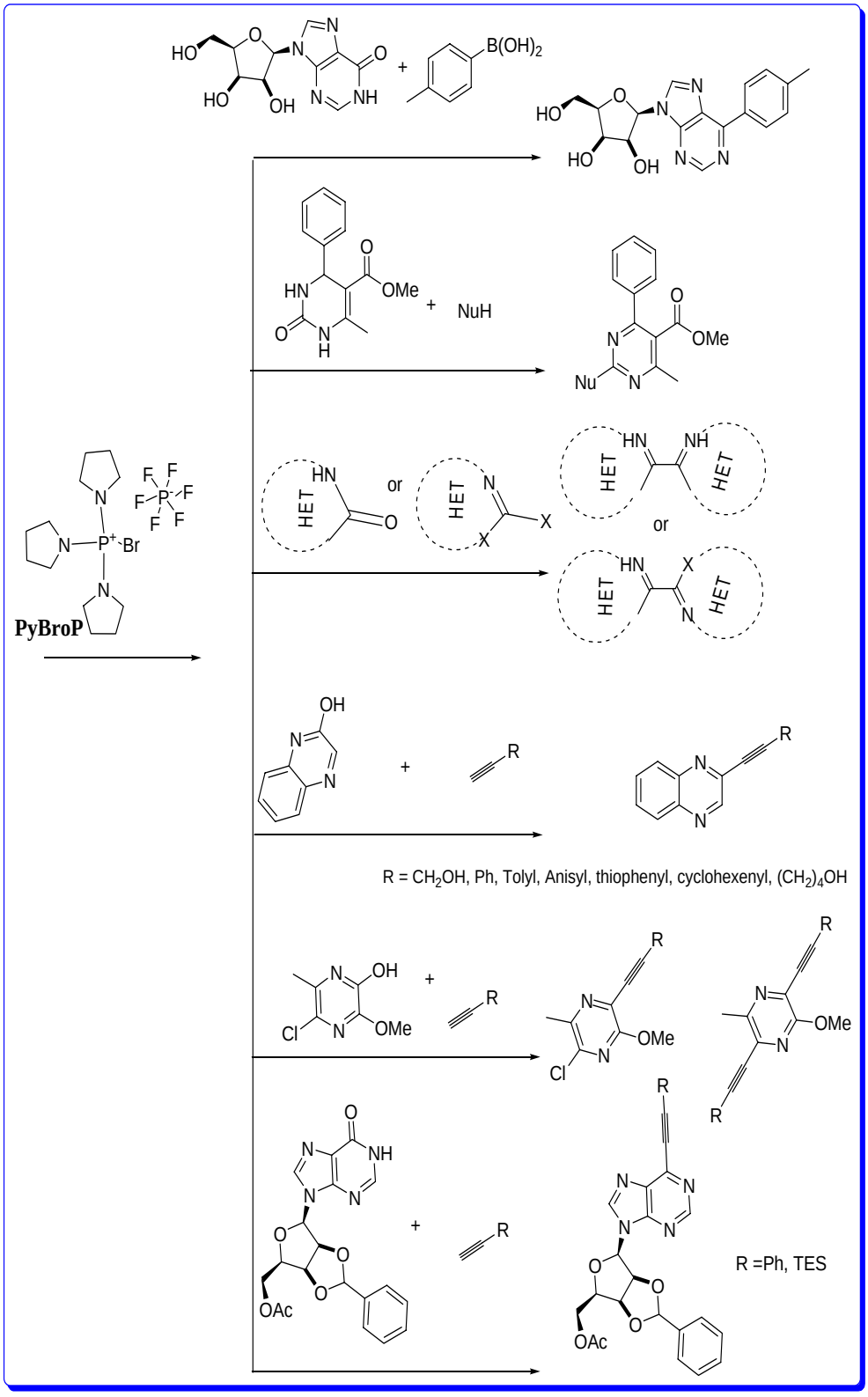

Fig 2 Tautomerizable heterocycles in PyBroP mediated reactions[91-97]

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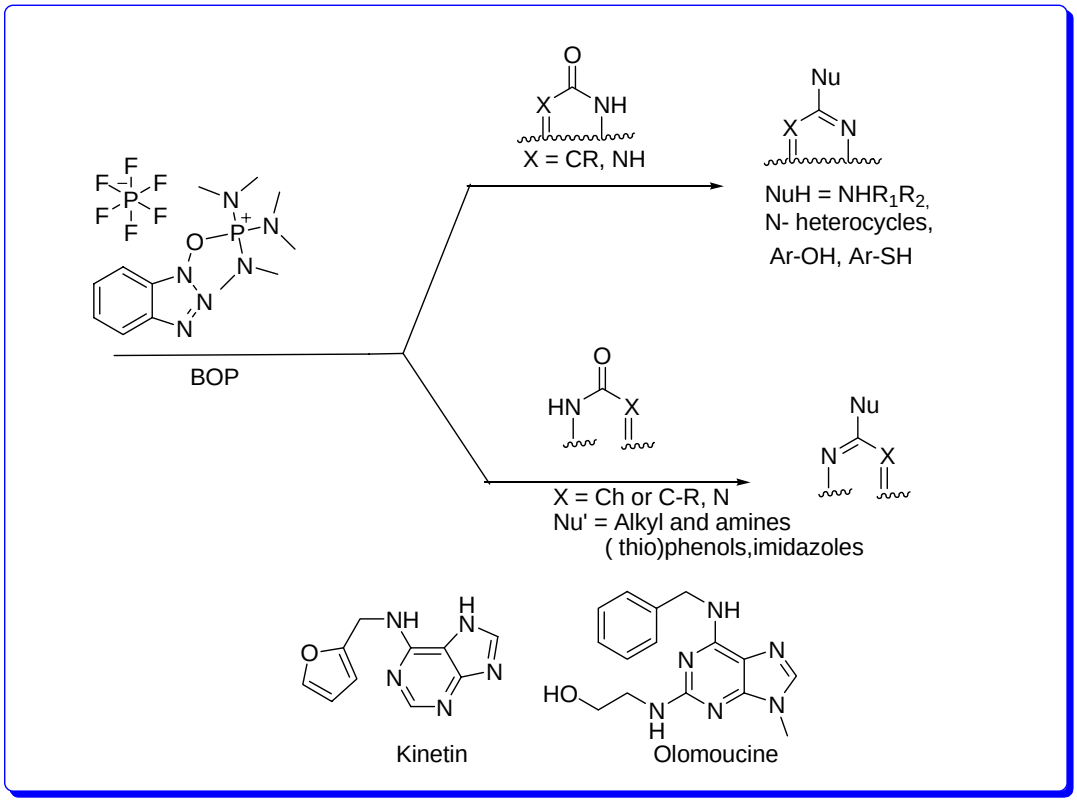
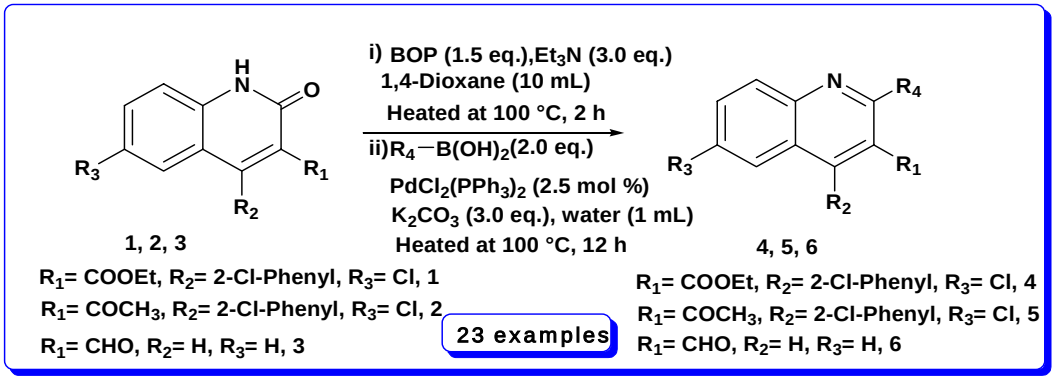


Fig 3 Tautomerizable heterocycles in BOP mediated reactions[98,99]

Further, the aromatic nucleophilic substitution of cyclic amides with nitrogen nucleophiles, phenols, thiophenol nucleophiles were achieved using benzotriazol-1-yloxytris(dimethylamino) phosphonium hexafluorophosphate (BOP) (Fig 3).[98, 99] Similarly the microwave-assisted palladium-catalyzed phosphonium coupling of tautomerizable heterocycles for efficient C−C cross-coupling has been reported.

With our longstanding interest in the synthesis and diversification of heterocycles, particularly in quinoline chemistry,[100-113] we became very interested in applying the C-OH activation strategy with other types of cross-coupling reactions. Herein, we report our studies of the Suzuki-type reactions of tautomerizable heterocycles activated by BOP reagent with various boronic acids (Scheme 1).



Scheme 1. General scheme for the synthesis of 2-substituted quinolines

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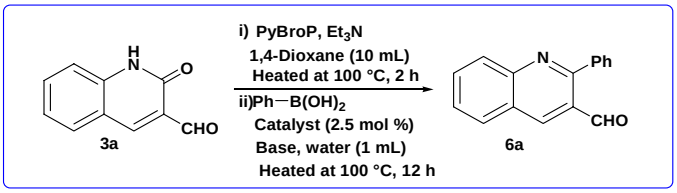
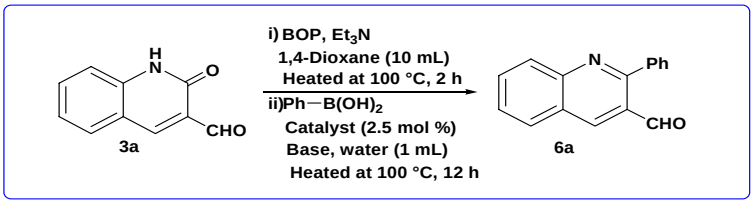
Table 1. Coupling of 3-substituted quinolin-2(*1H*)one with phenyl boronic acid: Optimization of the reaction conditions using PyBroP reagent[a]



Entry	Catalyst/ mol %	Solvent	Yield (%)[b]
1	$PdCl_2(PPh_3)_2$/10	Dioxane	49
2	$PdCl_2(PPh_3)_2$/5	Dioxane	36
3	$PdCl_2(PPh_3)_2$/10	Dioxane	39[c]
4	$Pd(OAc)_2$/10	Dioxane	15
5	$Pd(OAc)_2$/5	Dioxane	Traces
6	$Pd_2(dba)_3$/10	Dioxane	21
7	$Pd_2(dba)_3$/5	Dioxane	Traces
8	$PdCl_2$(dppf):DCM /10	Dioxane	26
9	$PdCl_2$(dppf):DCM /5	Dioxane	Traces
10	$PdCl_2(PPh_3)_2$/10	Dioxane	47[d]
11	$PdCl_2(PPh_3)_2$/10	DMF	35
12	$PdCl_2(PPh_3)_2$/10	DCM	Traces
13	$PdCl_2(PPh_3)_2$/10	THF	Tracess
14	$PdCl_2(PPh_3)_2$/10	Toluene	32
15	$PdCl_2(PPh_3)_2$/10	CH_3CN	43

[a]Reaction Conditions: i) Amide (1 mmol, 1.0 equiv.), PyBroP (1.5 equiv.), Et_3N (3.0 equiv.) in 1,4-dioxane (10 ml) at 100 -C for 2h, ii) $PdCl_2(PPh_3)_2$ (10 mol%), K_2CO_3 (3.0 equiv.), boronic acid (2 equiv.), and water (1 mL) at 100-C for 12h; [b]isolated yield.. [c]K_3PO_4 (3.0 equiv.),' [d]Na_2CO_3 (3.0 equiv.).

Table 2. Coupling of 3-substituted quinolin-2(*1H*)one with phenyl boronic acid: Optimization of the reaction condition using BOP reagent[a]



Entry	Catalyst/ mol %	Yield (%)[b]
1	$PdCl_2(PPh_3)_2$/10	85
2	$PdCl_2(PPh_3)_2$/5	77
3	$PdCl_2(PPh_3)_2$/10	52[c]
4	$Pd(OAc)_2$/10	Traces
5	$Pd(OAc)_2$/5	Traces
6	$Pd_2(dba)_3$/10	32
7	$Pd_2(dba)_3$/5	Traces
8	$PdCl_2$(dppf):DCM /10	39
9	$PdCl_2$(dppf):DCM /5	Traces
10	$PdCl_2(PPh_3)_2$/10	56[d]
11	$PdCl_2(PPh_3)_2$/10	15-60[e]

[a]Reaction Conditions: Amide (1 mmol, 1.0 equiv.), BOP (1.5 equiv.), Et_3N (3.0 equiv.) in 1,4-dioxane (10 ml) at 100 _C for 2h and then $PdCl_2(PPh_3)_2$ (10 mol%), K_2CO_3 (3.0 equiv.), boronic acid (2 equiv.), and water (1 mL) at 100 _C for 12h; [b]isolated yield. [c]K_3PO_4 (3.0 equiv.),' [d]Na_2CO_3 (3.0 equiv.), [e]DMF 50%, DCM 15%, THF 22%, Toluene 53%, CH_3CN 60%

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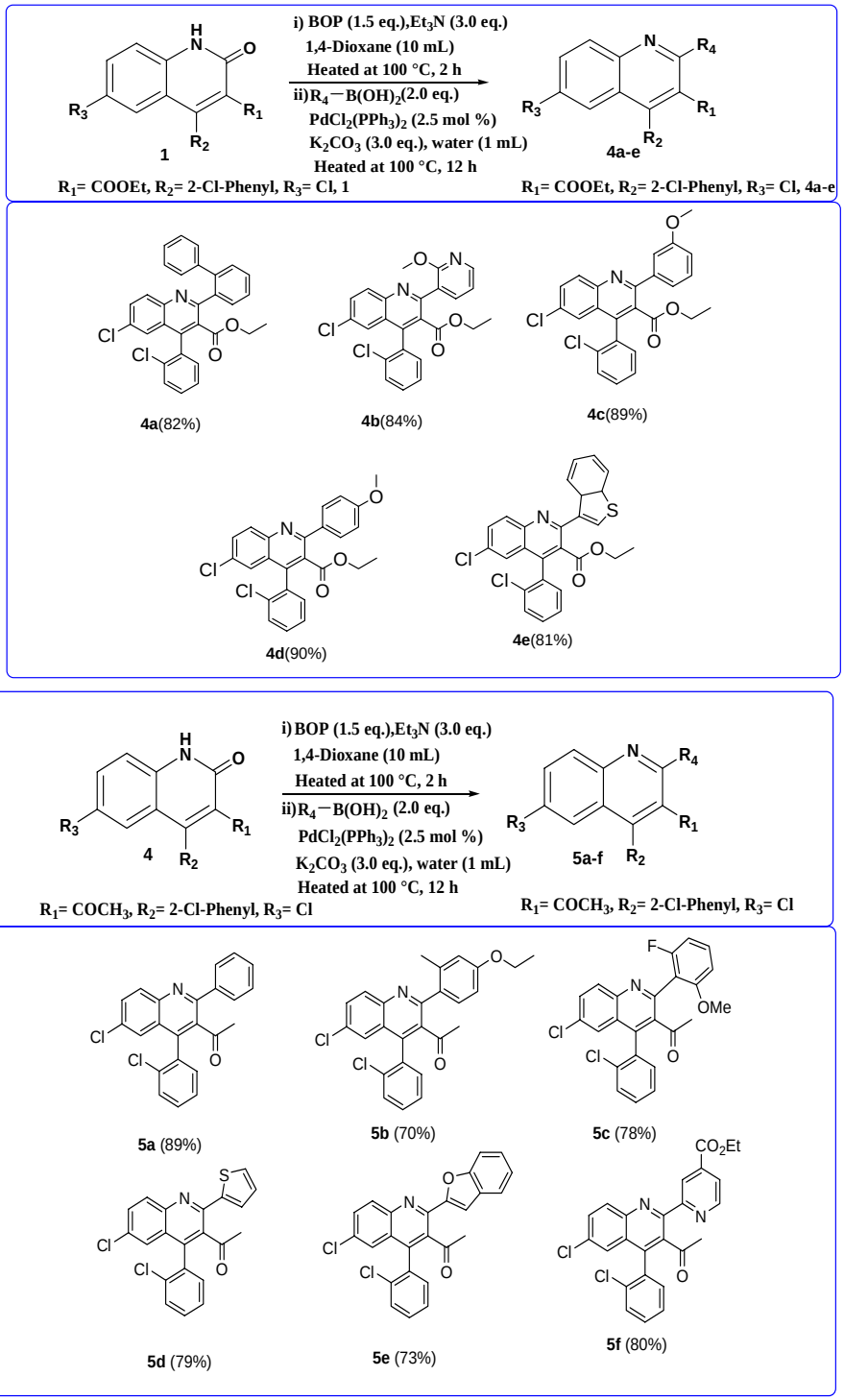
Table 3 Synthesis of 2-aryl -3-carbethoxy-6-chloroquinolines and2-aryl -3-acetyl-6-chloroquinolines [a] [a]



[a]Reaction Conditions: Amide (1 mmol, 1.0 equiv.), BOP (1.5 equiv.), Et_3N (3.0 equiv.) in 1,4-dioxane (10 ml) at 100 _C for 2h and then $PdCl_2(PPh_3)_2$ (10 mol%), K_2CO_3 (3.0 equiv.), boronic acid (2 equiv.), and water (1 mL) at 100 _C for 12h; isolated yield.

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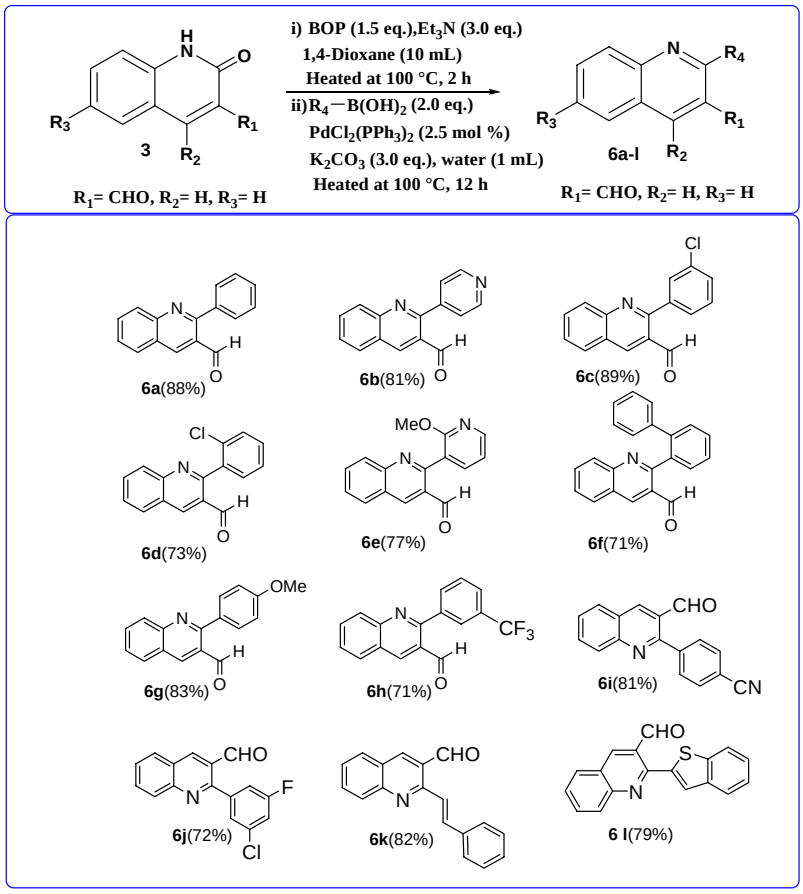
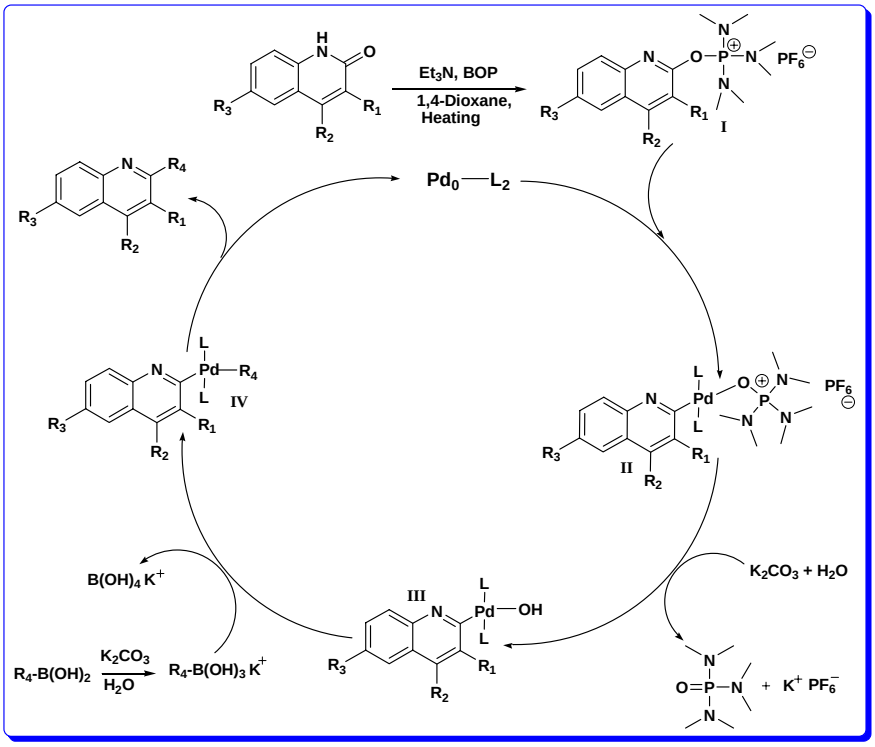
Table 4 Synthesis of 2-aryl -3-formyl-6-chloroquinolines [a]



[a]Reaction Conditions: Amide(1 mmol, 1.0 equiv.), BOP(1.5 equiv.), Et_3N(3.0 equiv.) in 1,4-dioxane (10 ml) at 100^0C for 2h and then $PdCl_2(PPh_3)_2$ (10 mol%), K_2CO_3 (3.0 equiv.), boronic acid(2 equiv.), and water(1 mL) at 100^0C for 12h; isolated yield.



Scheme 2 Possible mechanism of the reaction

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Results and Discussion

Kang et al. established PyBroP (bromotripyrrolidinophosphonium hexafluorophosphate) as the most suitable activator for in situ activation of phenolic C–O bonds,. With the above preliminary idea in mind, we continued the research on with diverse tautomerizable heterocycles and boronic acids. Initially explored a wide range of conditions for direct alkylation of the substrate 3-formyl quinolin-2(*1H*)one with phenyl boronic acid. The 3-formyl quinolin-2(*1H*)one was first activated in situ using PyBroP (1.5 eq.) and triethylamine (3 eq.) in 1,4-dioxane at 100 °C for 2 h. And then cross-coupling conditions have been developed for Suzuki coupling reactions (Table 1).

For the initial study, we followed Kang et al., condition using PyBroP for in situ actiavtion. Surprisingly, the tested 3-substituted quinolin-2(*1H*)one coupled with phenyl boronic acid (Table 1), but offered a poor yield. In order to get a good conversion, we screened the reaction with various palladium catalysts including $Pd(OAc)_2$, $Pd_2(dba)_3$ and $PdCl_2(dppf)$:DCM using a PyBroP activator, however lower yields less than 50% were obtained (Table 1, entry 1-10). While using 10 mol% $Pd(OAc)_2$, $Pd_2(dba)_3$ and $PdCl_2(dppf)$:DCM catalysts, the yield is very low and with 5 mol% load the conversion becomes more trace (entry 5-9). Next, we have tested with two bases such as K_3PO_4, Na_2CO_3 using 10 mol% of $PdCl_2(PPh_3)_2$ catalyst, but the results showed lower yield (Table 1, entry 3, 10). It must be noted that mild carbonate bases and water presence is essential for a neat conversion. In the absence of water, the reaction gave sluggish products. Further the effect of the solvent on this phosphonium coupling was investigated. Among the tested organic solvents e.g., 1,4-dioxane, DCM, DMF, THF, CH_3CN, the polar solvents 1,4-dioxane, CH_3CN was successful due to the solubility of intermediate heterocycle-phosphonium salts and the solvents toluene and DMF were the least efficient

In order to further increase the product yield, varied the activator to BOP (OBt-derived) reagent was used instead of PyBroP (Br-derived reagents) for a more effective reaction as summarized in Table 2. The results encouraged us to use 3-formyl quinolin-2(*1H*)one which underwent smooth coupling with phenyl boronic acid in the presence of the 10 mol% of $PdCl_2(PPh_3)_2$ catalyst, K_2CO_3 as the base and 1,4-dioxane solvent under aqueous conditions. With this good result, we have tested the coupling reaction using BOP activator with various catalytic conditions and solvents. The results are summarized in Table 2. We are pleased to inform that the coupling reaction of 3-formyl quinolin-2(*1H*)one with phenyl boronic acid was successfully achieved in a one-pot manner through *in situ* activation using BOP reagent (1.5 eq.), Et_3N base(3.0 eq.) and 1,4-dioxane solvent under reflux conditions . After which the subsequent coupling reaction to the same mixture with the addition of 10 mol% of $PdCl_2(PPh_3)_2$ catalyst, K_2CO_3 base (3.0 eq.) and water (1 mL under reflux conditions was observed.

Further the effect of the solvents on this phosphonium coupling was investigated using a BOP as the coupling reagent. Among the tested organic solvents 1,4-dioxane, CH_3CN was succesful due to the solubility of the heterocycle-phosphonium salts.

Encouraged by the results obtained through optimized direct arylation, we embarked on an investigation of the reaction scope. Several of tautomerizable 3-formyl, 3-acetyl, 3-carbethoxy quinolin-2-ones containing substitutions at varied positions were examined for the Pd-catalyzed direct arylation via C-OH bond activation using BOP reagent (Scheme 1, Table 3,4). The tested tautomerizable quinolines with electronegative nitrogen atom, electron-withdrawing acetyl, carbetoxy groups facilitate the phosphonium coupling reactions. The Pd-catalyzed BOP mediated phosphonium coupling condition was quite efficient for the direct arylation of these tested tautomerizable quinolines with various electron-rich and electron-poor aryl boronic acids through the heterocycle-phosphonium salt to afford the biaryl products. The reaction conversion was good and produced excellent isolated yields. Heteroaryl and sterically hindered aryl boronic acids also efficiently furnished the biaryl products in high yields. The list of synthesized compounds using this novel method is summarized in Table 3, 4. We have recognized the chemoselectivity of the reaction as amplified in the direct arylation of quinolinones containing chloro, enolisable acetyl as well as carbethoxy which remained intact during the reaction. Hence phosphonium coupling shows remarkable functionality compatibility. Therefore, have great utility, advantageous useful in the synthesis of many biologically interesting compounds.

We propose the following mechanism for the direct arylation of tautomerizable heterocycles, based on the Kang et al., (Scheme 2) study. The tautomerizable heterocycle is first activated by BOP in the presence of triethylamine to afford the phosphonium salt **I**. Once the active Pd(0) species is formed, the catalytic cycle begins with the oxidative addition of the phosphonium salt **I** to generate Pd(II) complex **II**. Next the reaction with a K_2CO_3 base producing the heterocycle-Pd(II)-OH species **III**. Followed by transmetalation of the heterocycle-Pd(II)-OH species with the activated aryl boron-ate complex giving the heterocycle-Pd(II) aryl species **IV**. This undergoes reductive elimination to afford the cross-coupling product and regenerate the Pd(0) species.

The overlap of the NMR spectra of a starting material and the phosphonium salt intermediate formed in the first stages is provided as an evidence for its formation along with the ^{31}P NMR of the phosphonium salt as seen in the supporting document

Conclusions

In summary, we have developed an efficient and straightforward pathway for the diverse synthesis of 2-arylated quinoline derivatives via the one-pot cross-coupling of insitu activated 2-OH quinoline derivatives and boronic acids. More importantly, we have established a catalyst-controlled highly chemo- and regioselective protocol for the construction of two different aryl–aryl bonds via the one-pot procedure. The results obtained would be of great importance because the concepts can be used to improve the synthetic efficiency in modern organic chemistry. A one pot reaction with high selectivity has been recognized as the especially effective way for atom-efficient and environmentally benign synthesis. Consequently, these methods should find more practical applications in pharmaceuticals, functional materials, catalysts, and coordination chemistry owing to the unique property of 2-arylated quinolines in these areas.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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