Chapter I

A brief review on synthesis and functionalization of 4-quinolones

INTRODUCTION

I.A. 4-quinolone

In the 20th century, the most leading cause for human illness and death was bacterial infections.[1] Over 200 million cases of malaria and 600,000 deaths were recorded in each year.[2] Several therapies were applied but the introduction of antibiotic agents brought a new route for the treatment of these bacterial infections. Synthesis of sulfonamide, penicillin by Alexander Fleming and also the synthesis of quinolones were the great success in science at that time.[3,4] George Lesher and his colleagues were first isolated the nalidixic acid (1962), the first member of quinolone drug as a byproduct in the synthesis Chloroquine.[5] In 1960's, the nalidixic acid was used for the treatment Urinary tract infections (UTI) caused by enteric bacteria.[6] Afterwards in 1970's, several new generation of quinolones such as oxolinic acid, pipemedic acid, cinoxacin and flumequine were synthesized and oxolinic acid proved itself as most prominent and notable drug.[6,7,8] Until 1980's, quinolones were little-used drugs and later second generation of quinolones were developed.[6,9,13] In search for better quinolones, the substitution at C-6 and C-8 displayed the remarkable activity against the antibacterial infections.[9] Most importantly, the position of fluorine atom at C-6 position and nitrogen heterocycles (piperazine, pyrollidinyl, piperadinyl moiety) at C-7 position remarkably enhanced the pharmacokinetic and pharmacodynamic properties e.g., Norfloxacin, ofloxacin etc.[10,11,12]

Norfloxacin, a fluoro containing quinolone, was utilized as first broad-spectrum quinolone but due to low serum level and poor tissue penetration, its applicability became restricted into the Urinary tract infections (UTI) and sexually transmitted diseases. Then, Ciprofloxacin used as the most commonly prescribed antibacterial drugs.[6,7,9] It showed its efficacy towards a variety of Gram-negative bacteria. Many fluoro quinolones have broad array of medical application in the treatment of Urinary tract infections (UTI), sexually transmitted diseases, tissue infections, pelvic infections and intra-abdominal infections. [14]

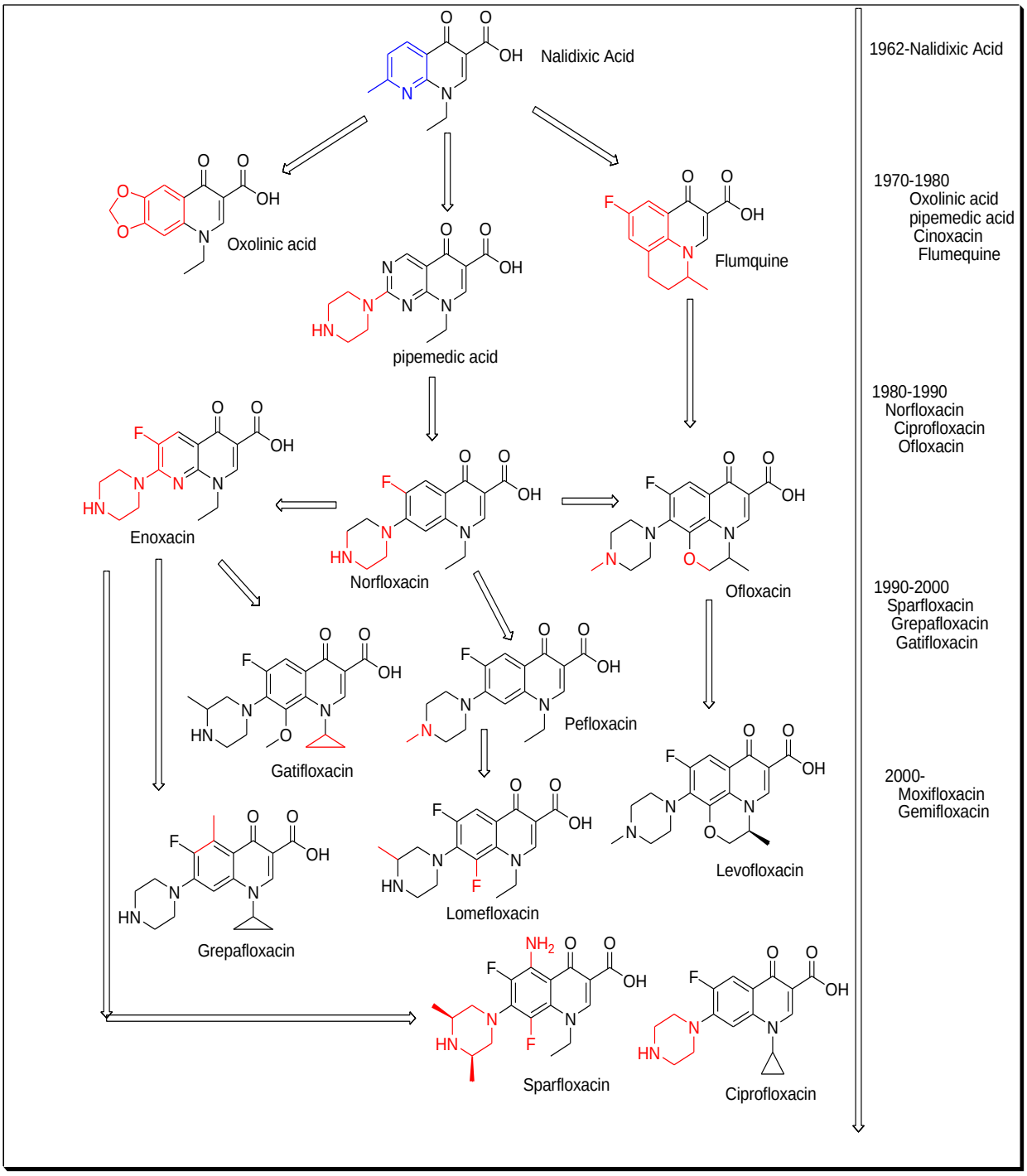


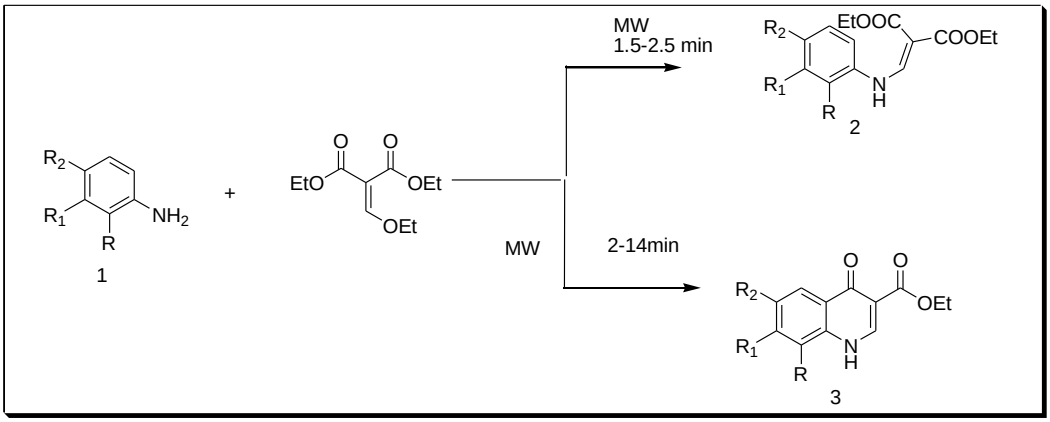
Figure-I.1 Chemical structure of 4-quinolones

I.A.1 Development of the Synthesis of 4-quinolones:

Quinolones are very omnipotent class drug due its broad-spectrum antibacterial, antimalarial and anti cancer activity. The development of the synthesis of 4-quinolones as well as its functionalisation at different position is still going on to increase its activity. Generally, these procedures involve harsh condition, domino reaction, and multi-step strategy, use of lewis acid and base, expensive transition metal catalyst or metal free condition. In this review, we mainly highlight the different route of synthesis part of 4-quinolones and functionalisation.

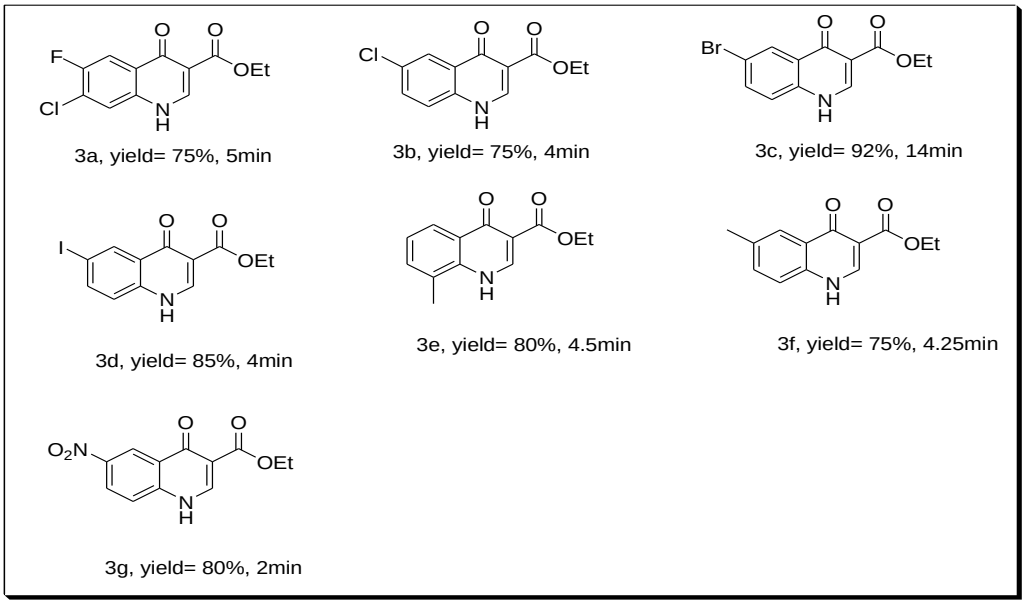
I.A.1.a Metal free synthesis of 4-quinolones

In 2002, Dave firstly reported the microwave assisted 4-quinolone synthesis under solvent free condition.[15] This method involved the condensation between aromatic amines and diethyl ethoxy methylenemalonates to afford the intermediate (2) in 1.5-2.5 min and corresponding cyclised product (3) in 2-14 min. Generally, this process was quite superior to Gould-Jacob method with respect to reaction time and product isolation.

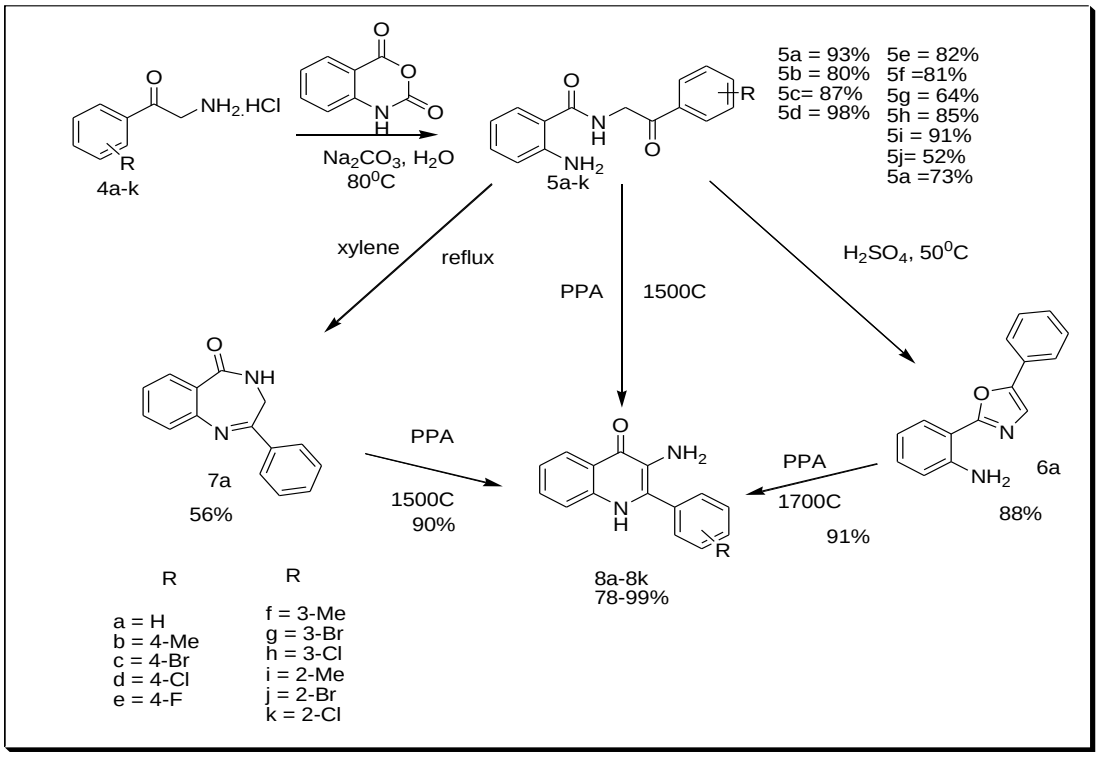


Scheme-I.1. Microwave assisted synthesis of 4-quinolones under solvent free Conditions

Selected examples

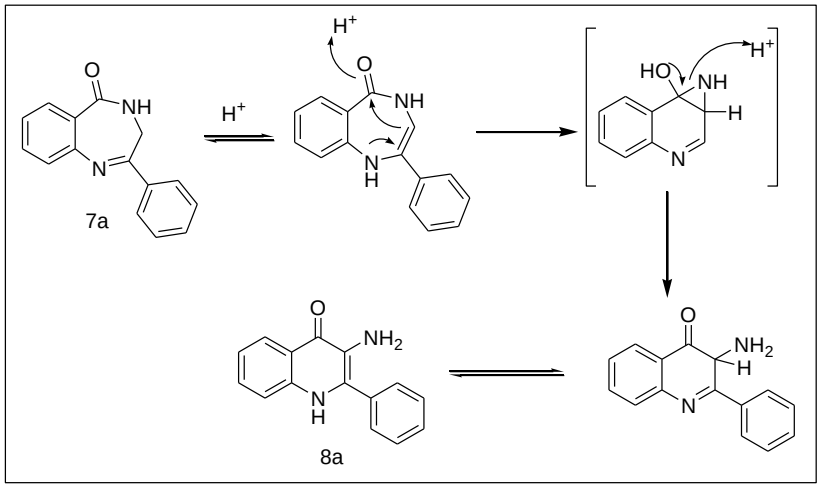


In 2006, Hradil and his coworkers developed a straight forward method for the synthesis of 3-Amino-2-phenyl-4(1H)-quinolinones from Anthranilamides in presence of PPA (poly phosphoric acid) at 150°C.[16]



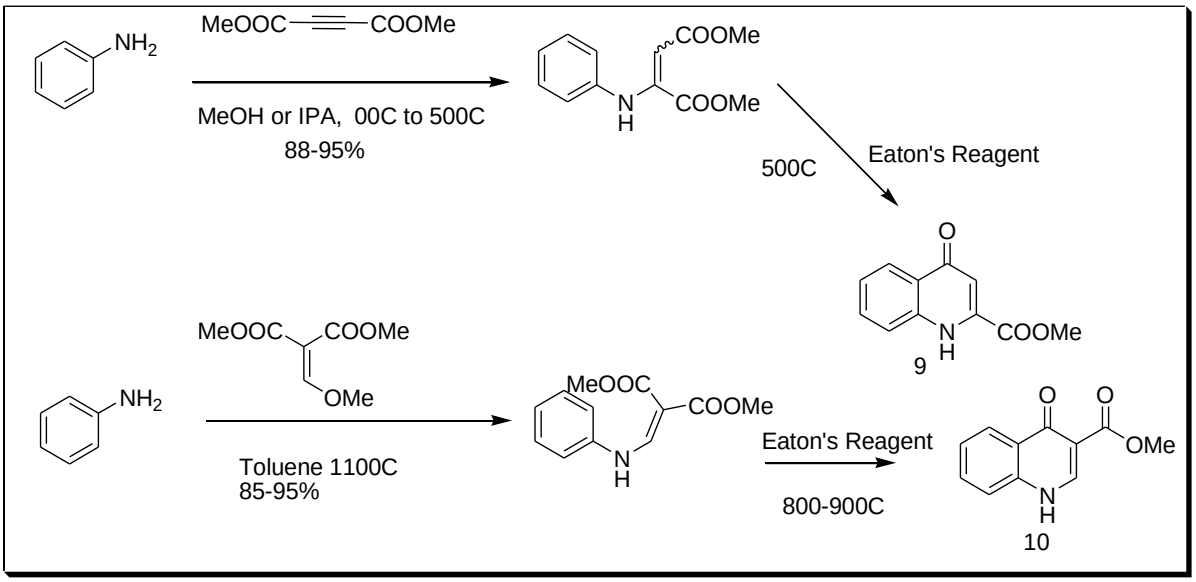
Scheme-I.2. PPA mediated synthesis of 3-Amino-2-phenyl-4(1H)-quinolinones from Anthranilamides

Plausible Mechanism



They proposed a plausible mechanism in which primarily 2-aminoacetophenones were reacted with isatoic anhydride to form anthranilamide derivatives. Afterwards, in presence of PPA (polyphosphoric acid) at 150°C resulted the diazepinone (7a) a seven memebered ring .Then it rearranged itself in presence of acid to afford the final 3-amino-2-phenyl-4-1(H)-quinolinone 8a . In presence of H_2SO_4 anthranilamide 5a afforded oxazole 6a due to intermolecular dehydration. Further, the oxazole 6a with PPA at 170°C gave aminoquinolone 8a with high yield.

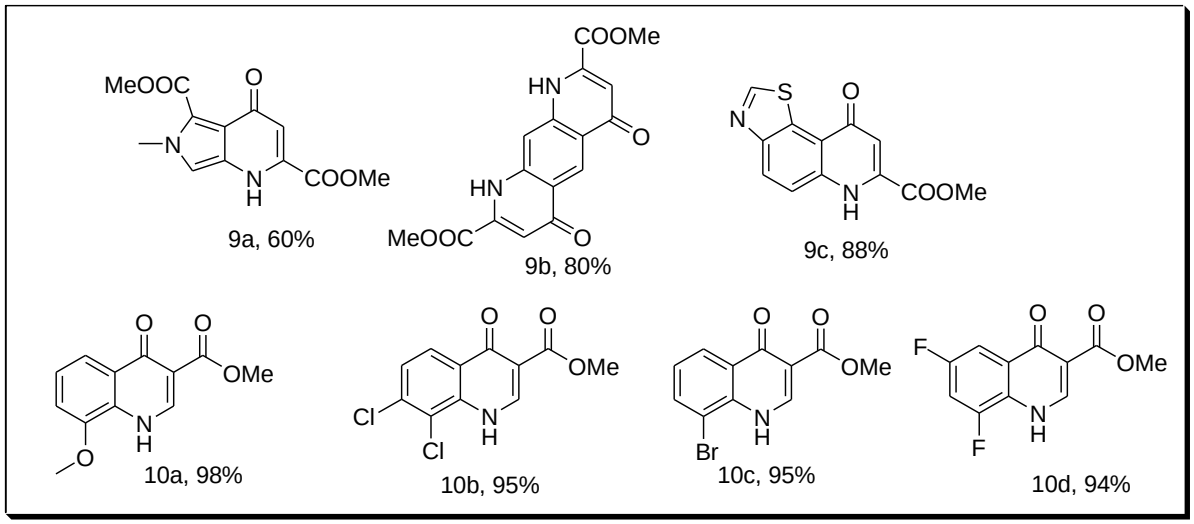
In 2007, Zewge and his co workers demonstrated the utility of Eaton's reagent (a mixture of P_2O_5 and $MeSO_3H$) for the cycloacylation of aniline derivatives to 4-quinolones. This present protocol has several advantages in compare to traditional approaches, like high yielding methodology, low reaction temperature and easy product isolation.[17]



Scheme-I.3. Eatons reagent mediated synthesis of 4-quinolones

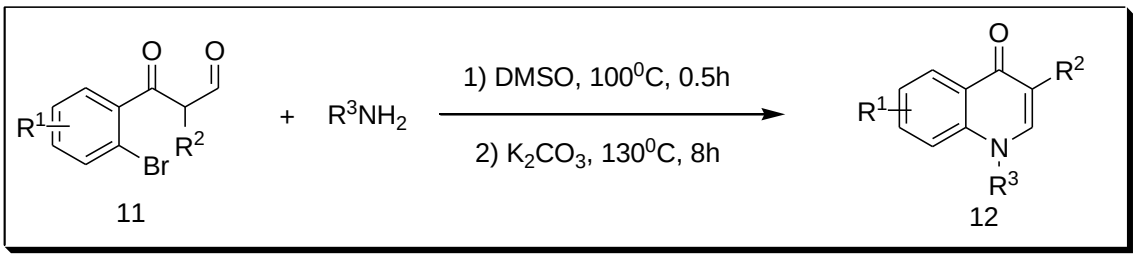
They had focused their attention on the application of the cyclisation protocol towards the synthesis of the 4-quinolone molecules such as tetracyclic bis quinolones and quinolone heterocycles (9a).

Selected examples



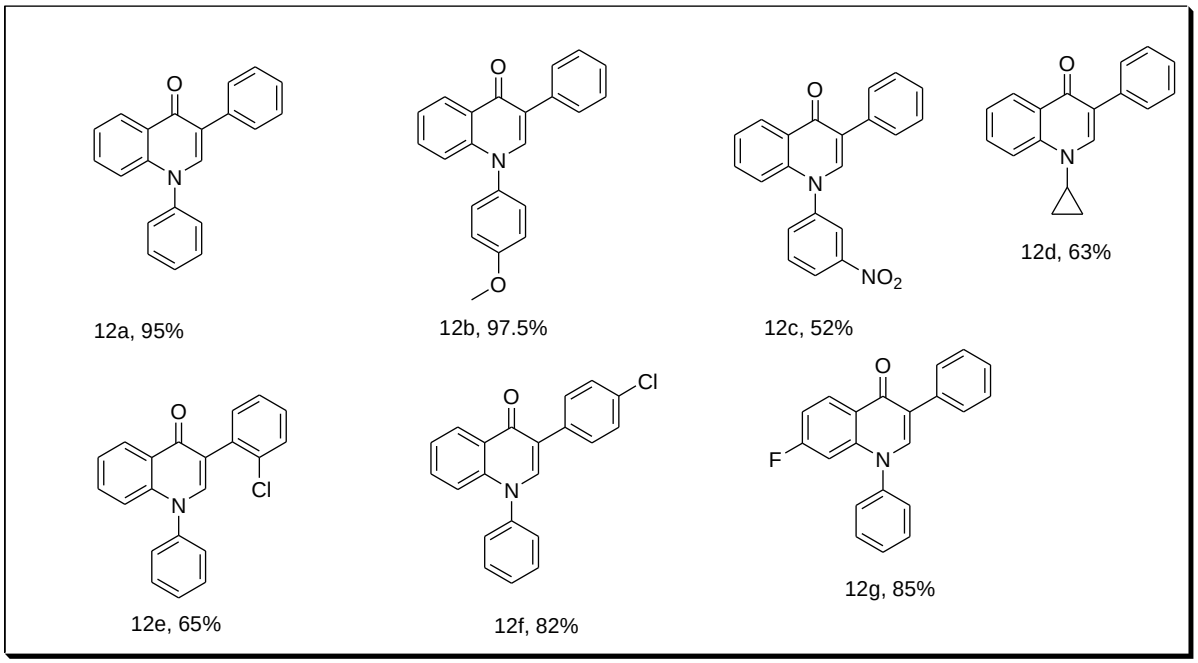
Most importantly, the cyclization of 1, 8-naphthalene diamine derivative resulted in 85% of quinolinoquinolinedione after isolation whereas the same transformation at 230 °C in diphenyl ether gave only 58% yield of product. In spite of this applicability, it had certain limitations such as regioselectivity and resulted several products when this protocol applied to derivatives.

Herein, an efficient one-pot metal-free process for the synthesis of 3-substituted 4-quinolones using amines and 3-(2-bromophenyl)-3-oxopropanal derivatives was described.[18]

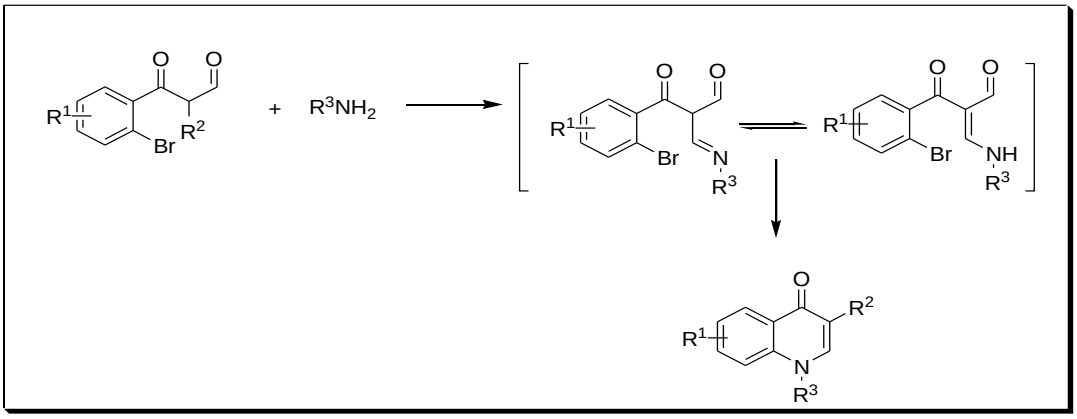


Scheme-I.4. Metal free synthesis of 3-substituted 4-quinolones from 3-(2-bromophenyl)-3-oxopropanal derivatives

Selected examples

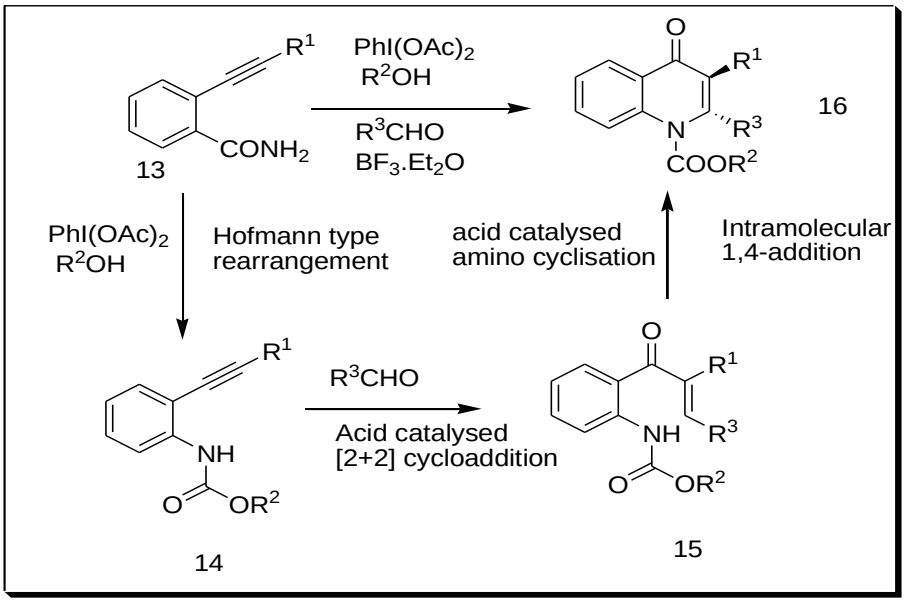


Plausible mechanism



A plausible mechamism was depicted which involved intramolecular cyclization/ amination of the enamines formed insitu (Figure). Actually, the base promoted the enamine-imine transformation and facilitated the dehydrobromination process to undergo the cyclization reaction. Electron rich amine furnished better yields than the electron poor counterparts.

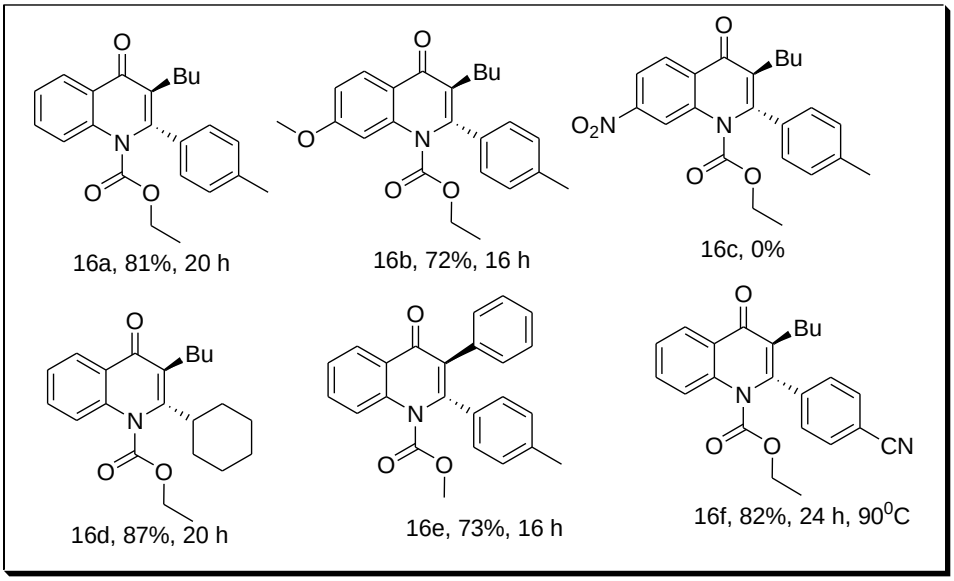
Yanada et.al reported the one-pot tandem process for the synthesis of various trans-2,3-disubstituted-2,3-dihydro-4-quinolones from 2-alkynylbenzamide derivatives.[19]

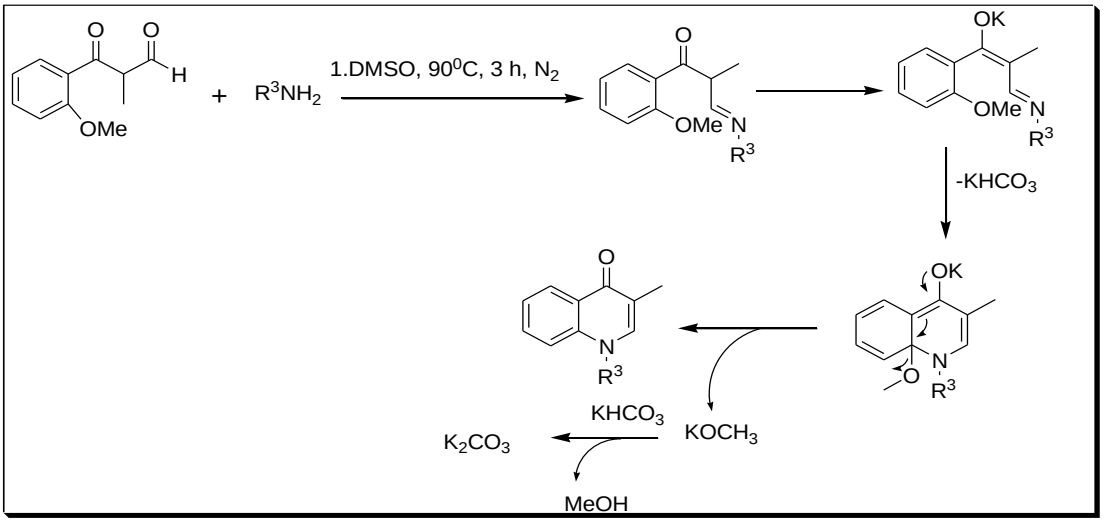


Scheme-I.5. $PhI(OAc)_2$ mediated synthesis of trans-2,3-disubstituted-2,3-dihydro-4-quinolones from 2-alkynylbenzamide derivatives

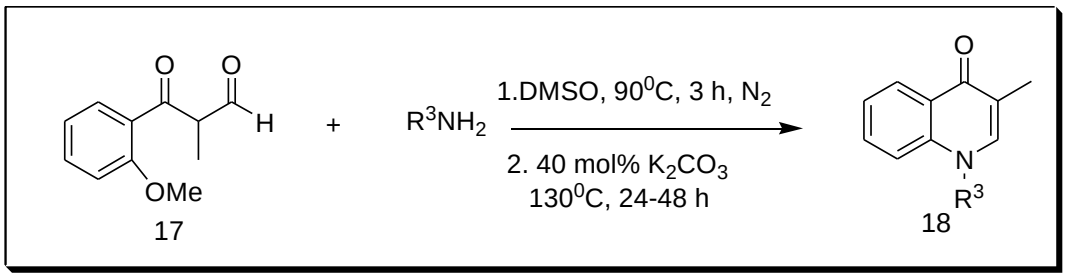
This tandem process comprised of following sequential steps. Compound 13 in the presence of hypervalent iodine underwent Hoffmann-type rearrangement followed by the addition of alkoxide resulted the intermediate 14. Then, intermolecular cycloaddition [2+2] took place in between the aldehyde and the triple bond of the alkyne. Finally, the desired product 16 obtained via the intramolecular aminocyclization of intermediate 15 and α,β-unsaturated ketones. Some selected examples of synthesized compounds were shown below.

Selected examples



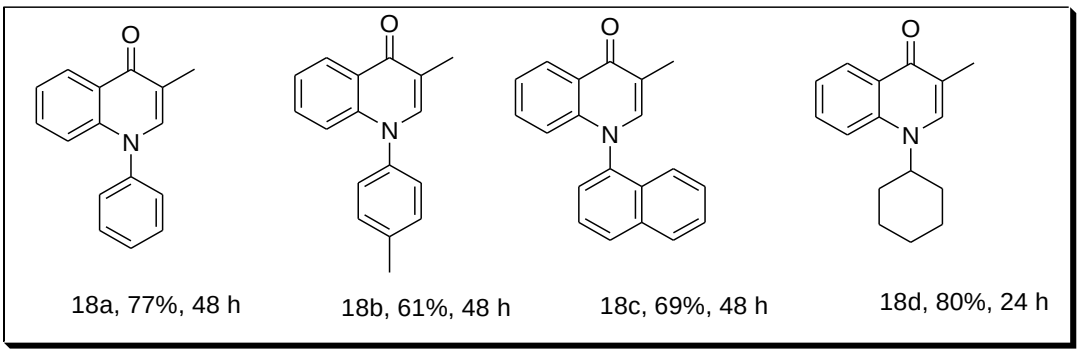


In 2012, Fu *et al.* accomplished the selective cleavage aromatic C-O bonds under base catalysed and metal free condition to synthesize the 4-quinolone in moderate yields. The whole process followed via coupling of aldehyde with primary amine to form imine intermediate, 3-(alkylimino)-1-(2-methoxyphenyl)2-methylpropan-1-one (III), and then it underwent intramolecular cyclization providing the 4-quinolone derivative.[20]



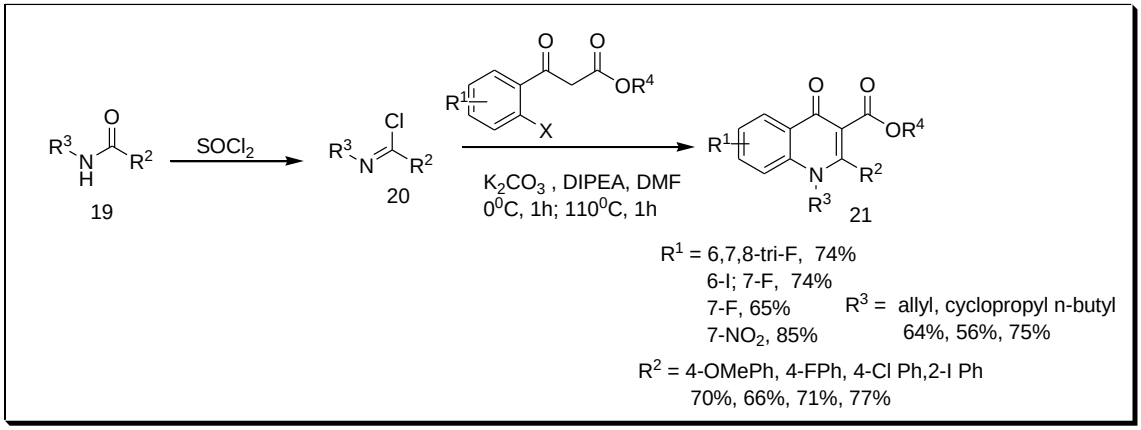
Scheme-I.6. K_2CO_3-Catalyzed synthesis of 4-quinolones through the Cleavage of Aromatic C-O Bonds

Selected examples



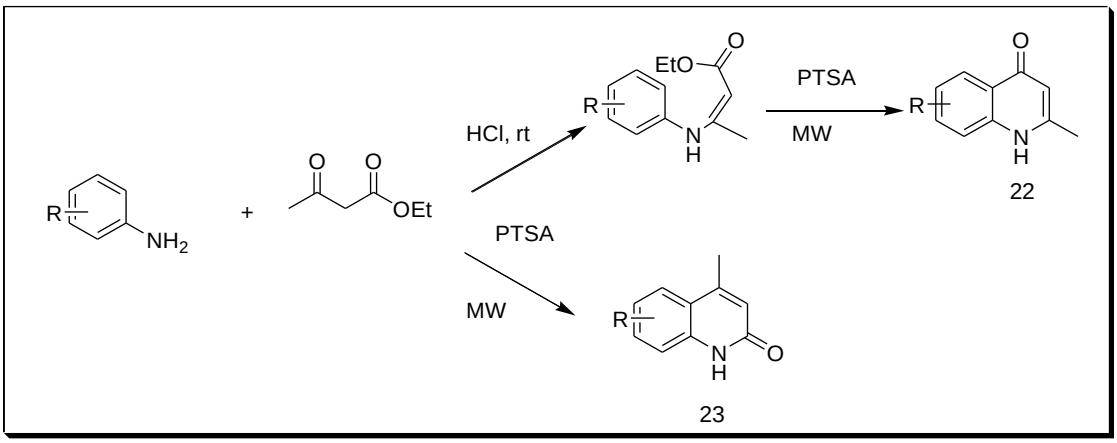
Plausible mechanism

Long.et.al reported the novel and efficient route of transition metal free synthesis of structurally diverse 2-substituted 3-carboxy-4-quinolone derivatives from 3-oxo-3-arylpropanoates and amides in a one pot approach. The methodology involves the intramolecular N-arylation in presence of base.[21]



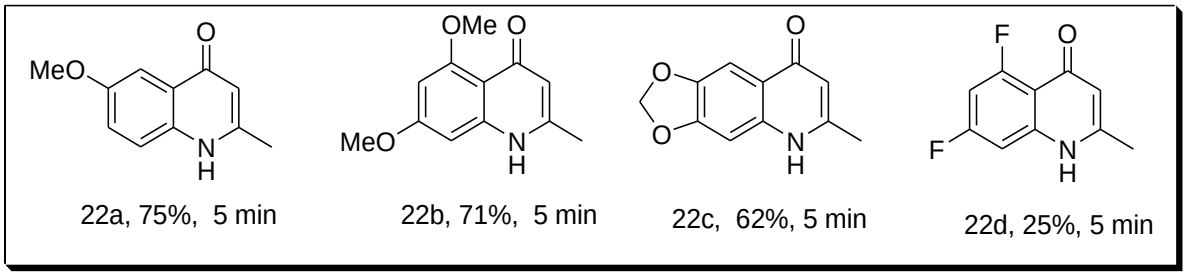
Scheme-I.7. Metal free synthesis of 2-substituted 3-carboxy-4-quinolone derivatives from 3-oxo-3-arylpropanoates and amides

Corrêa and his coworkers reported the microwave assisted synthesis of 4-quinolones in one step reaction between ethyl acetoacetate and electron rich anilines with diphenyl ether as a solvent.[22]

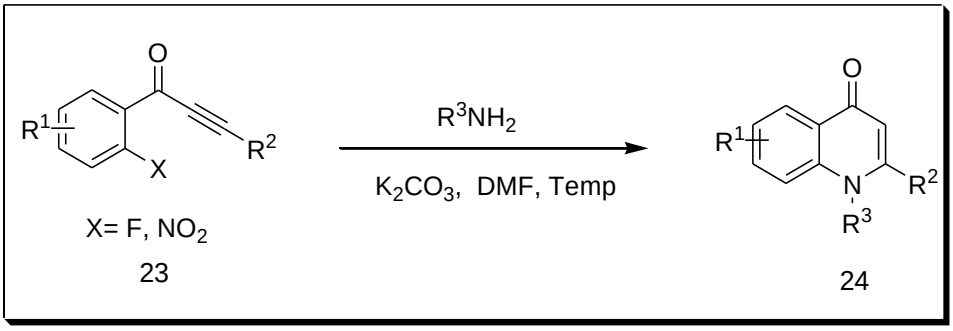


Scheme-I.8. Microwave assisted synthesis of 4-quinolones

Selected examples



Herein, Iaroshenko et.al described the catalyst free approach for the synthesis of functionalized quinolin-4-ones via tandem amination/conjugated Michael addition in between 1-(2-fluoro/2-nitrophenyl)prop-2-yn-1ones with amines.[23]

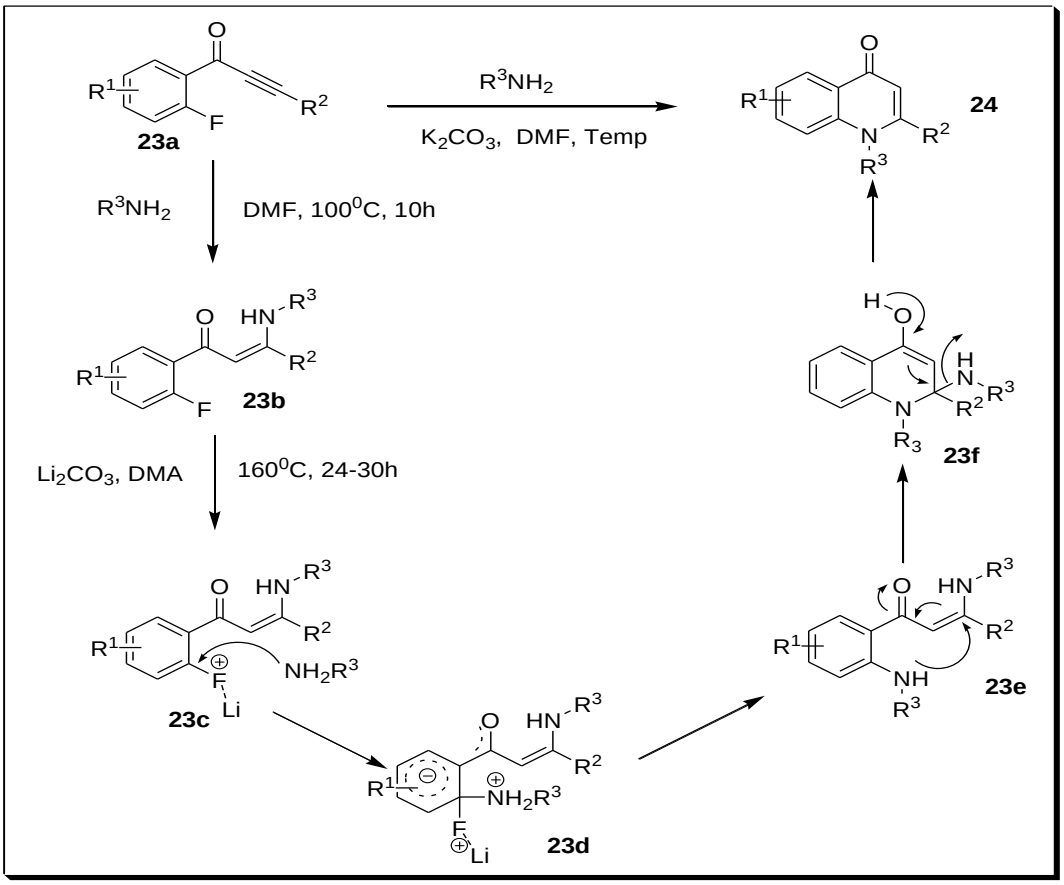


Scheme-I.9. Metal free synthesis of functionalized quinolin-4-ones from 1-(2-fluoro/2-nitrophenyl)prop-2-yn-1ones

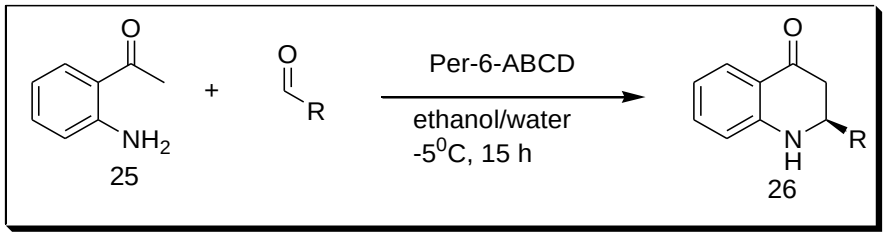
Generally, aliphatic amines responded well and gave moderate to excellent yields of the corresponding products, but anilines gave good yields. Electron-deficient heteroaromatic amines such as benzo[d]thiazol-2-amine, pyrimidin-2-amine, or pyridine-2-amine did not respond under this optimized condition.

Plausible mechanism

They proposed a stepwise mechanism for the one-pot synthesis of 4-quinolones 24 was shown above. Preliminary, the alkynone 23a underwent hydroamination reaction gave intermediates 23b. In the next, the lithium cation coordinated with the fluorine atom of the intermediate 23b to produce the intermediate 23C, which readily transformed into the Meisenheimer complex 23d via an aromatic nucleophilic substitution reaction. The fluorine anion eliminated as lithium fluoride to give the intermediate 23e. Further, it underwent an intermolecular Michael addition to generate the quinolin-4-one 24 via forming an intermediate 23f.

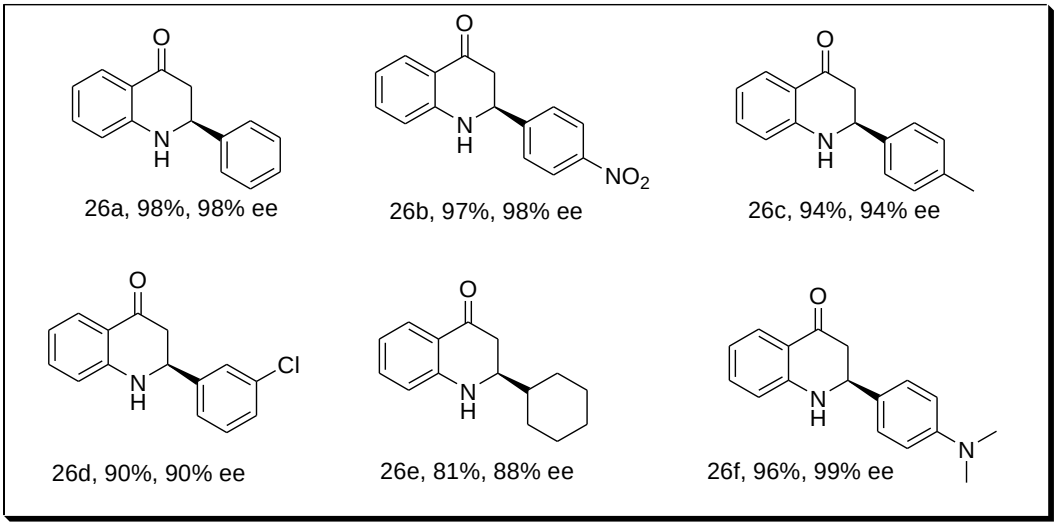


Pitchumani demonstrated the novel and efficient one-pot synthesis of enantiomerically enriched 2-aryl-2,3-dihydroquinolin-4(1H)-ones from o-aminoacetophenone and substituted aldehyde in the presence of per-6-ABCD (per-6-amino-β-cyclodextrin) which acted as a supramolecular host, chiral base catalyst, and also a reusable promoter to give the desired scaffold with excellent yield (up to 99%) and enantiomeric excess (up to 99%).[24]



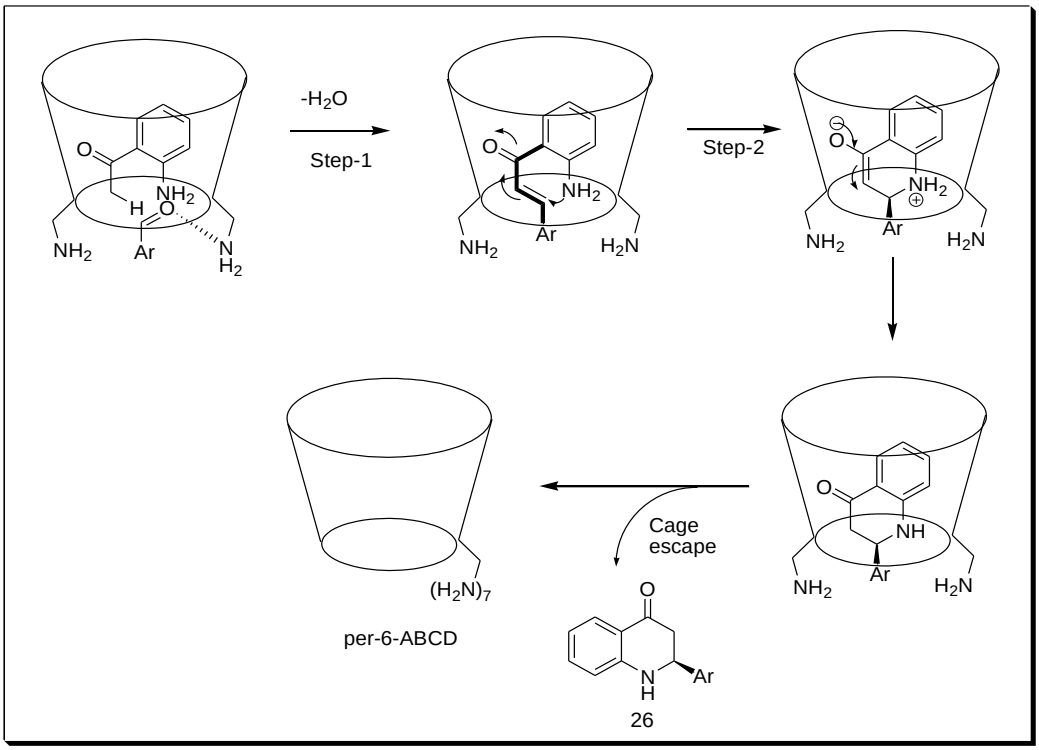
Scheme-I.10. Per-6-ABCD induced synthesis of enantiomerically enriched 2-aryl-2,3-dihydroquinolin-4(1H)-ones

Selected examples



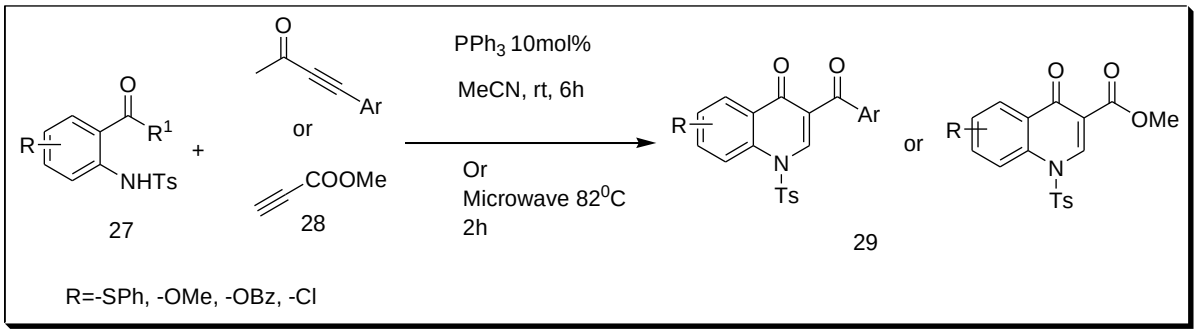
Both heterocyclic and cyclic aldehydes participated in reaction very well and resulted the products with high yield and excellent enantioselectivity. Electron releasing group and electron with drawing group possessing aldehydes were well tolerated in the reaction. Para-substituted aldehydes accomplished better yield than the ortho and meta substituted aldehydes due to stronger binding and deeper inclusion in the cyclodextrin cavity. Electronic factor was not very prominent than the steric factor in enhancing the enantiomeric excess (ee).

Plausible mechanism



A plausible mechanism was proposed to provide the asymmetric synthesis of 2-Aryl-2,3-dihydro-4-quinolone. Initially, o-aminoacetophenone and aldehydes underwent the condensation reaction to form chalcone. Then, isomerization of chalcone occurred via Aza-michael addition and readily it tautomerized to provide the 2-aryl-2, 3-dihydro-4-quinolone with high enantioselectivity (ee > 99%). The amino group of per-6-ABCD activated the Aza-michael addition into the cavity through its *Si*-face and resulted the stereochemical outcome.

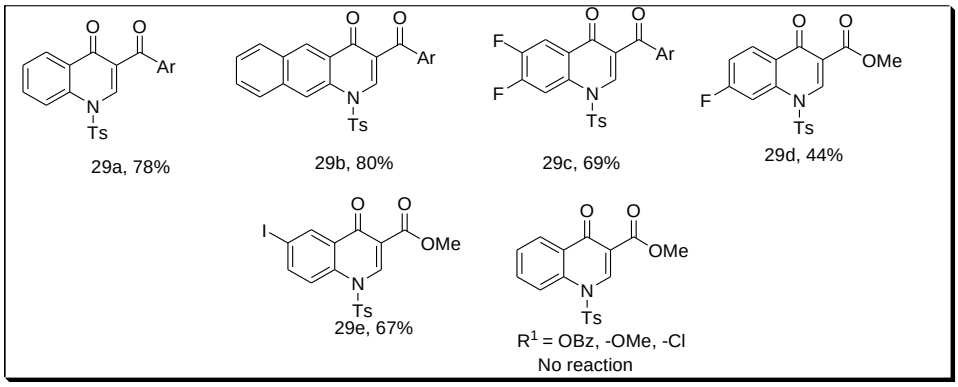
Kwon *et al.* reported a metal free approach for the synthesis of 3-substituted 4-Quinolones using an inexpensive cheap phosphine catalyst.[25]



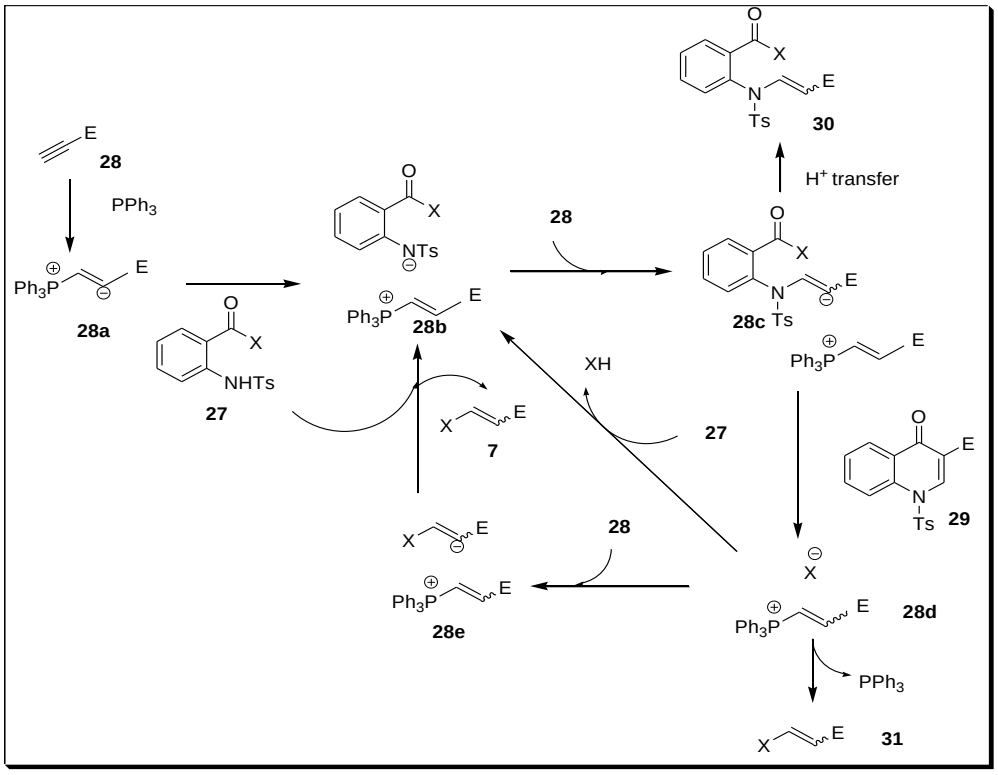
Scheme-I.11. PPh_3 catalysed synthesis of 4-quinolones

The reaction took 6h at rt to complete conversion whereas under microwave irradiation at 82°C it completed within 2h and resulted in the decent yield of the final product. Using this reaction condition, they synthesized a number quinolone structures in which electron-deficient aromatic rings gave the lower reaction yields than the electron-rich aromatic rings. Particularly, the electron-withdrawing halide substituents, at the meta position showed a contradictory trend in the reaction. More electron-withdrawing halides led the better reaction yields of quinolone formation.

Selected examples



Plausible mechanism



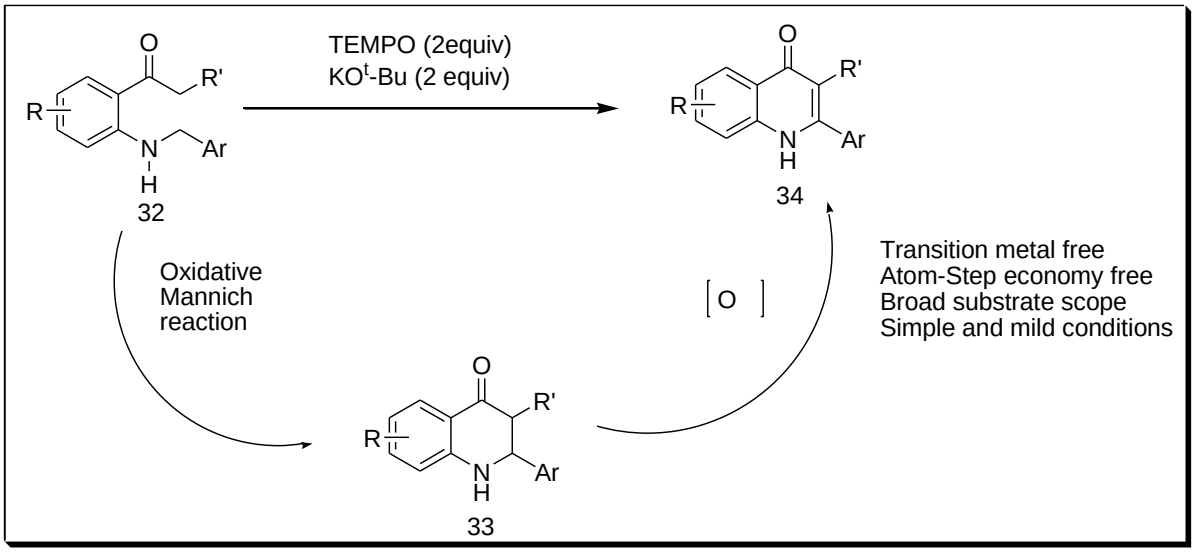
A mechanistic pathway was proposed by Kwon et.al where reaction began with the nucleophilic addition of triphenyl phosphine to the activated alkyne 28 and subsequently generated the phosphonium based zwitterions 28a. By deprotonation, the intermediate 28a activated the pronucleophile 27. The resulting nucleophile in 28b readily added to the activated alkyne 28 to form the ion pair 28C.

Then, it underwent the cyclization to generate the desired 4-quinolone 29 via acyl substitution (X=SPh) pathway whereas it also formed to the Michael adduct 30 as a byproduct. During the formation of the quinolone 29, the leaving group X in the ion pair 28d further added to the activated acetylene **28** to regenerate the PPh_3 derived base for continuing the catalytic cycle.

Other possibility, the departing group X^- might be functioning as a base to activate the starting pronucleophile 27. In this case , the proton donor HX would also generate the byproduct 30 via proton transfer mechanism. Lastly, the Ph_3P initiator might be reformed from the ion pair 28d followed by addition/elimination reaction.

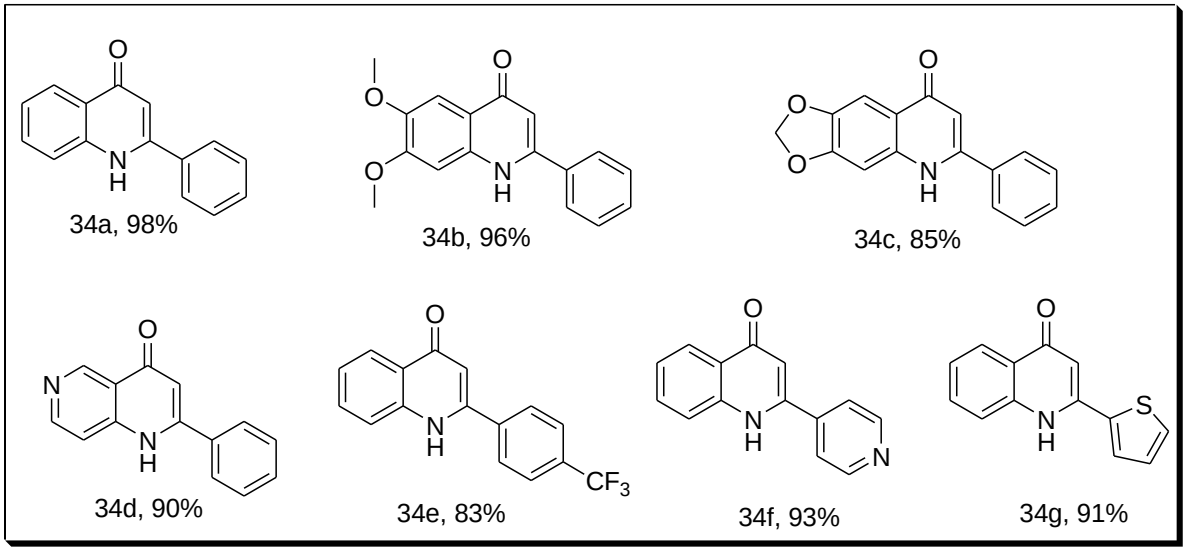
In 2015, a novel approach for the synthesis of diverse 2-aryl-4-quinolone derivatives via a TEMPO-mediated intramolecular oxidative Mannich reaction from N-arylmethyl-2-aminophenyl ketones was reported by Long et al.[26] This transition metal-free oxidative Mannich reaction followed a tandem oxidative $C(sp^3)–H/C(sp^3)–H$

coupling and aromatization to afford a broad range of 2-arylquinolin-4(1H)-ones as a final product.



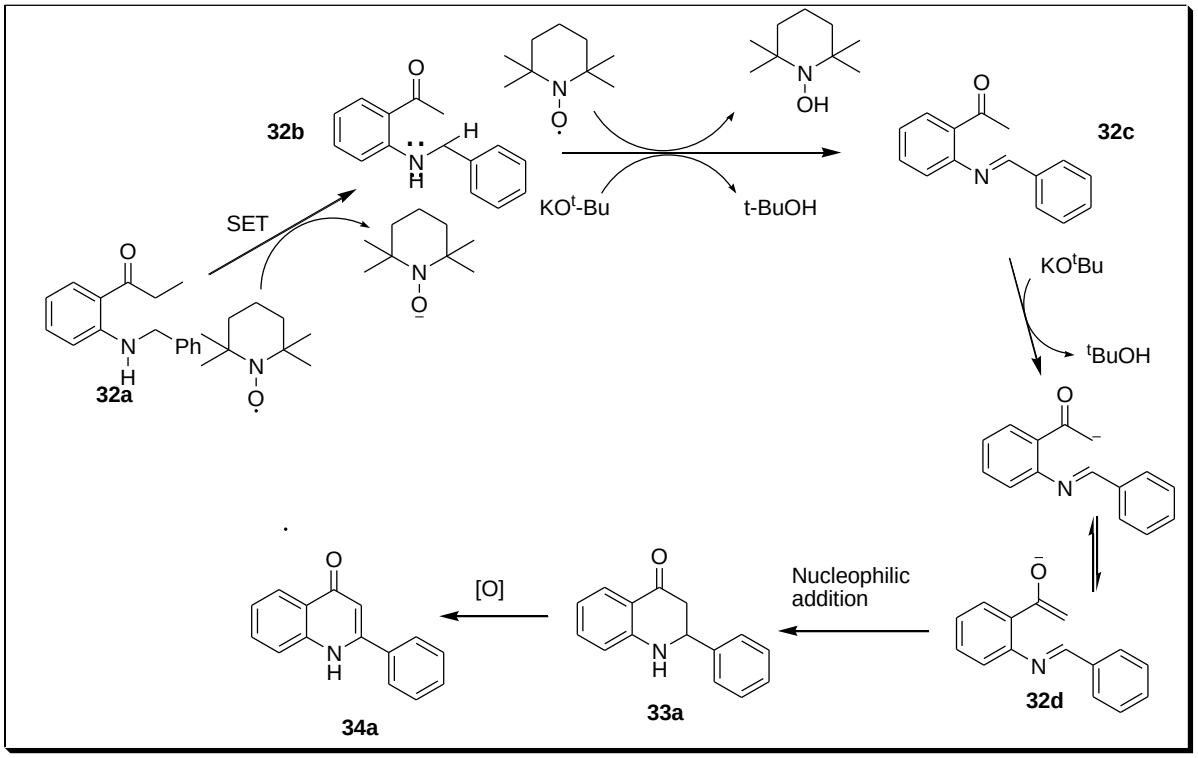
Scheme-I.12. TEMPO catalysed intramolecular tandem oxidative C(SP^3)-H/ C(SP^3)-H coupling

Selected examples



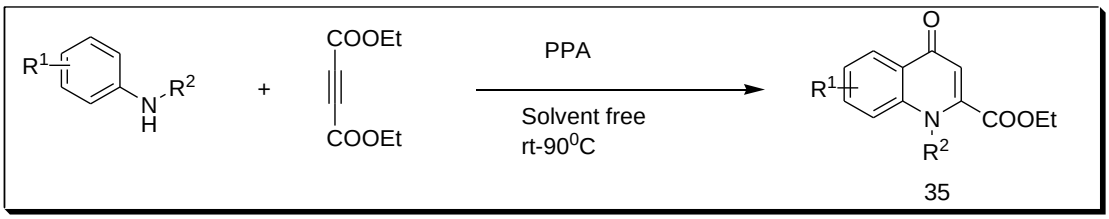
Aromatic rings possessing the electron-donating or -withdrawing or sterically hindered groups, all underwent the oxidative cyclization smoothly and furnished the desired 4-quinolone products in good to excellent yields. Aliphatic substituent could not be incorporated at the 2-position of 4-quinolone using this protocol rather it gave an oxidized cleavage benzoic acid derivative.

Plausible mechanism for the TEMPO promoted oxidative annulations



A plausible mechanism for this protocol was given in above figure. Initially followed by the SET pathway, TEMPO generated an anilinium radical cation 32b. This radical cation yielded an iminium-type intermediate via a hydrogen transfer from the adjacent carbon. Afterwards under the basic conditions, it rapidly converted to imine 32c and subsequently to an enolate form 32d. Finally, nucleophilic addition occured to the imine and the annulated product 33a is readily oxidized to give the desired quinolone product 34a.

In 2015, Huang and his co workers designed a protocol for the construction of 4-quinolone-2carboxylates via a cascade reaction between commercially available aromatic amines and diethyl acetylene dicarboxylate.[27]

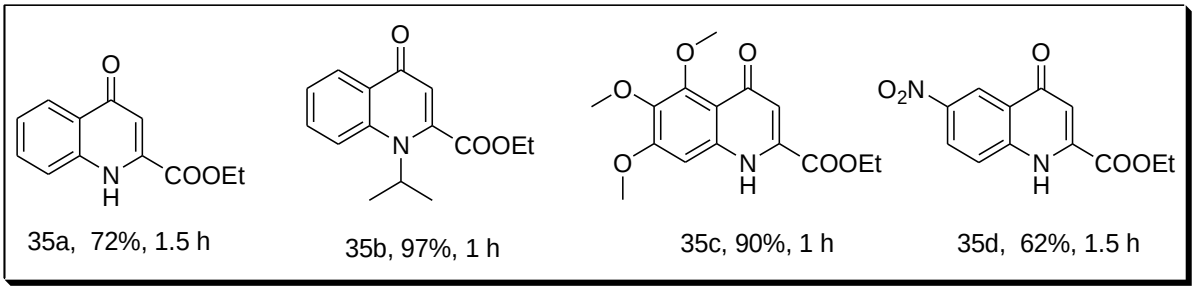


Scheme-I.13. PPA catalysed synthesis of 4-quinolones.

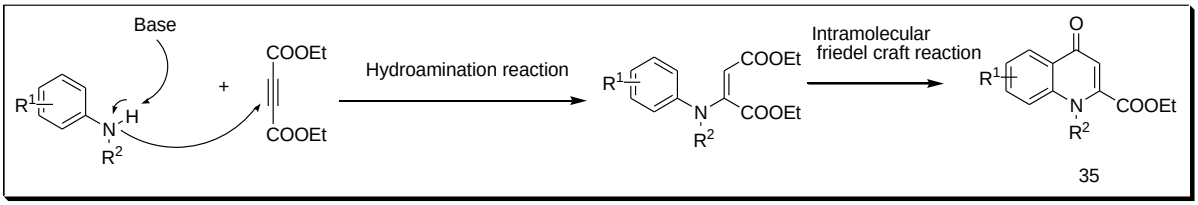
Electron density effect of aromatic amines plays the pivotal role for the formation of 4-quinolone. As the electron density on the nitrogen atom increases, the yield of the product gradually increases. Electron withdrawing group substituted primary amine

took longer reaction time than those for electron donating groups. The steric hindrance and electron density of diphenylamine and benzylamine failed to give the desired product.

Selected examples

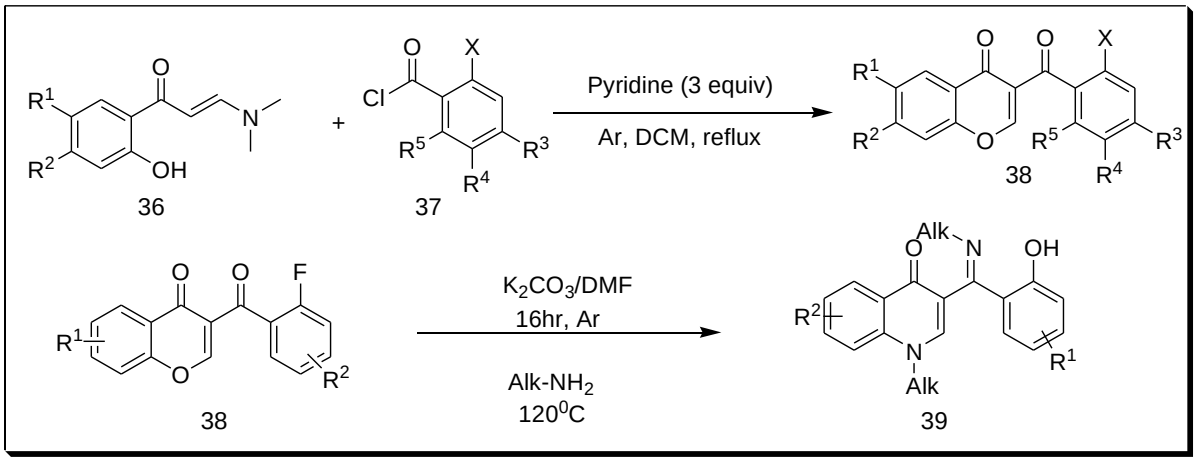


Plausible mechanism



A plausible mechanism for the formation of the desired product 35 is mentioned in following scheme. The activated non-terminal alkyne participated in hydroamination reaction with diethyl acetylenedicarboxylate in presence of aromatic amine affording the intermediate. Subsequently, the intermediate underwent an intramolecular Friedel–Crafts reaction to furnish the product 35 with PPA as catalyst. Due to the effect of electron density and steric hindrance of nitrogen atom, the structure of aromatic amine had a significant influence in the protocol.

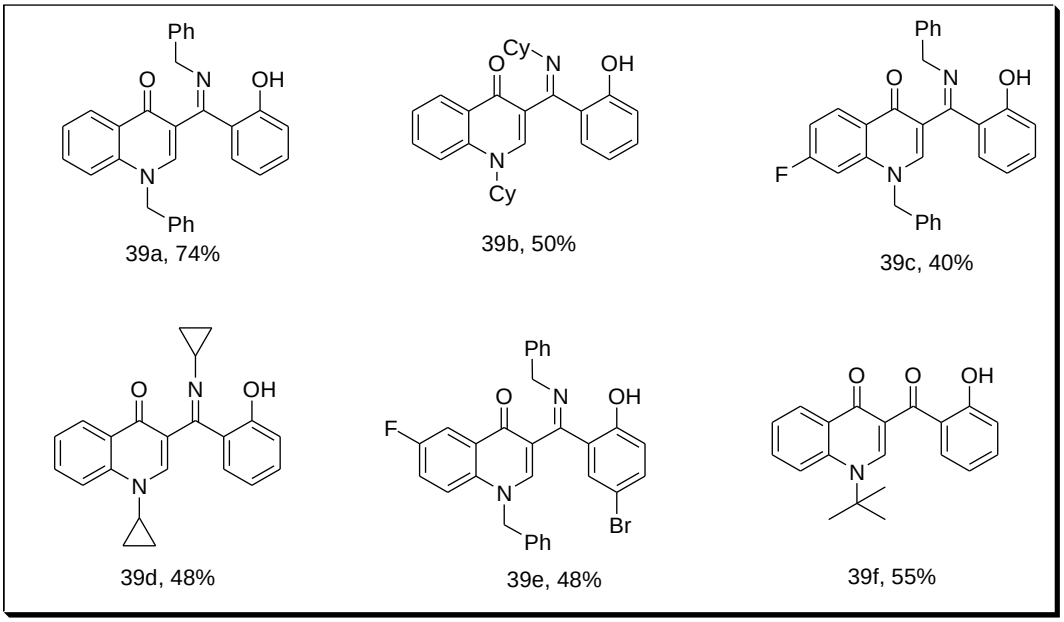
A transition metal free strategy for the synthesis of 4-quinolones *via* domino reaction of 3-benzoyl-chromones with aliphatic amines, anilines was demonstrated.[28]



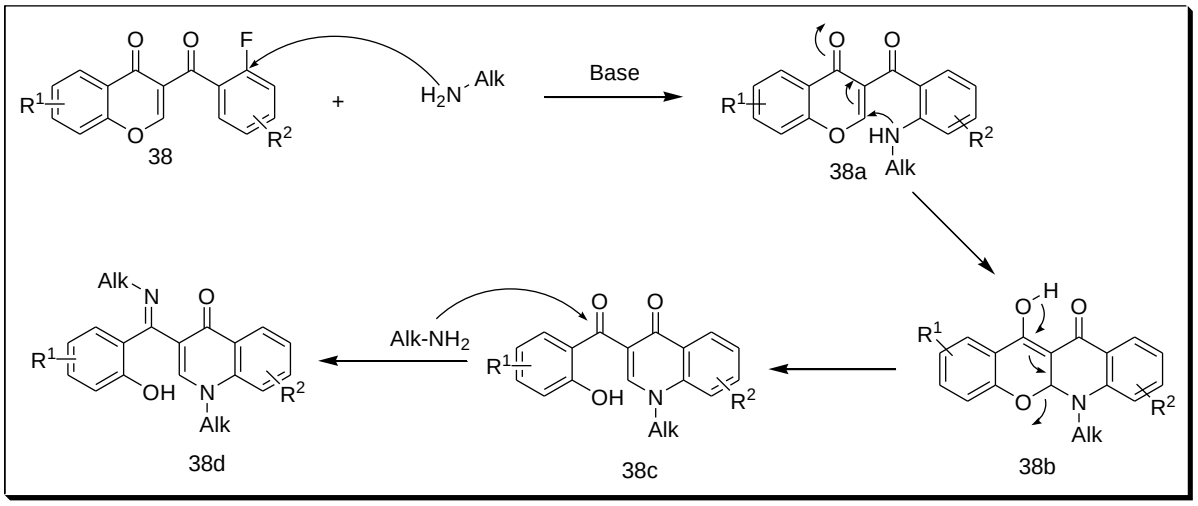
Scheme-I.14. Transition metal free synthesis of 4-quinolones *via* domino reaction of 3-benzoyl-chromones with aliphatic amines, anilines

All reactions responded well and provided the desired products ranging from moderate to excellent yields, with excellent chemoselectivity. Sensitive functional groups on the chromone were well tolerated.

Selected examples

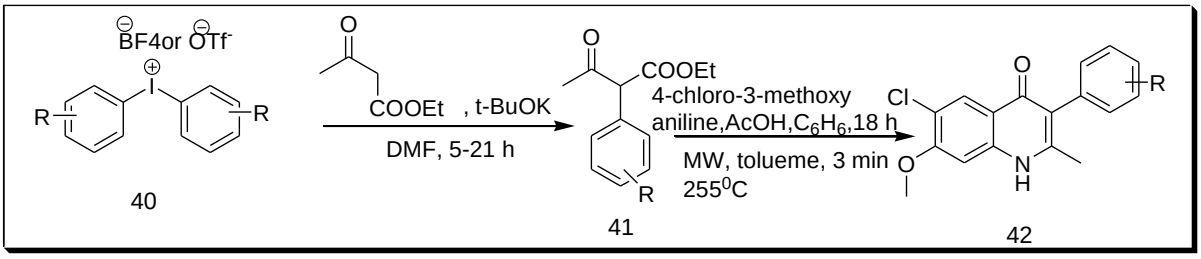


Plausible mechanism



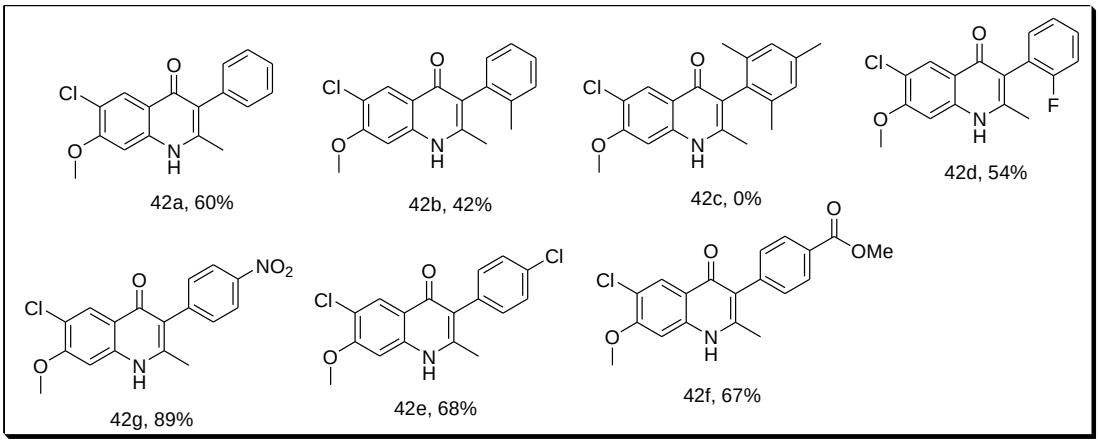
This domino sequence was initiated by the aromatic nucleophilic substitution of fluorine atom. This was followed by the intramolecular attack of amino group to the position 2 of chromone moiety. Finally the ANRORC (Addition of the Nucleophile, Ring Opening, and Ring Closure) transformation of the pyrone ring delivered the desired 4-quinolones. In most of the cases the reaction proceeded further with second molecule of amine leading to the formation of corresponding Schiff bases.

Manetsch et al. recently reported a new convenient and operationally simple protocol for the arylation of ethylacetoacetate under metal free and mild condition in the presence of hypervalent iodine reagents. Further, this technology was applied by them to prepare the antimalarial ELQ-300 compound under modified Conrad Limpach cyclisation.[29]



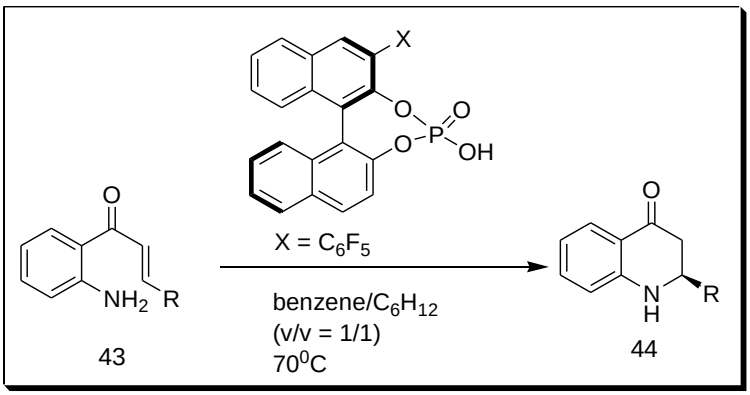
Scheme-I.15. Hypervalent iodine reagent mediated arylation of ethylacetoacetate

Selected examples



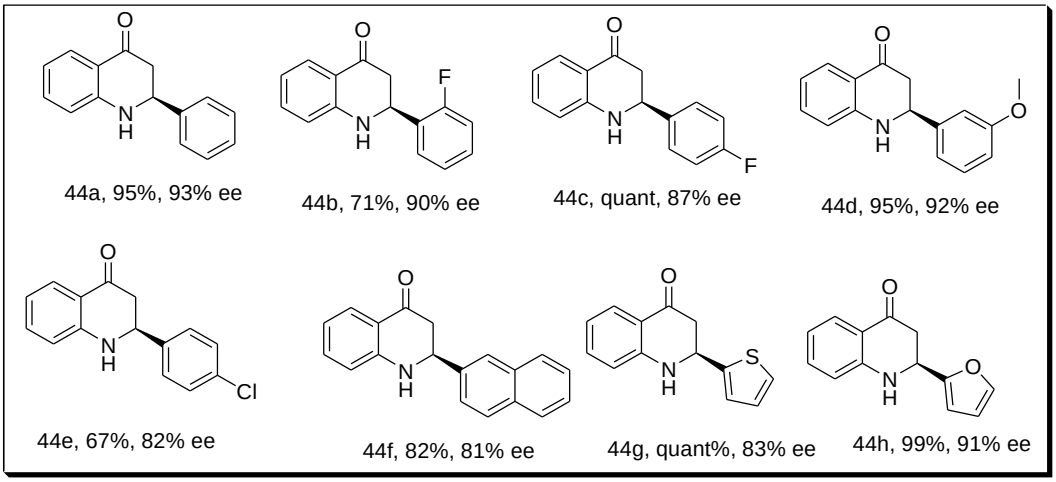
Major advantage of this protocol was that ortho substituted substrates were well tolerated and converted to moderate yield of the arylated product. 4-methoxy substituted aryliodonium salt did not provide any product after prolonged reaction because +R effect of methoxy group reduced the electrophilicity of the iodine centre. In contrast, electron withdrawing group substituted iodonium salt reacted in a very short time and provided excellent yield.

In 2015, Akiyama and his coworkers developed a new method to synthesize the asymmetric 2-substituted 2,3-dihydro-4-quinolones via chiral phosphoric acid catalyzed intramolecular aza-Michael addition reaction from *N*-unprotected 2-aminophenyl vinyl ketones . This method furnished the broad array products with high enantioselectivities and yield.[30]



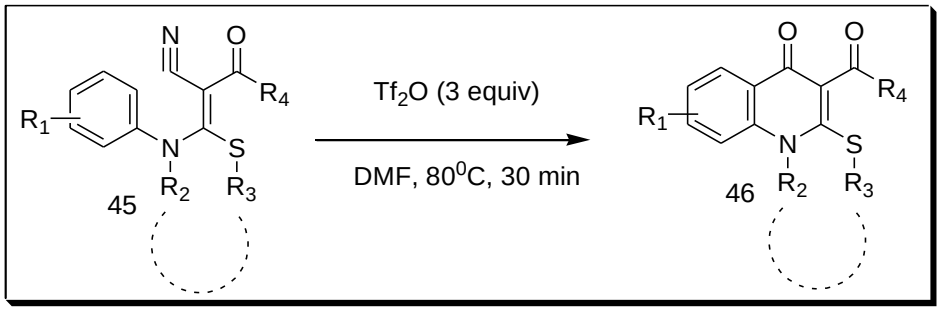
Scheme-I.16. chiral phosphoric acid catalyzed synthesis of 2-substituted 2,3-dihydro-4quinolones via intramolecular aza-Michael addition reaction from N-unprotected 2-aminophenyl vinyl ketones

Selected examples



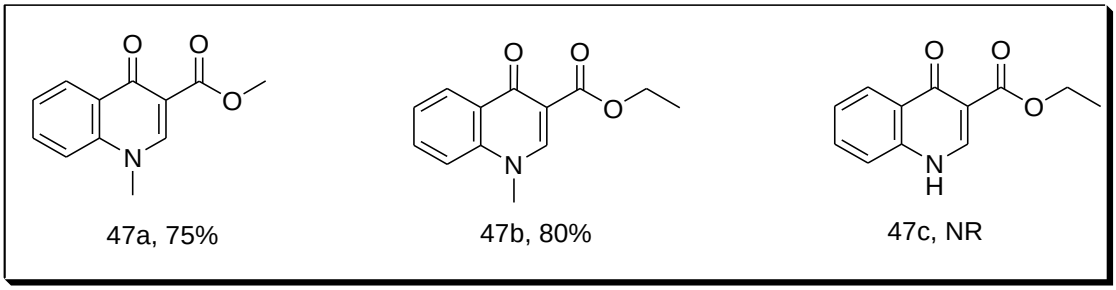
Ortho substituted arenes at the β-position furnished both high yield and excellent enantioselectivity. Electron with drawing and electron donating group substituted substrates were easily converted into the desired products with high enantiomeric excess.

Huang and Ge reported an efficient approach to synthesize the 4-quinolones via intramolecular Houben-Hoesch reaction of β-arylamino acrylonitriles mediated by triflic anhydride in N,N-dimethylformamide.[31]

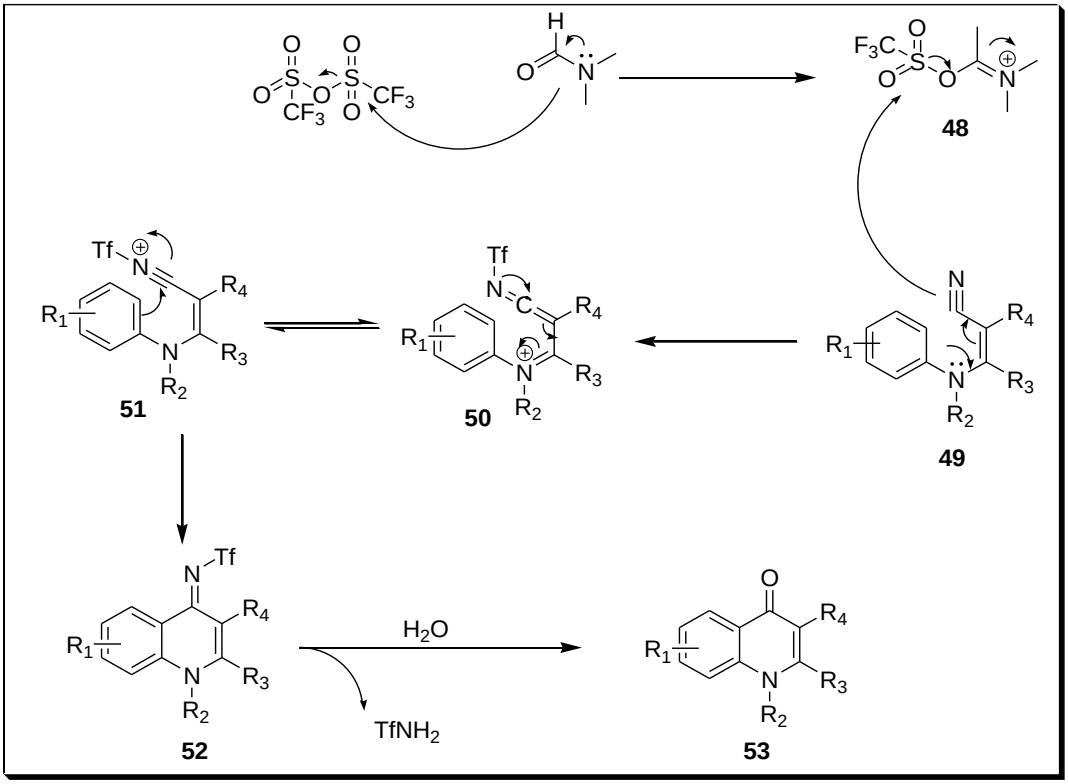


Scheme-I.17. Synthesis of 4-quinolones from N-aryl ketene-N,S-acetals

Selected Examples

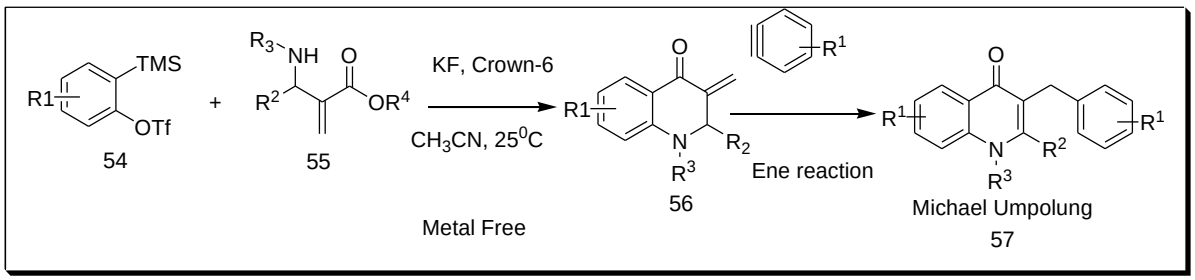


Plausible reaction mechanism



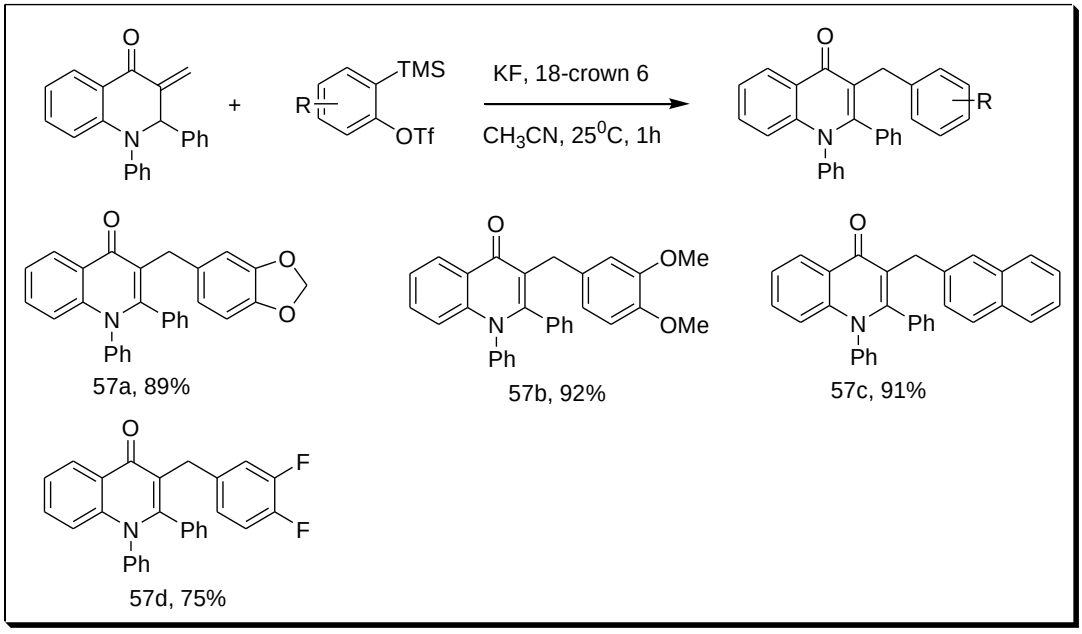
Initially, iminium triflate derived in situ via the reaction between DMF and Tf_2O. Then, the triflation of β-arylacryloaminonitrile occurred with iminium triflate to produce the intermediate 50 and its tautomer 51. Subsequently, the intermediate 51 underwent intramolecular Houben-Hoesch reaction which leads to the intermediate 52. Then, intermediate 52 hydrolyzed to provide the final product 53.

Here in , a mild and novel one pot aryne transformation for the construction of various substituted 4-quinolones through a cascade –insertion cyclisation followed by a rare inverse electron demand ene reaction was demonstrated by He et al. [32]

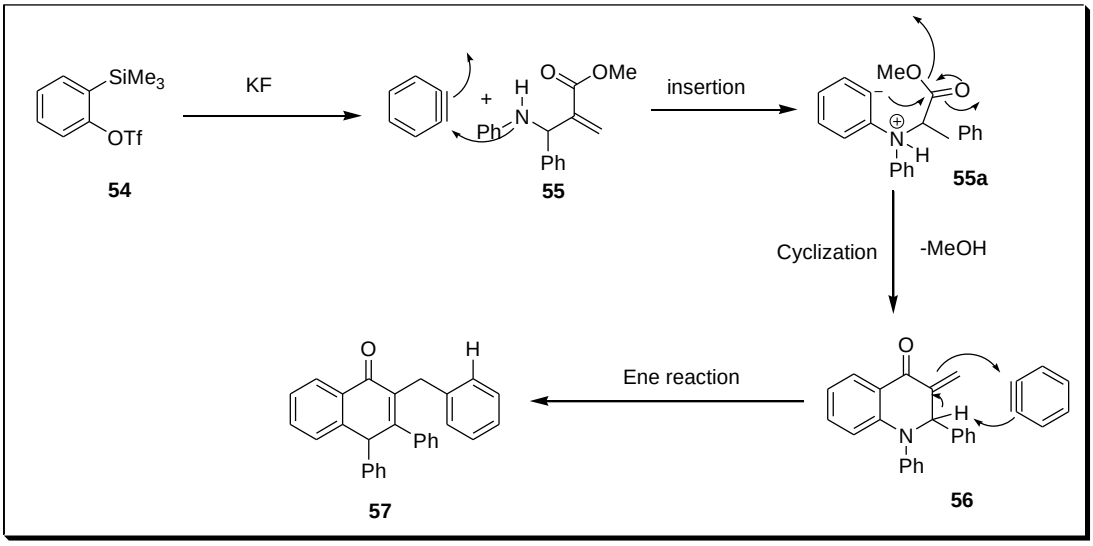


Scheme-I.18. Cascade Reaction of Aryne and AMBH (aza-Morita-Baylis Hilmann) Adduct

Selected examples



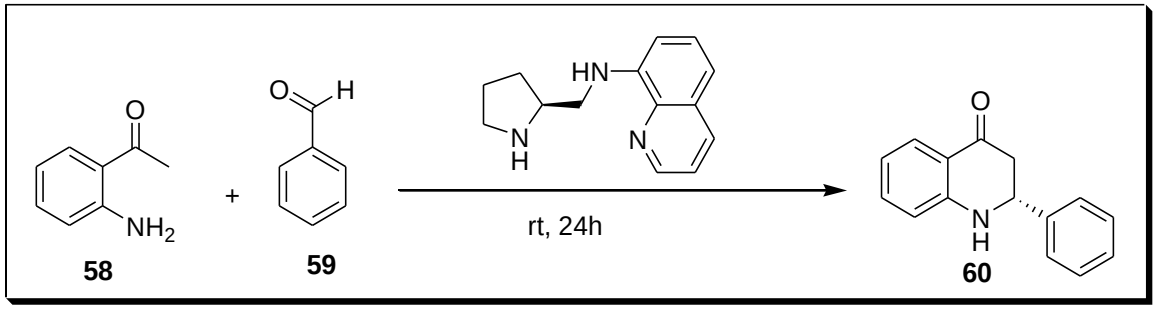
Plausible mechanism



A probable mechanism for the synthesis of 4-quinolone derivatives was outlined in the above Scheme. The reaction of the AMBH adduct with an aryne generated the intermediate 5a followed by a cascade insertion−cyclization process.[44] Subsequently, intermediate 56 reacted with another molecule of electrophilic aryne in a concerted way proceeding through an inverse electron demand ene reaction to furnish the product 57.

In recent years, Wang and his group accomplished the highly efficient organocatalytic one-pot enantioselective synthesis of (R)-2-aryl-2,3-dihydro-4-quinolones from o-amino

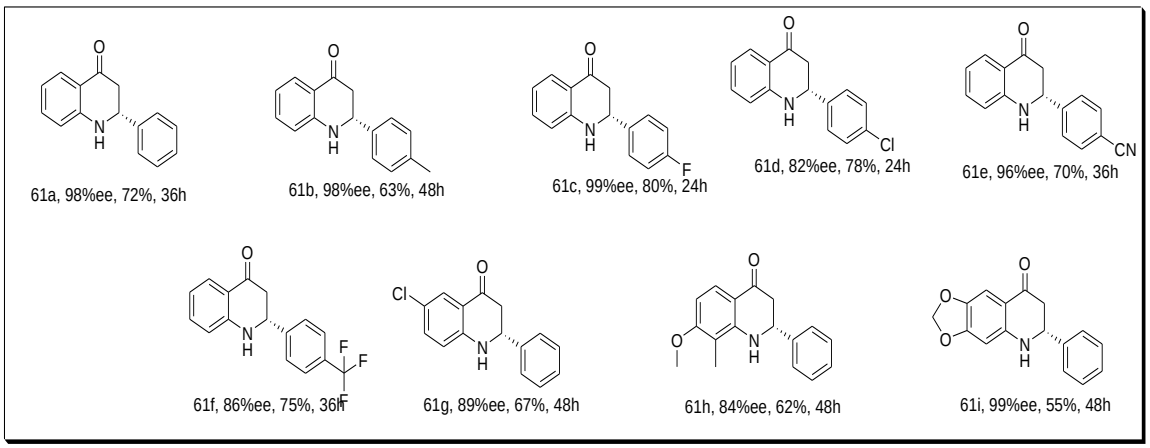
acetophenones and aryl aldehydes under metal free, solvent free and protecting group free approach.[33]



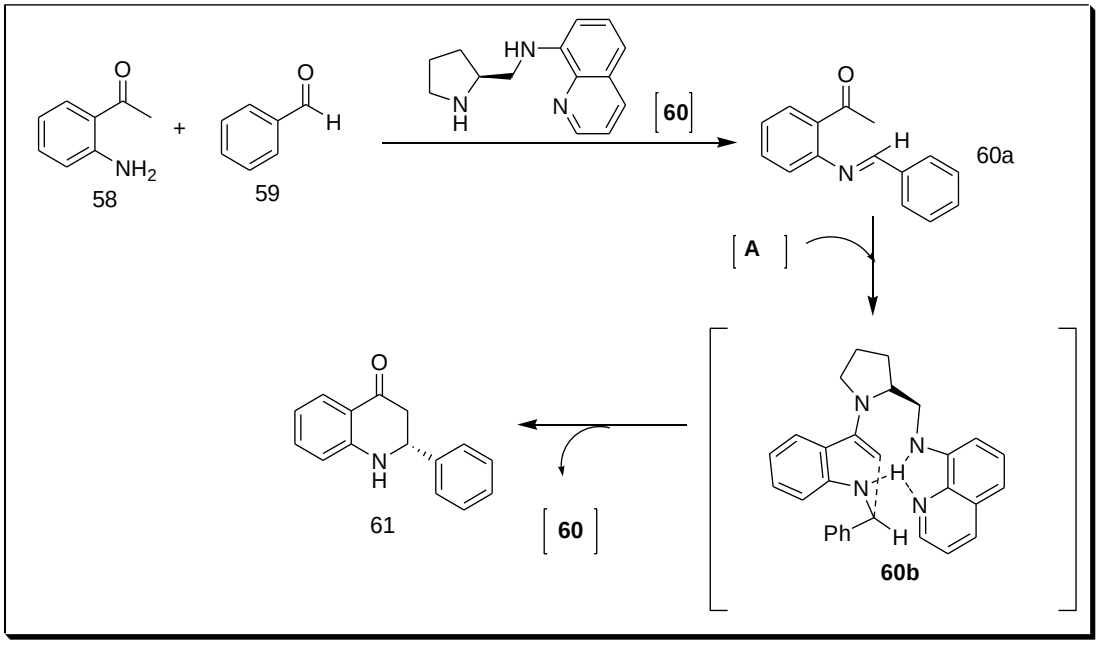
Scheme-I.19. Metal free, solvent free enantioselective synthesis of dihydro 4-quinolones

Electron-donating groups or electron withdrawing groups substituted aryl aldehydes reacted nicely and provided the corresponding (*R*)-2-aryl-2,3-dihydro-4-quinolones in moderate to excellent yields and ee values. Sterically hindered substituted aryl aldehyde gave much lower yield. 5-chloro-2-aminoacetophenone, 3-methyl-4-methoxyl-2-aminoacetophenone and 4,5 methylenedioxy-2-aminoacetophenone reacted smoothly with benzaldehyde, resulting the desired products (67% yield, 89% ee), (62% yield, 84% ee) and (55% yield, 99% ee), respectively.

Selected examples

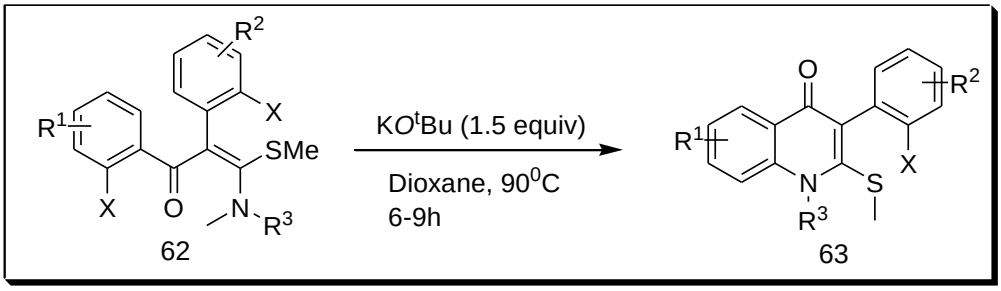


Plausible mechanism



Probably this one pot approach formed via imine formation and it underwent the intramolecular asymmetric Mannich reaction to give the 2-aryl-2,3 dihydro-4-quinolone. Catalyst [60] might be promoted the subsequent Mannich reaction followed by the intermediate 60b, in which the C=O group of imine was readily activated by the catalyst [60] via formation of an enamine. Also the hydrogen-bond between the nitrogen atom and the N–H activated the C=N of the imine. From the molecular modeling studies, the author believed that phenyl ring of the substrate and quinolinyl ring of the catalyst possess arene pi–pi stacking which contributed to the high enantioselectivities.

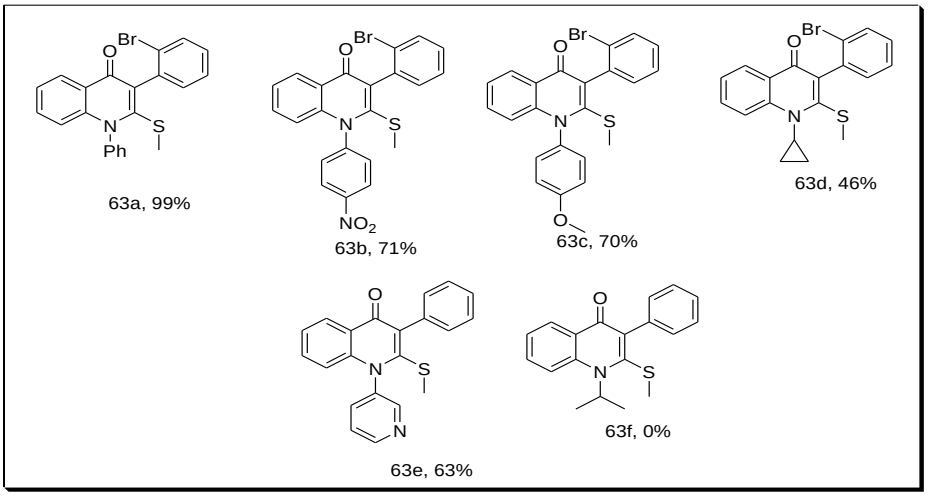
Recently, Peruncheralathan and his coworkers unfolded a new method to prepare the quinolone fused heterocycles under transition metal free condition from single S, N-acetal precursors *via* double heteroannulation.[34]



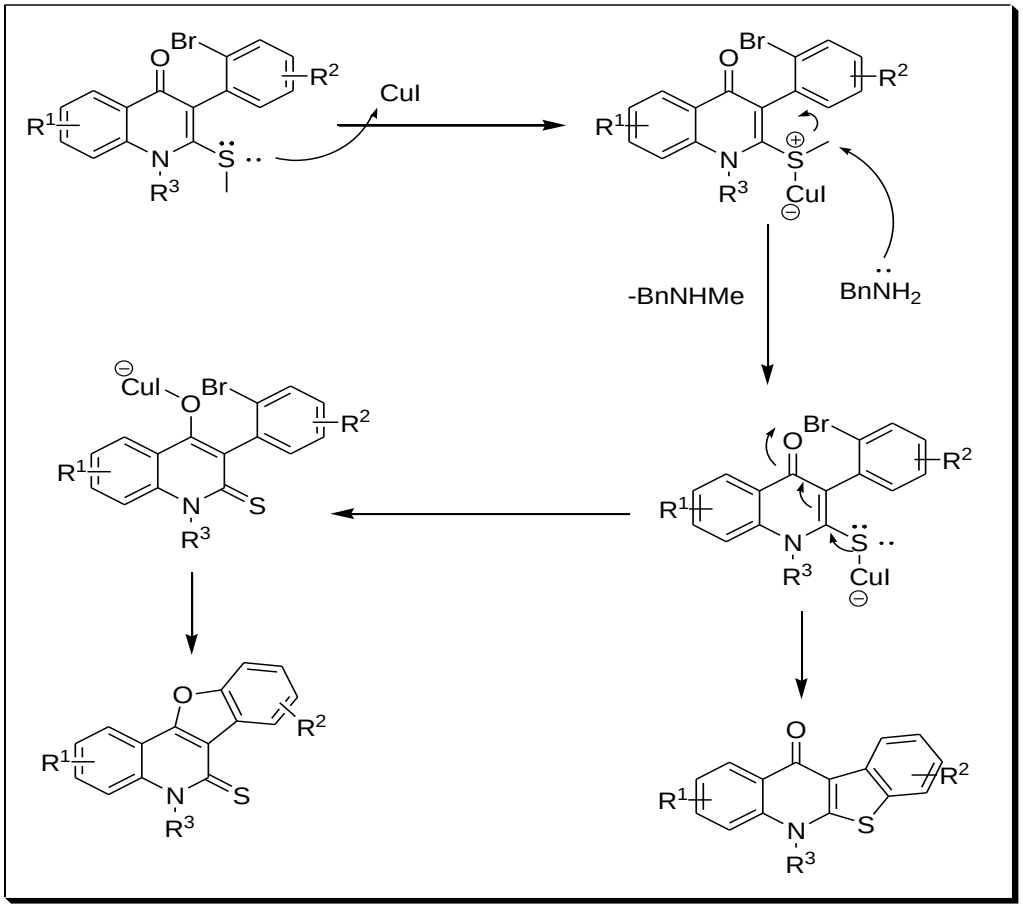
Scheme-I.20. KO-*t*Bu catalysed synthesis of 4-quinolones

It has been found that the substituted aniline nitrogen atom of S,N acetals bearing both Electron withdrawing and electron releasing group responded equally. Unfortunately, aliphatic amino *S,N* acetals gave poor yield. In the amination process, Steric hindrance effect profoundly.

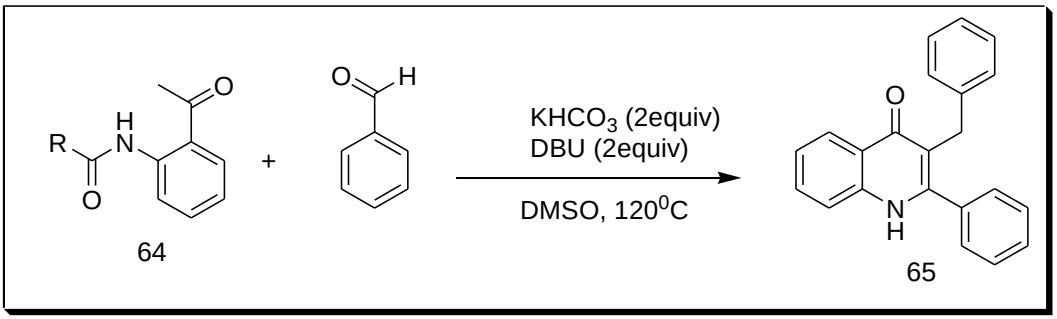
Selected examples



Plausible pathway for the formation fused heterocycles



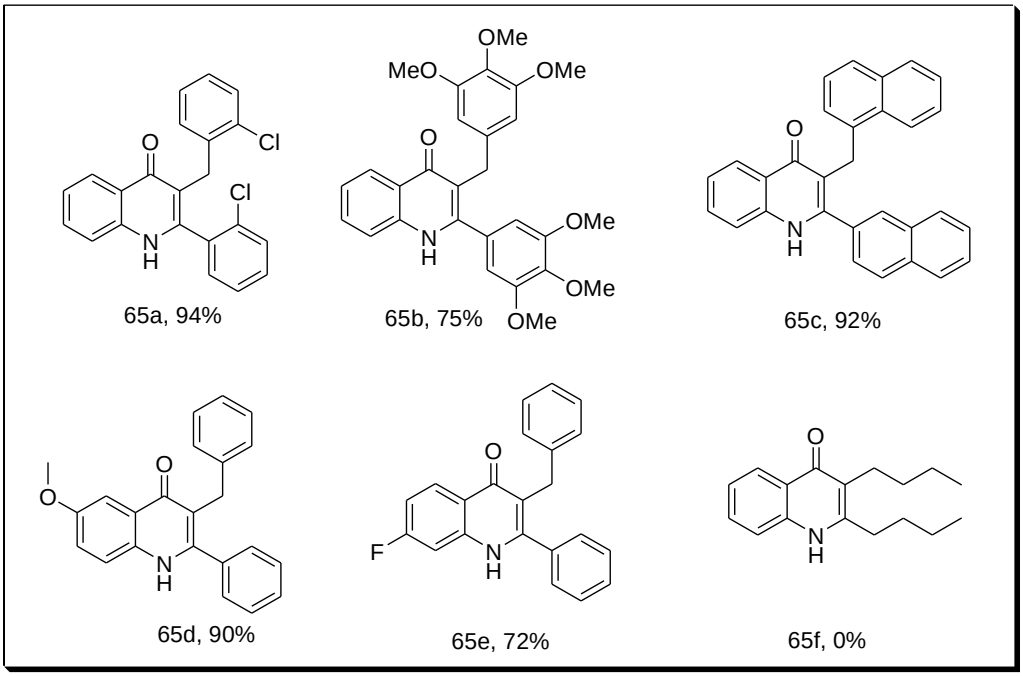
More recently Huang *et al.* described an efficient strategy for the transition metal free synthesis of 3-Benzyl-2-phenylquinolin-4(1H)-ones via $KHCO_3$ and DBU promoted cascade reaction. [35]



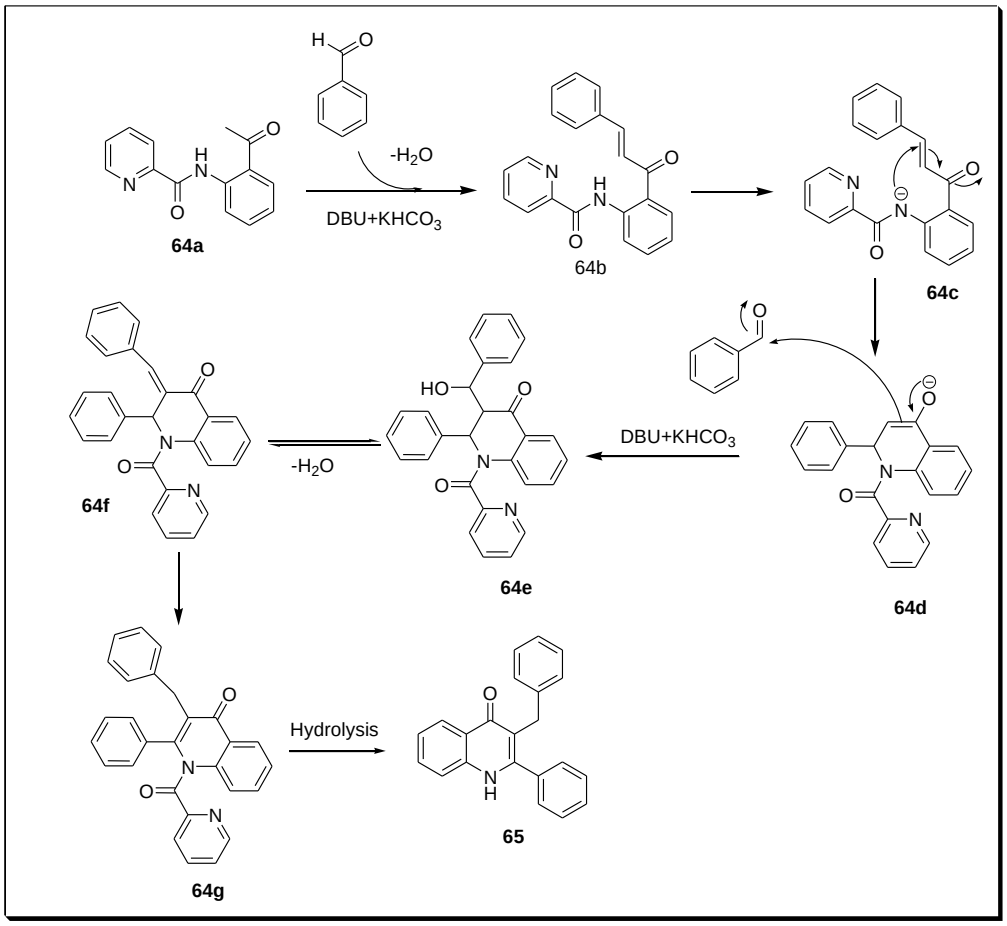
Scheme-I.21. Synthesis of 3-benzyl-2-phenylquinolin-4(1H)ones *via* cascade reaction

Due to the greater stability of iminium intermediate the starting material N-picolinoyl amide responded very well in the reaction and gave very good results. The aldehydes possessing the electron withdrawing group took participated in the reaction very smoothly than comparison to electron donating groups.

Selected examples

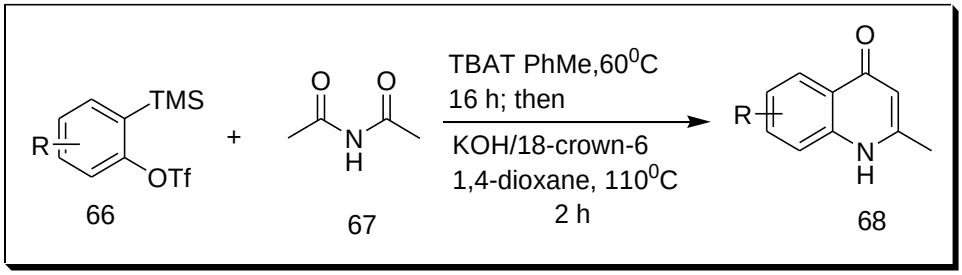


Plausible Mechanism



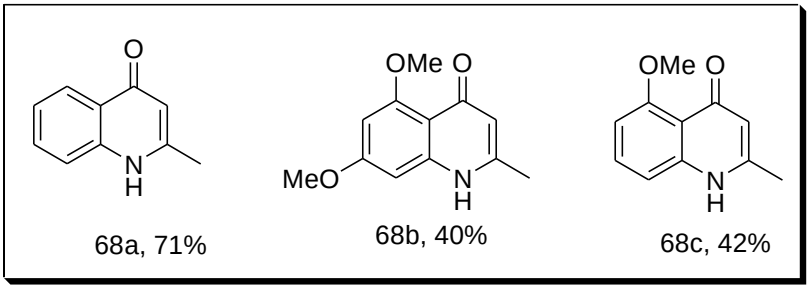
In this reaction, primarily the starting material 64a and benzaldehyde formed the intermediate 64b through aldol reaction in presence of DBU and $KHCO_3$. Then, the intermediate 64b readily converted to the 64c *via* abstraction of proton in presence of DBU and $KHCO_3$. Rather, the intermediate 64d might be underwent the intramolecular cyclization reaction to form the intermediate 64d through the Michael addition.The starting material benzaldehyde and intermediate 64d participated in aldol reaction to generate the intermediate 64e. Intermediate 64f readily formed in situ *via* elimination of hydroxyl group, it afforded the 64g through isomerisation. Finally, the intermediate 64g could be hydrolysed to result the desired products 65.

More recently, Stoltz *et al.* demonstrated the insertion of arynes into acyclic imides and anhydrides to provide aryl ketoamides under mild conditions. Further, the aryl keto amides were converted into 2-substituted 4-quinolones *via* base-catalysed Camps cyclization.[36]



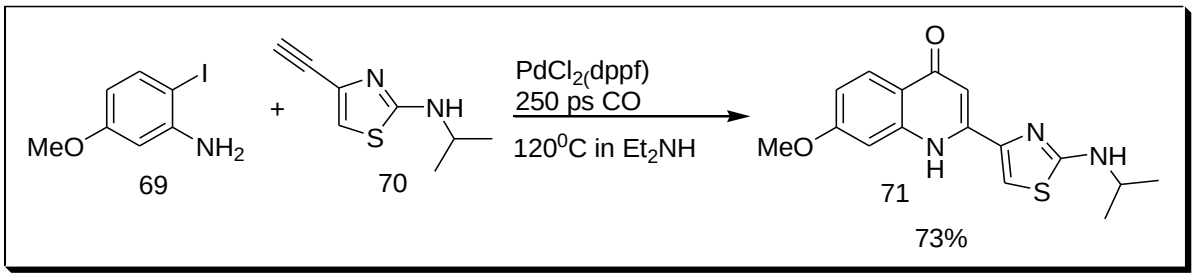
Scheme-I.22. Camps cyclization of ketoamide insertion products to provide quinolones.

Selected examples



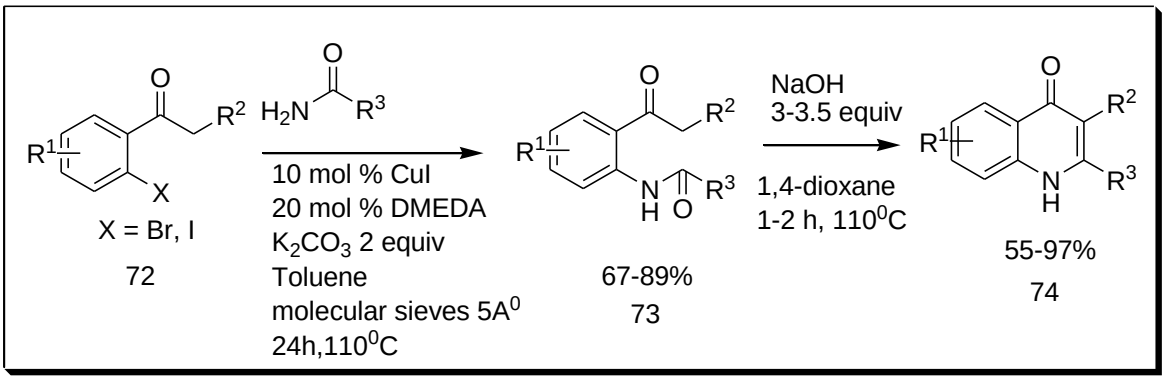
I.A.1.b Metal catalysed synthesis of 4-quinolones

Haddad. et al. also described the synthesis of the 4-quinolone Substructure of **BILN 2061** via Carbonylative Sonogashira Coupling/Cyclization of 2-iodo-5-methoxyaniline with thiazolylacetylene.[37]



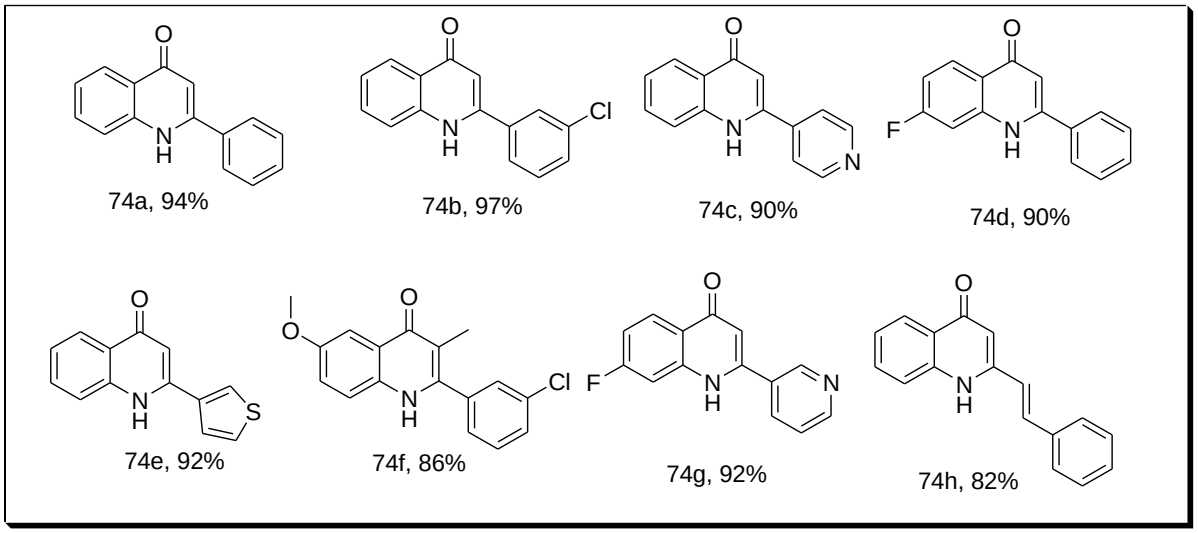
Scheme-I.23. $PdCl_2$ catalysed Carbonylative sonogashira coupling

In 2007, Buchwald *et al.* developed a new method for the synthesis of 2-vinyl and 2-aryl quinolones from N-(2-ketoaryl)amides under the base catalysed camps cyclization . The reaction offered two step processes. Initially, the starting material N-(2-ketoaryl)amides was synthesized by Cu catalysed amidation of 2-halophenones in excellent yields.[38]

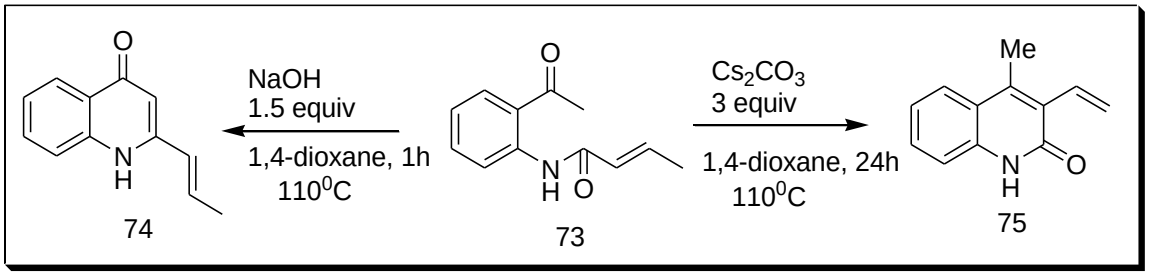


Scheme-I.24. CuI catalysed Camps cyclisation to synthesize 2-vinyl and 2-aryl quinolones from *N*-(2-ketoaryl)amides

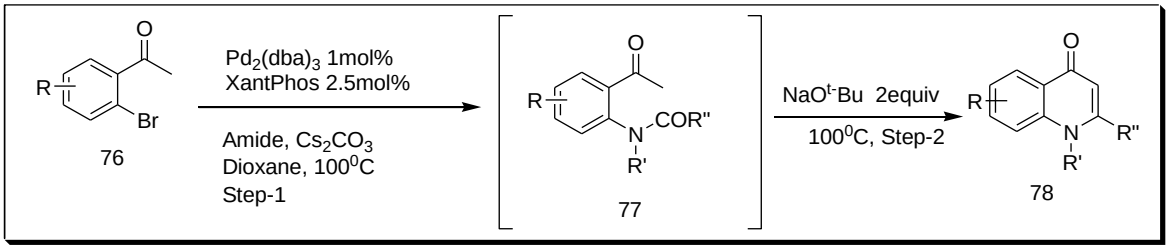
Selected examples



Depending on the nature of the base utilized, the derivative of N-(2-ketoaryl)amides was able to cyclise to afford the 2-quinolone and 4-quinolone. In presence of stronger base NaOH, deprotonation occurred at the α-position of keto methyl group of N-(2-ketoaryl)amides which underwent aldol condensation to furnish the 2-quinolone whereas Cs_2CO_3 abstracted the Y-proton of the amide to afford the 4-quinolones respectively.



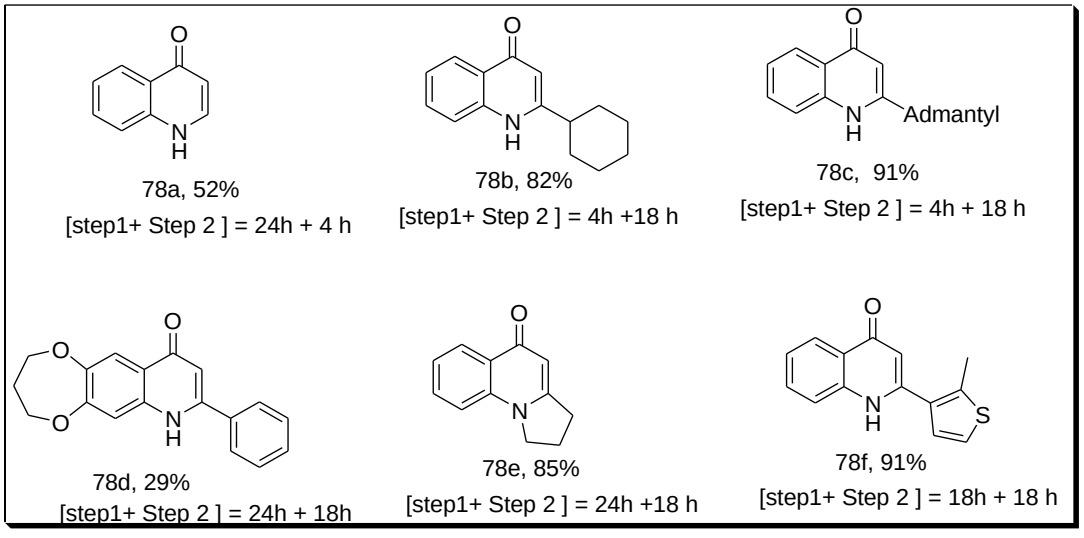
Huang and his coworkers reported the efficient route for a wide range of 4-quinolones synthesis in one pot reaction from base-catalysed cyclization N-(o-ketoaryl) amides. The starting material derived formed Pd-catalyzed amidation of 2-acetylbromoarenes.[39]



Scheme-I.25. Synthesis of 4-quinolones from base catalysed cyclisation of N-(o-ketoaryl) amides.

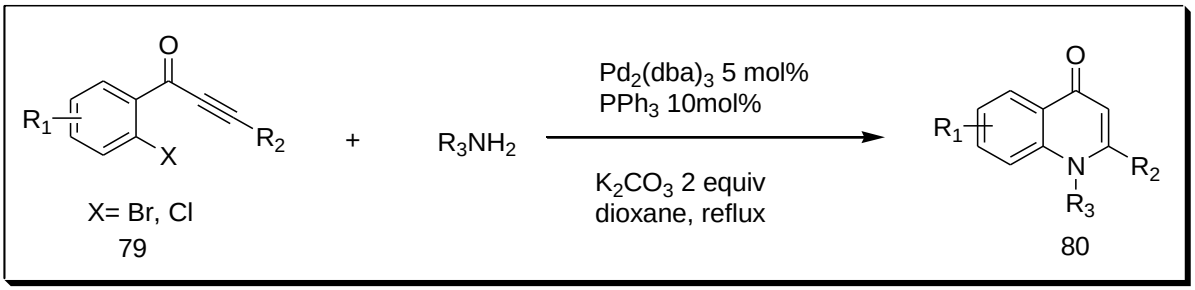
Initially, they used a mild base Cs_2CO_3, appropriate ligand XantPhos and the solvent dioxane to suppress the side reaction of ketone arylation. Then, the stronger base sodium tertiary butoxide performed the cyclization step. Dioxane proved to be a better solvent for the highest yield of both amide and quinolone. Alkyl, aryl, and heterocyclic amides afforded very good yields. Alkylamides with one or no proton (R) substrates provided promising yield of the desired quinolone products.

Selected Examples



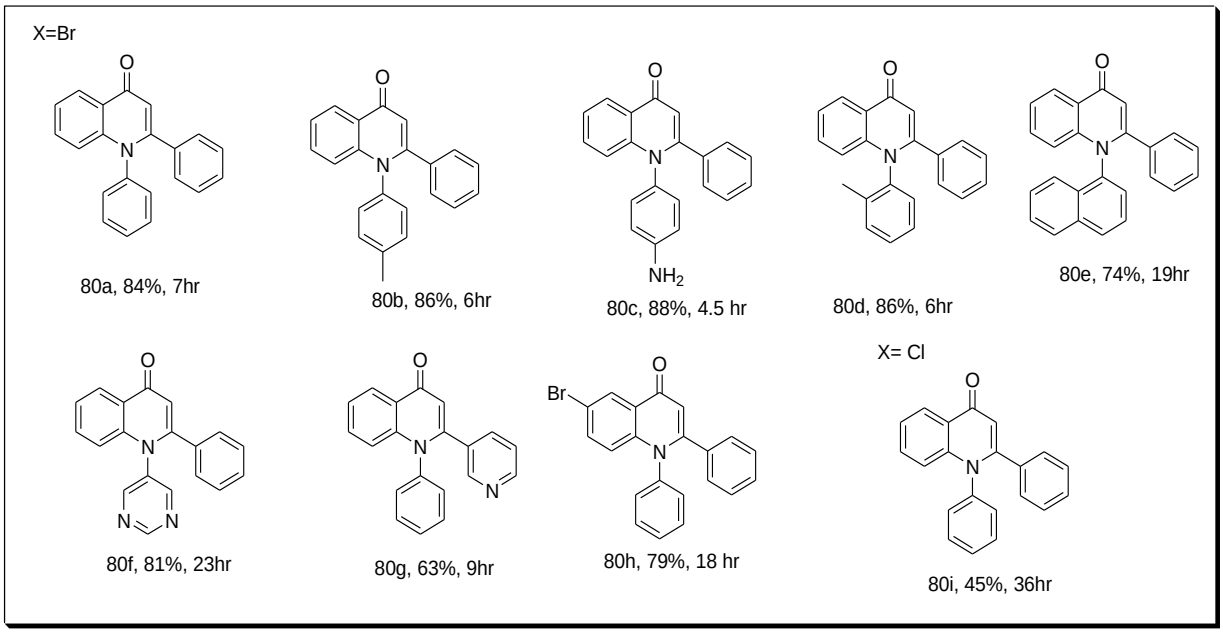
Zhao and Xu have developed a new procedure for synthesizing the substituted 4-quinolones *via* palladium-catalyzed tandem reaction. The reaction followed the sequential double C-N

bond formation from easily available o-haloaryl acetylenic ketones and primary amines.[40]

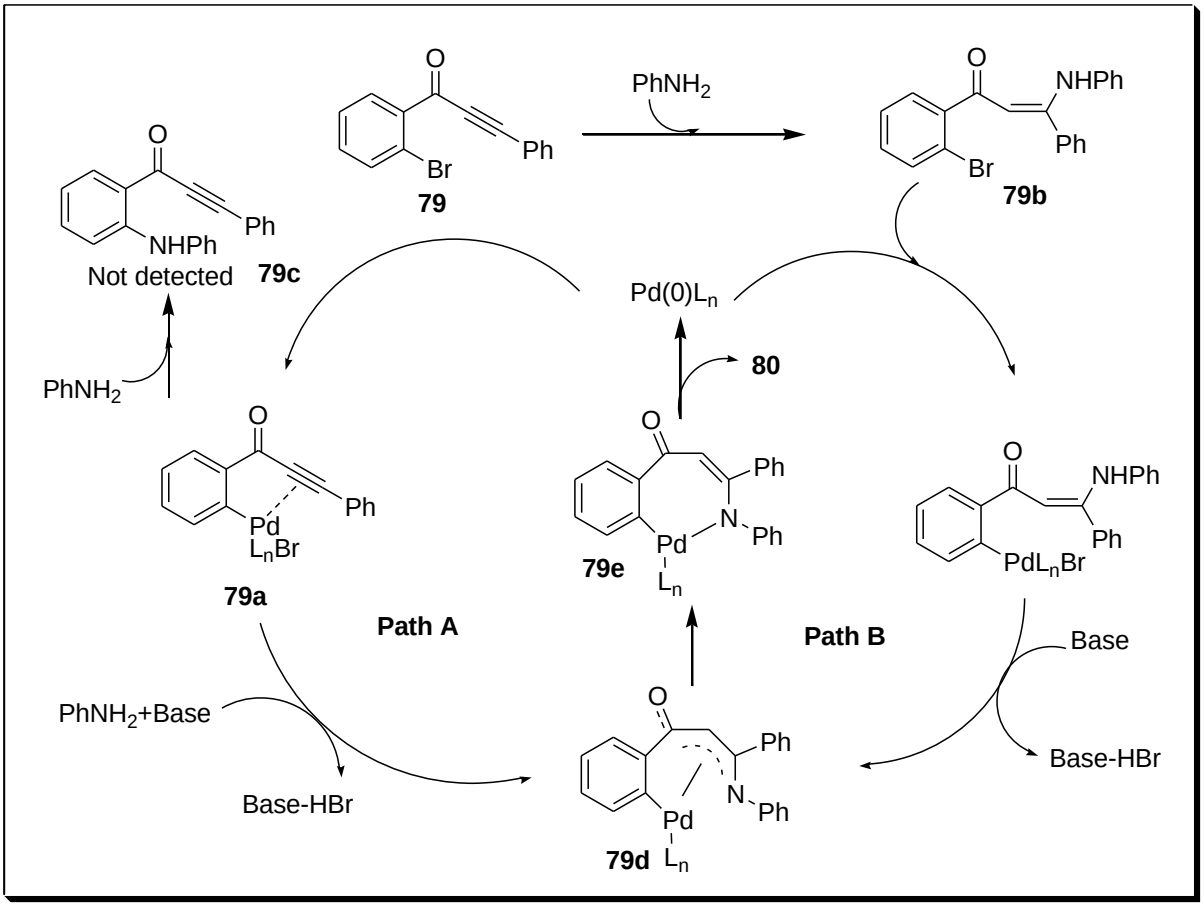


Scheme-I.26. Pd catalysed tandem reaction of o-haloaryl acetylinic ketones and primary amines.

Selected Examples



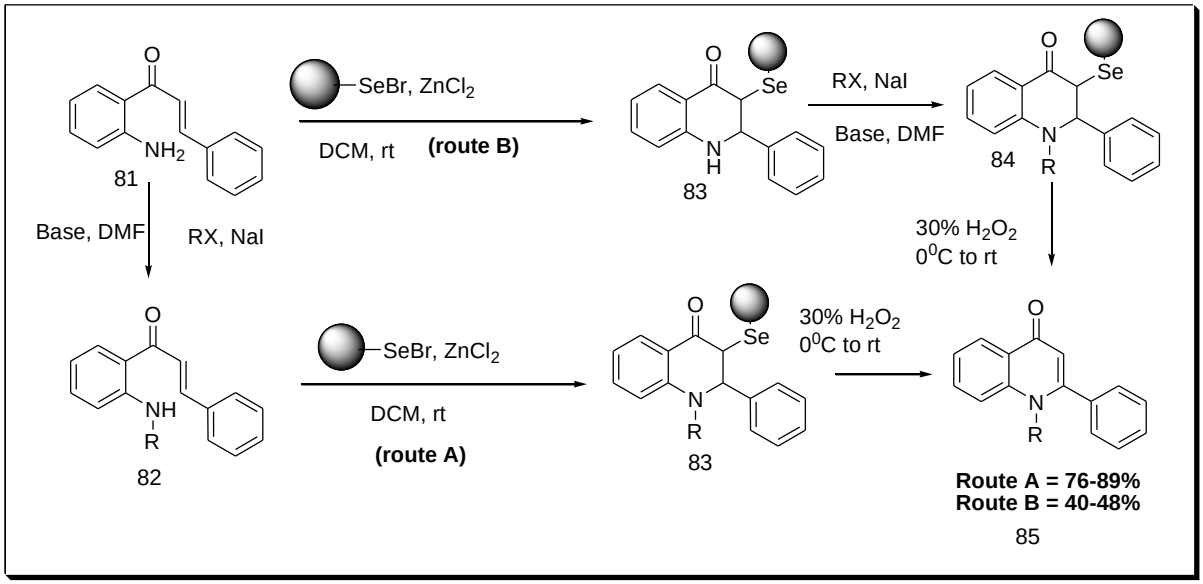
Plausible reaction mechanism



The authors postulated the mechanism for the above mentioned reaction which follows the two different routes (Route A & Route B). Initially in the 1st step, the reaction may proceeds via the oxidative addition of Pd(0) to the C-Br bond in 79 (intermediate 79a in Route A)or direct conjugate addition of aniline may takes place to 79 (intermediate 79b in Path B).[41]Most probably, the intermediate 79c formed from 79a through the Buchwald-Hartwig amination.[42] In another case, the intermediate 79d formed via the activation of triple bond in alkynone followed by the coordination to the palladium and simultaneous attacked by aniline. [43] These two pathways will go through intermediates 79d and 79e,[44] followed by reductive elimination of Pd(0) to give product 80.

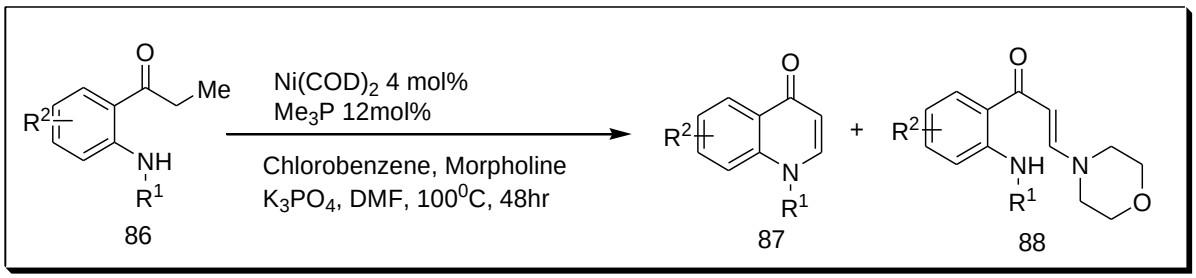
Herein, Tang et al. reported the $ZnCl_2$ mediated intramolecular cyclization of 2-aminochalcones to the solid phase synthesis of of 2-aryl-4-quinolones and 2-phenyl-2,3-dihydroquinolin-4(1H)-ones. Polymer supported organoselenium reagents mainly

induced the total transformation process. The conversion generally proceeded via oxidation, elimination reaction of selenides or free-radical hydrogenation and allylation reaction of selenides.[45]



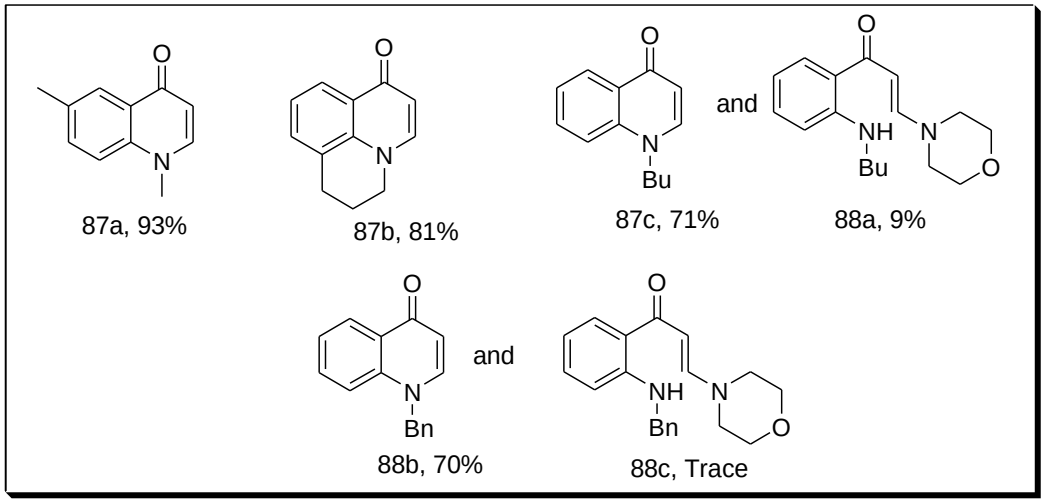
Scheme-I.27 $ZnCl_2$ mediated intramolecular cyclisation of 2-amino chalcones to the solid phase synthesis 4-quinolones

Ueno et al. reported the methodology for the conversion of o-(N-Alkylamino) propiophenones into 4-quinolones in the presence of chlorobenzene, potassium phosphate, morpholine, and nickel(0) catalyst. The reaction proceeds through the nickel-catalyzed formation of β-enaminones from o-(N-alkylamino)propiophenones and morpholine, followed by the intramolecular transamination. [46]



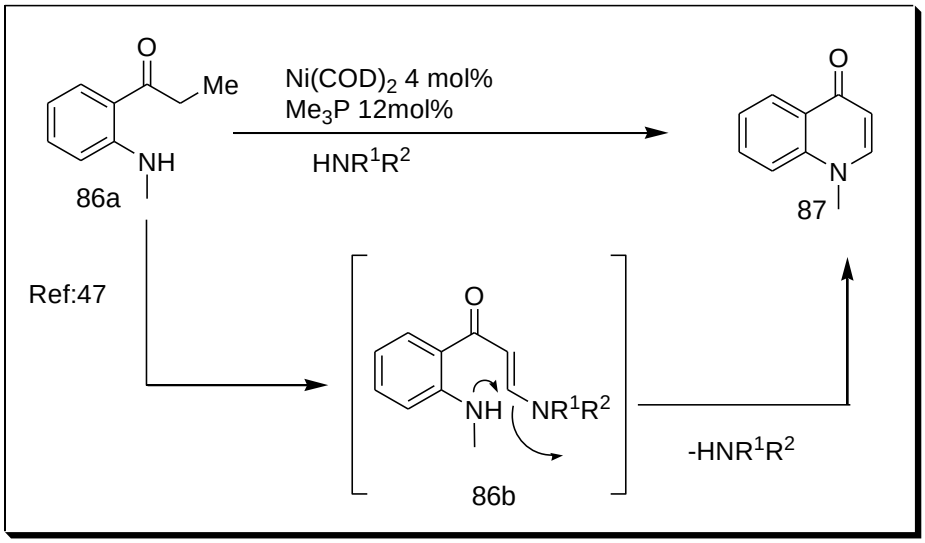
Scheme-I.28. Ni(0) catalysed synthesis of 4-quinolones from o-(N-Alkylamino) propiophenones

Selected examples



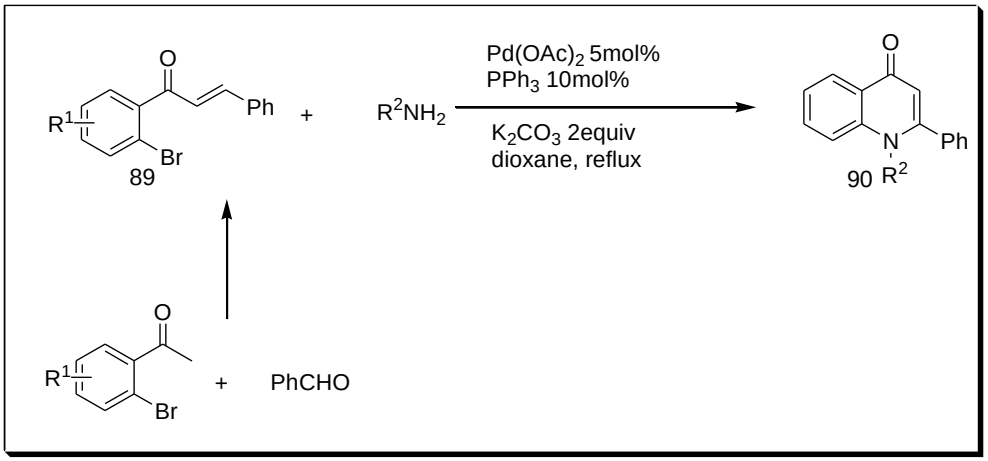
Morpholine was the effective additive for the above cyclisation whereas piperdine, pyrrolidine, acyclic amines failed to produce the 4-quinolone.

Plausible pathway



The N-benzyl-protected 4-quinolone was obtained in 70% yield In contrast, the reaction of possessing of the bulkier isopropyl group on the nitrogen atom, gave undesirable β-enaminone as the major product.

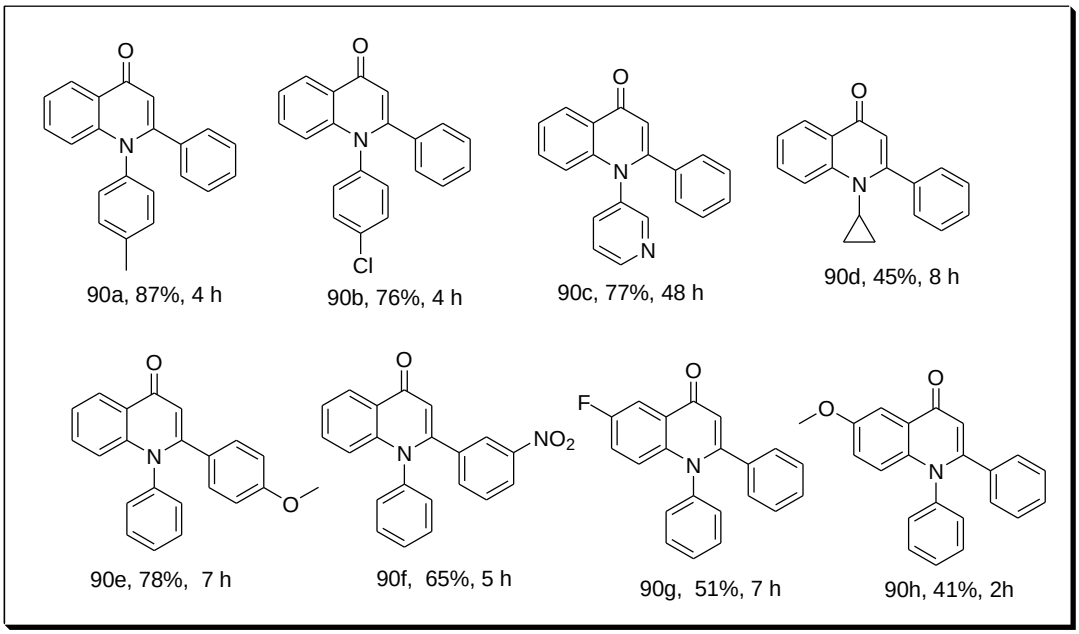
A more general strategy for the synthesis of 1,2-disubstituted 4-quinolones by Palladium catalysed tandem amination reaction using chalcones as substrates was reported here. [48]



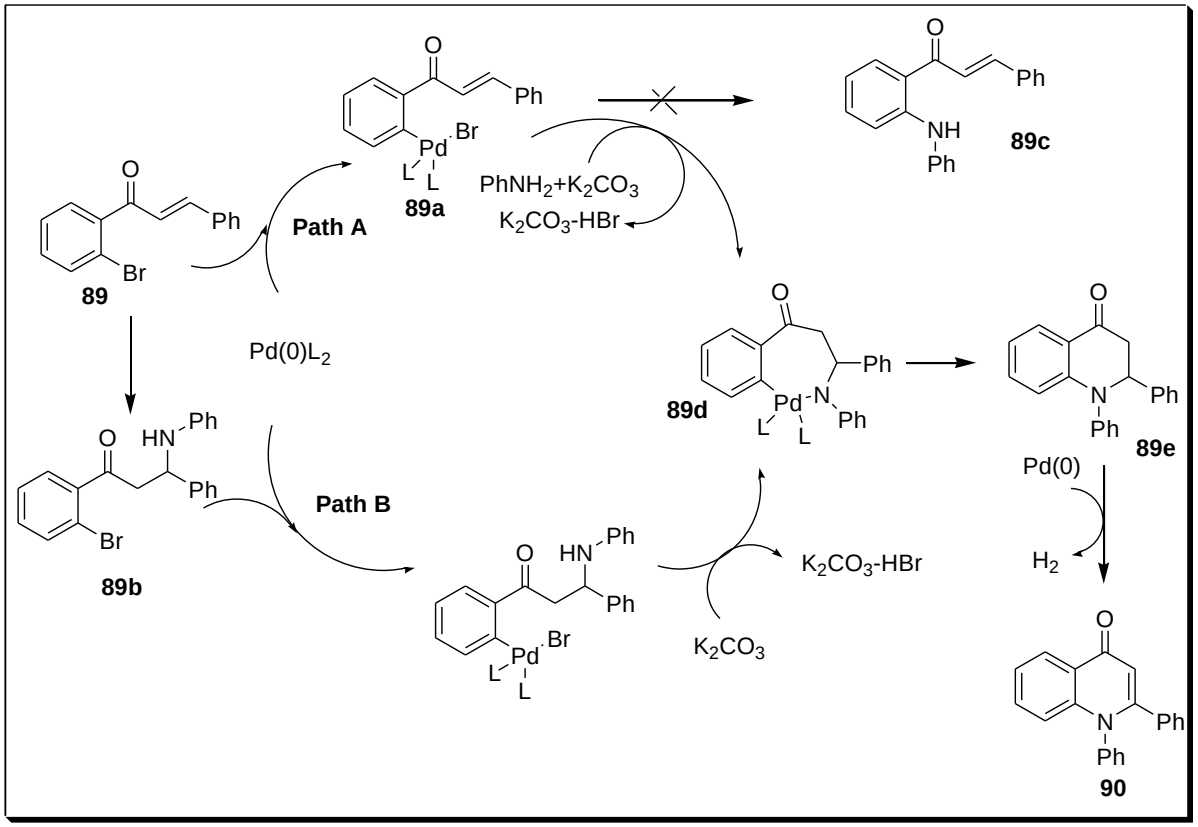
Scheme-I.29. Pd catalysed tandem amination reaction

Arylamines containing electron-donating groups gave higher yields than those with electron-withdrawing groups. However, this reaction was not limited to simple aromatic amines; the pyridine-containing substrate also afforded in good yield.

Selected examples

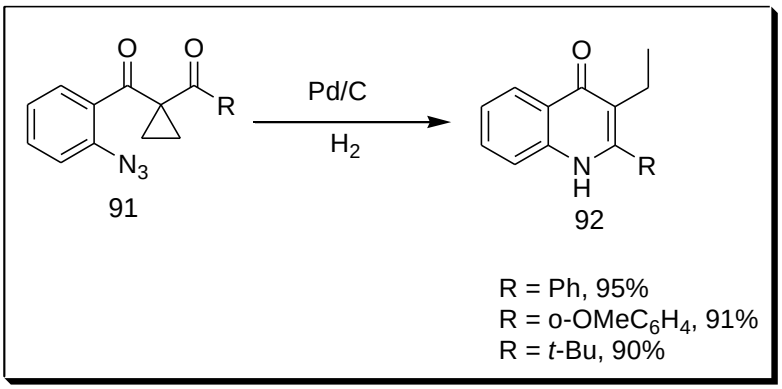


Plausible mechanism



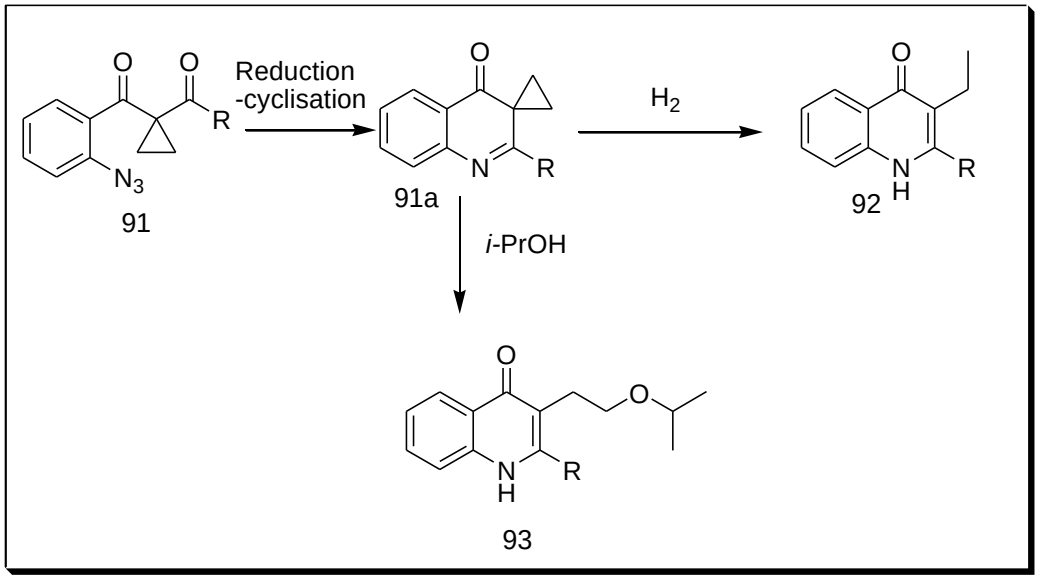
A plausible reaction mechanism for this one-pot synthesis of 1,2-disubstituted 4-quinolones was proposed in Scheme 2 (Paths A and B).[49] In Path A, oxidative addition of 89 to the Pd(0) catalyst leads to palladium complex 89a. The C=C bond in 89a can be activated through coordination to the Pd(II) and attacked by aniline to form intermediate D. Note, intermediate C was not formed from complex A under these conditions. Path B involves the Michael addition of aniline to 89 and oxidative addition, and then intermediate 89d is formed by elimination of HBr. Both pathways proceed via intermediate 89d, followed by reductive elimination of Pd(0) to yield 89e. Intermediate 89e leads to 90 by catalytic dehydrogenation of Pd(0), which is the key step.

Ren and his coworkers successfully reported a useful method to synthesize the 4-quinolone derivatives via reduction of azido-cyclopropyl ketones.[52]

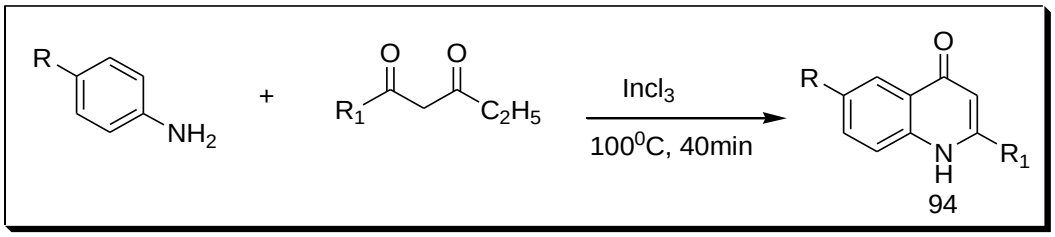


Scheme-I.30. Synthesis of 4-quinolones from azido cyclopropyl ketones

Plausible mechanism

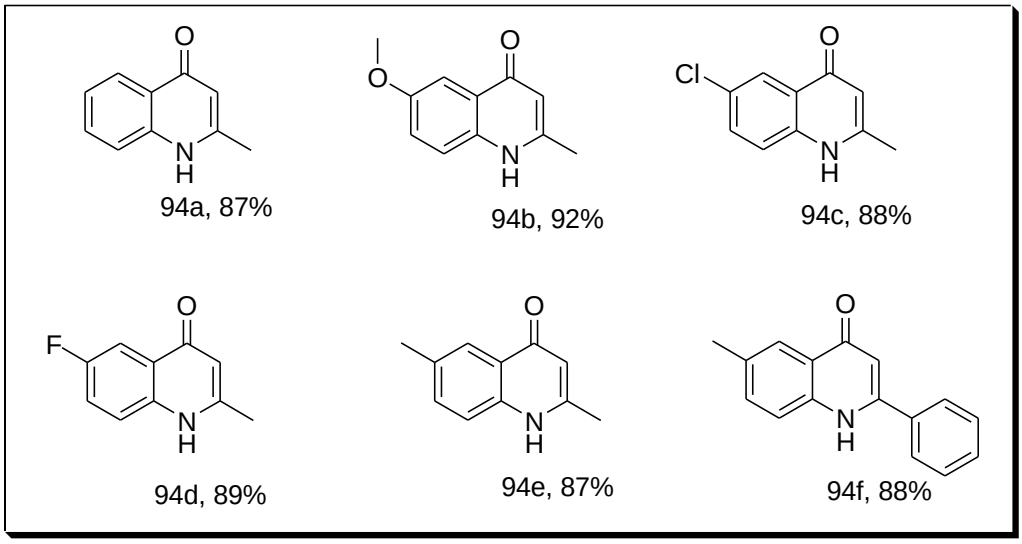


In 2013, Bhupathi and his coworkers derived a facile and efficient one pot method for the synthesis of 4-quinolones in high yields under solvent-free conditions at 100^0C. The reaction generally employed substituted amines and β-ketoesters to prepare the 2-aryl or 2-alkyl quinolones *via* Conrad-Limpach reaction in presence of Indium (III) chloride. The advantage of the reaction is that the catalyst is reusable and easily recoverable.[51]

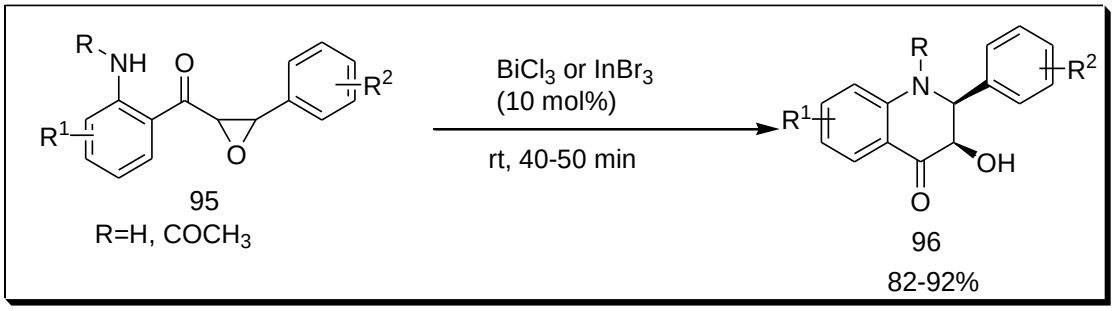


Scheme-I.31. $InCl_3$ mediated synthesis of 4-quinolone

Selected Examples

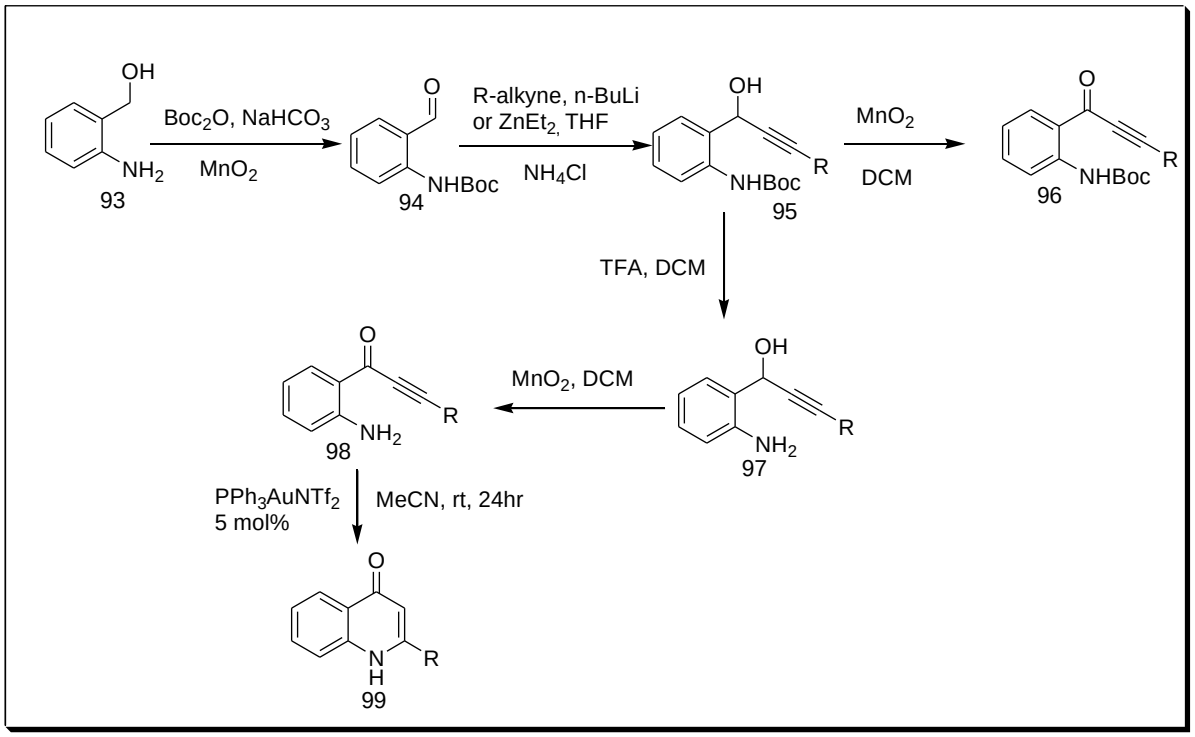


In 2013, Ahmed and his coworkers reported the $BiCl_3$ or $InBr_3$ catalyzed the ring opening of 2-aminochalcone epoxides followed by intramolecular aminolysis under mild conditions. The reactions proceed efficiently at room temperature to afford highly functionalized 2-aryl-3-hydroxy-2,3-dihydro-4-quinolones (aza-flavanones) in excellent yields (82– 92%).[52]



Scheme-I.32. $BiCl_3$ or $InBr_3$ induced ring opening reactions of 2-amino chalcone epoxides.

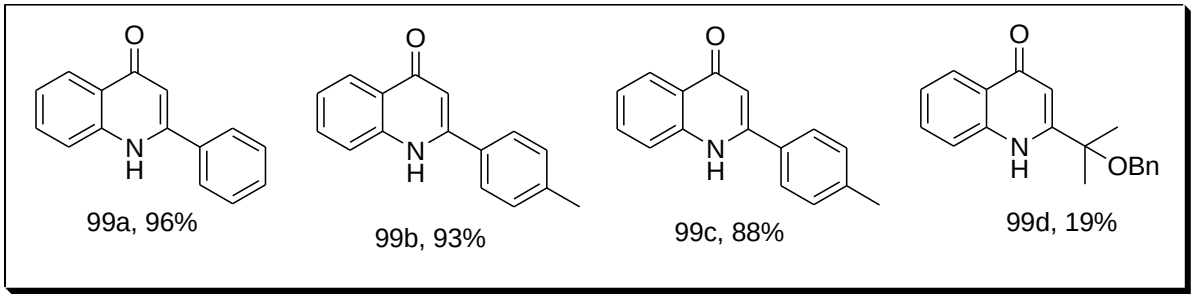
In 2014, Helaja and his coworkers prepared the 2-substituted 4-quinolones from the 1-(*o*-aminophenyl)-2-propyn-1-ones in the presence of gold catalyst. [53]



Scheme-I.33. Gold catalysed synthesis of 4-quinolones

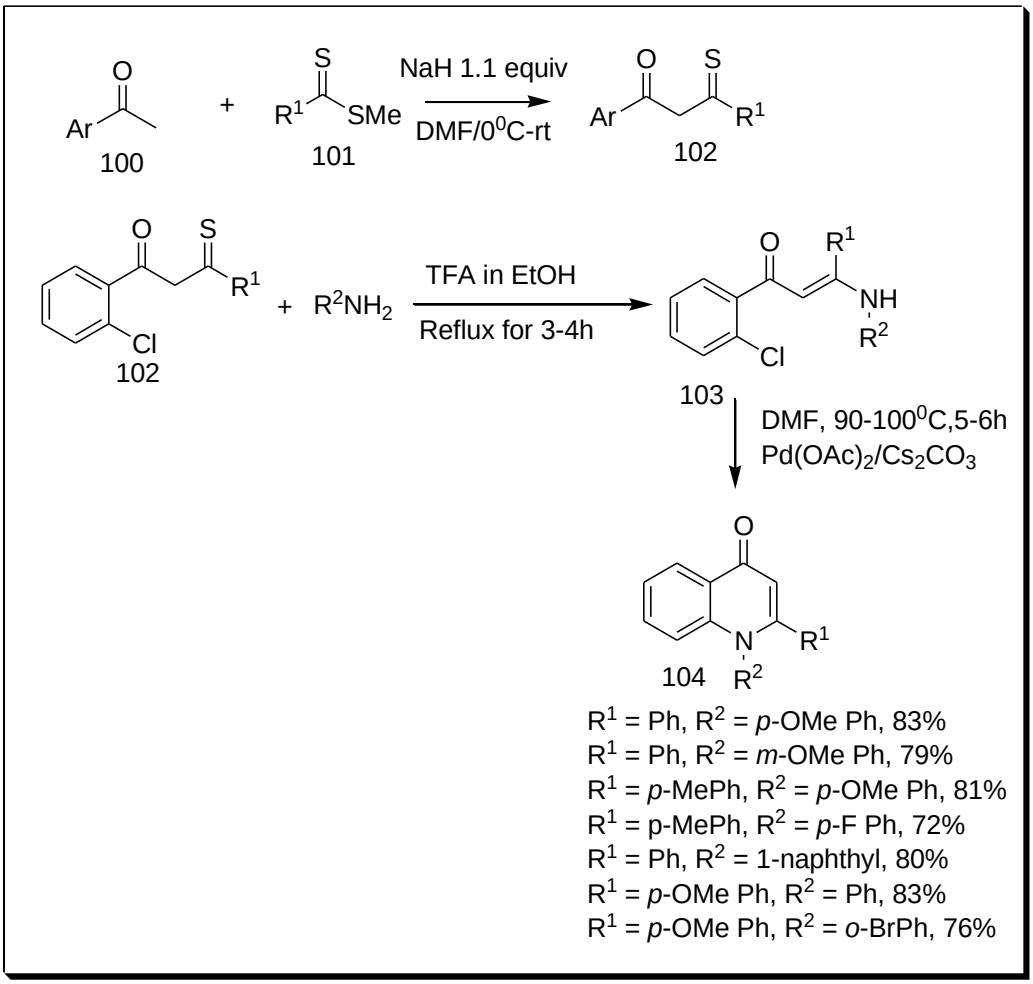
It has been found that the both electron-withdrawing and donating substituents 2-Aryl-4-quinolones could be isolated with excellent yields. Similarly, straight chain alkyl substitution gave high yields. Cyclization protocol did not proceed at all with a simple TMS protected substrate. Rather in absence of the gold catalyst, the unprotected derivative underwent oligomerization to tar.

Selected examples



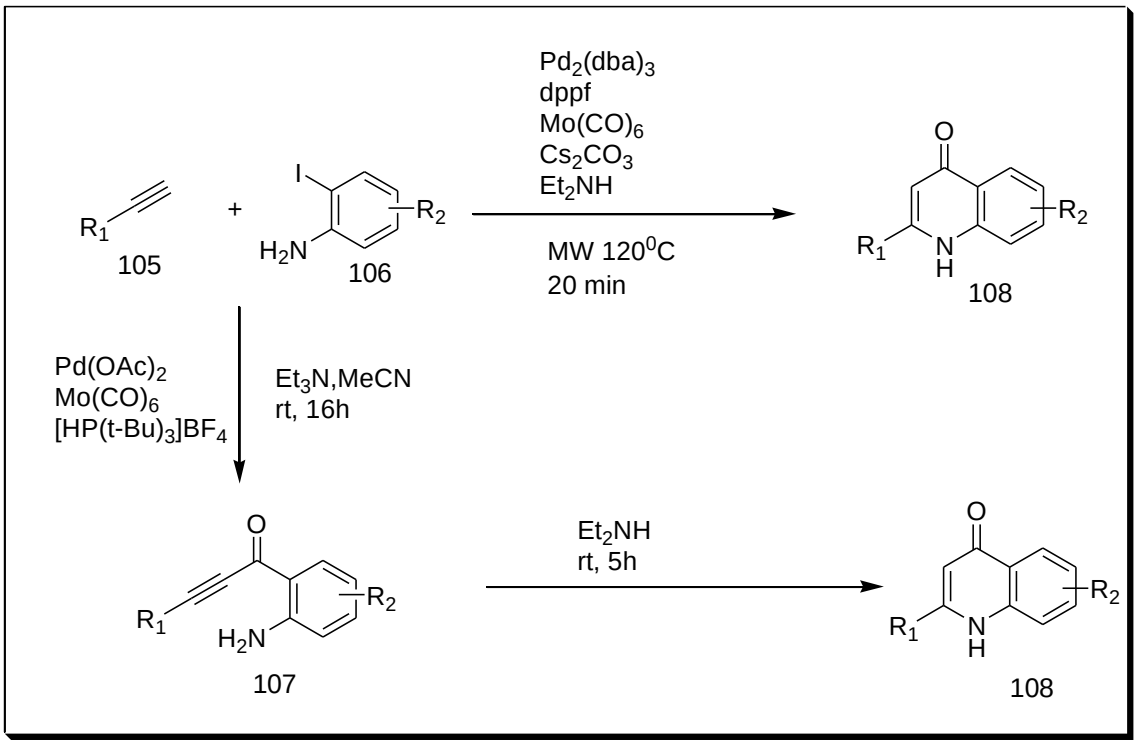
A novel strategy for the synthesis of 1, 2-disubstituted 4-quinolones in moderate to excellent yield from 1,3-bisaryl-monothio-1,3-diketone and arylamine substrates was reported. This protocol involved two steps for providing the cyclised quinolone products. Initially, enaminones were formed by condensation of the substrates in

presence of TFA. Then, it underwent cyclisation using the $Pd(OAc)_2$ catalyst and the Cs_2CO_3 base. In the cyclisation step, the substituents had no profound impacts on the yield.[54]



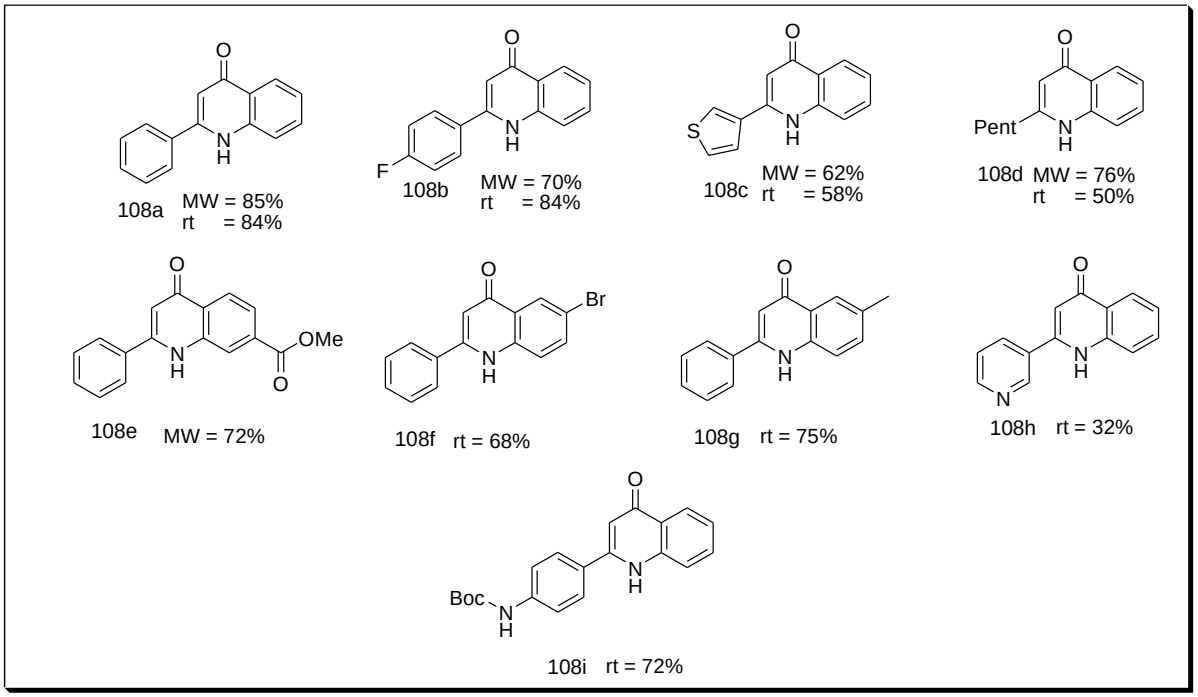
Scheme-I. 34. Synthesis of 1, 2 –disubstituted 4-quinolones from monothio-β-diketones.

Here in, $Mo(CO)_6$ has been used as a solid CO source instead of toxic CO gas for the synthesis 4-quinolones *via* two pathway. The first route encountered the desired compound in a very short time under microwave irradiation whereas the one-pot two-step approach (second method) preceded the reaction at ambient temperature. Both the methods are usually effective to synthesize the large variation 4-quinolones in moderate to excellent yields. [55]

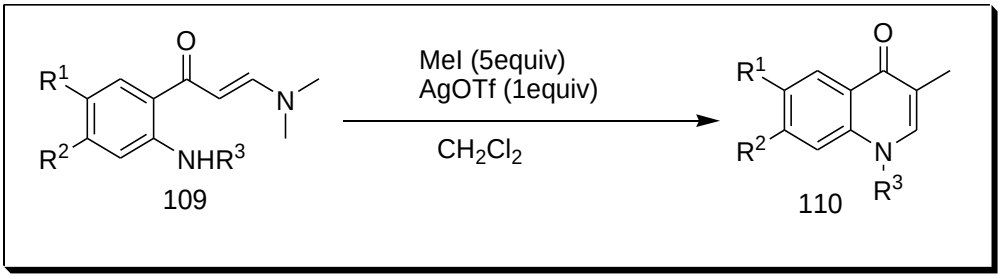


Scheme-I.35. $Mo(CO)_6$ as CO source for synthesis of 4-quinolone

Selected Examples

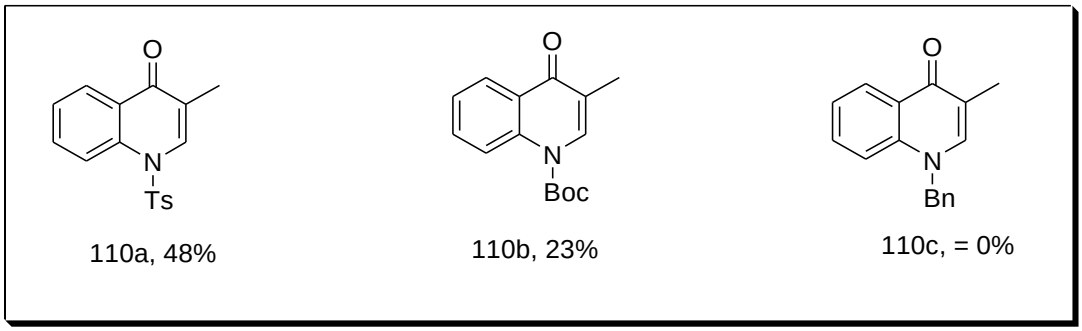


Here in, Joussot *et al.* described a method to synthesize the 3-substituted quinolones easily in a one-pot technique which involved the cyclization of appropriate enaminones and subsequently quenched with diverse electrophiles.[56]

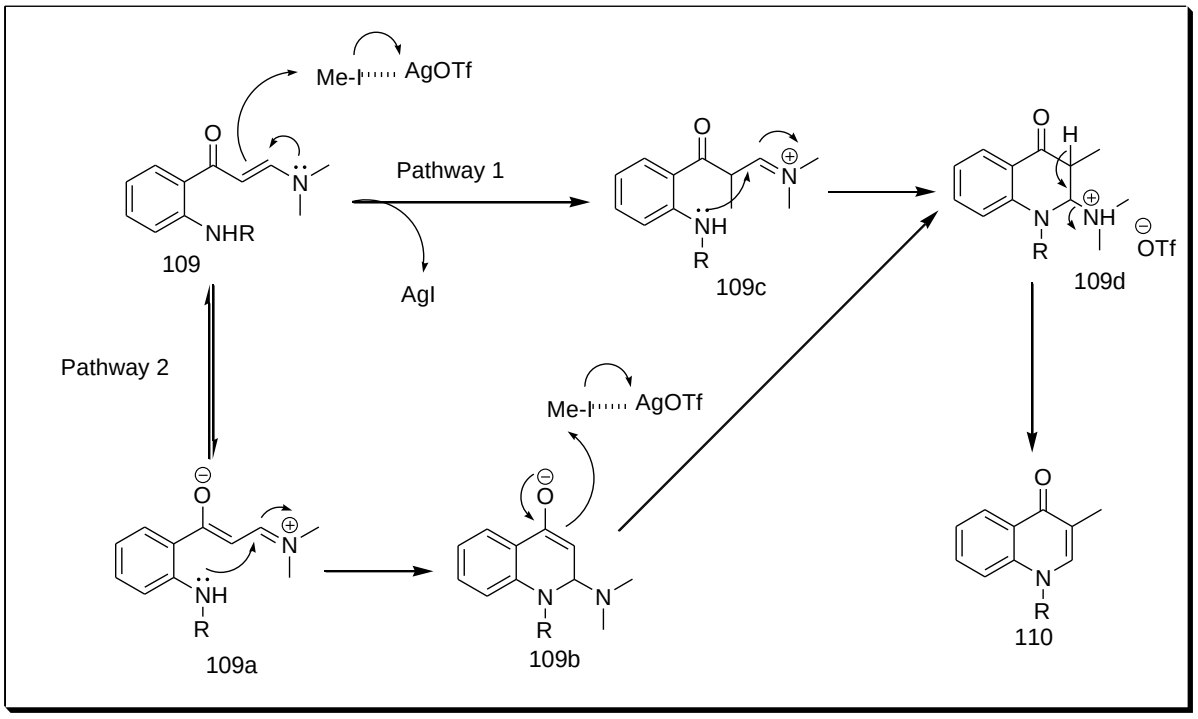


Scheme-I.36. Ag(I) catalysed cyclisation of enaminones to 4-quinolones

Selected examples



Plausible mechanism



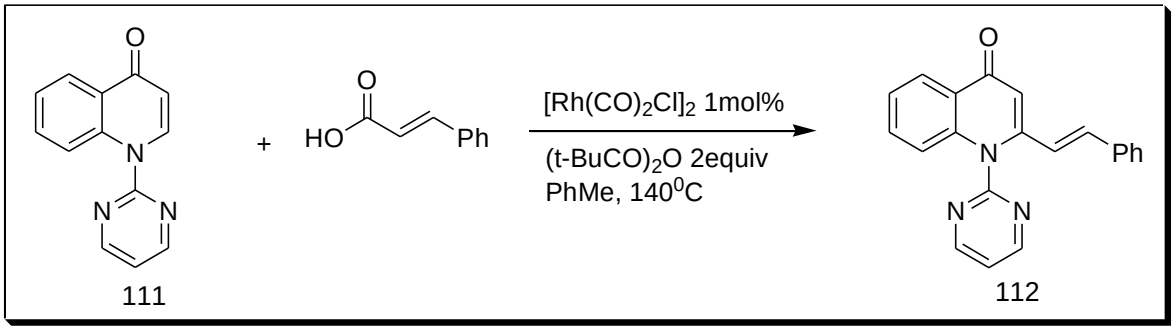
The cyclization procedure proceeded via two pathways as predicted in the above scheme. In pathway 1, the alkylation occured first, leading to form iminium salt, and then underwent the cyclization to generate a new iminium salt. In pathway 2, the

cyclization occured first followed by alkylation to result the same iminium salt. Lastly, the 3-substituted quinolone was formed with the elimination of the dimethyl amine.

I.B. Functionalization of 4-quinolones

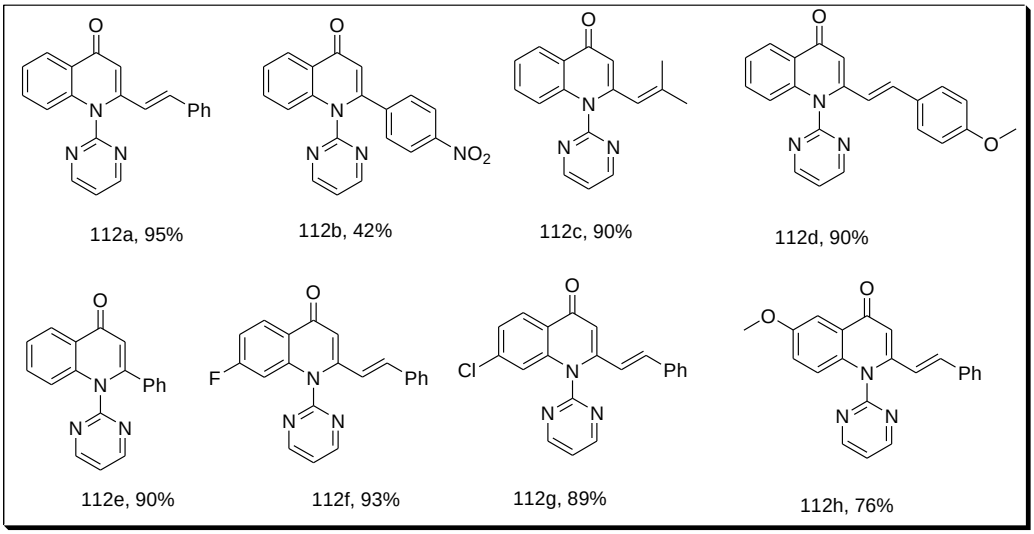
I.B.1. Decarbonylative cross coupling reaction

Kwon *et al.* established a site-selective decarbonylative cross-coupling method to promote the direct C-H functionalisation at the 2-position of 4-quinolones *via* the presence of N-pyrimidyl group on the quinolone nitrogen atom. [57] Under the optimized protocol, decarbonylative coupling reactions were successful in between various functionalized quinolones and alkenes. Fluoro, chloro substituted quinolones smoothly underwent the C-2 alkenylation with cinnamic acid.

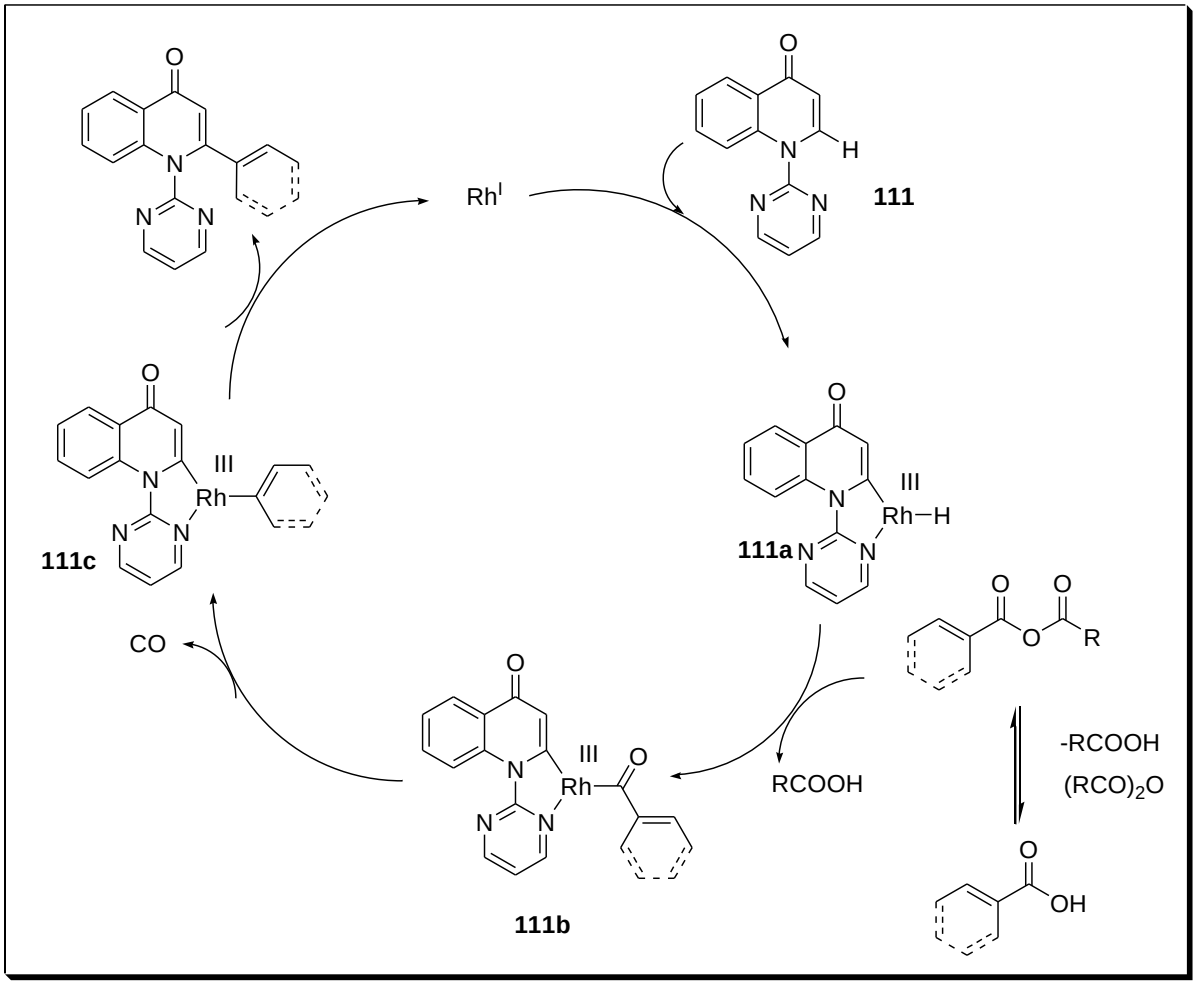


Scheme-I. 37. Rhodium-catalyzed decarbonylative cross couplings of 4-quinolones

Selected examples



Plausible mechanism

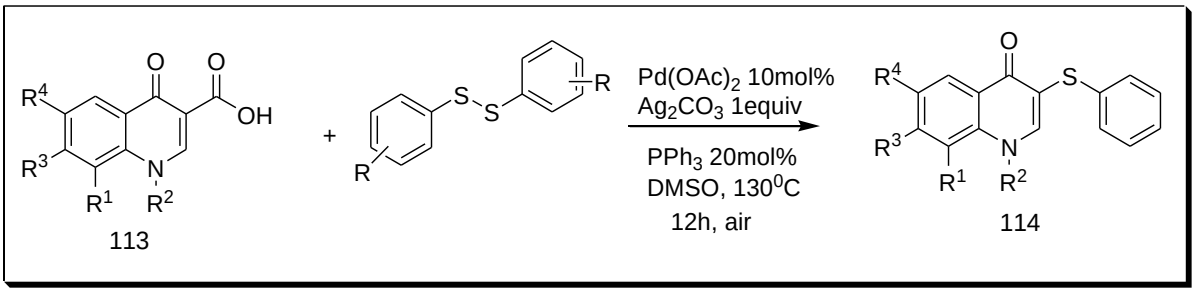


A plausible mechanism was proposed for the decarbonylative C–H coupling reaction. Preliminary, Pyrimidyl directing group inserted the Rh(I) into the C-2–H bond, which gives rhodacycle 111a (Scheme above). An appropriate anhydride which is formed by the equilibrium of the anhydride and acid underwent the oxidative addition to the substrate. Then, it produces the acyl rhodium species 111b. Later, complex 111c is generated *via* the extrusion of carbon monoxide. Finally, reductive elimination occurred and resulted the desired product 112 with the regeneration of active Rh(I) catalyst.

I.B.2. Decarboxylative C-S coupling reaction

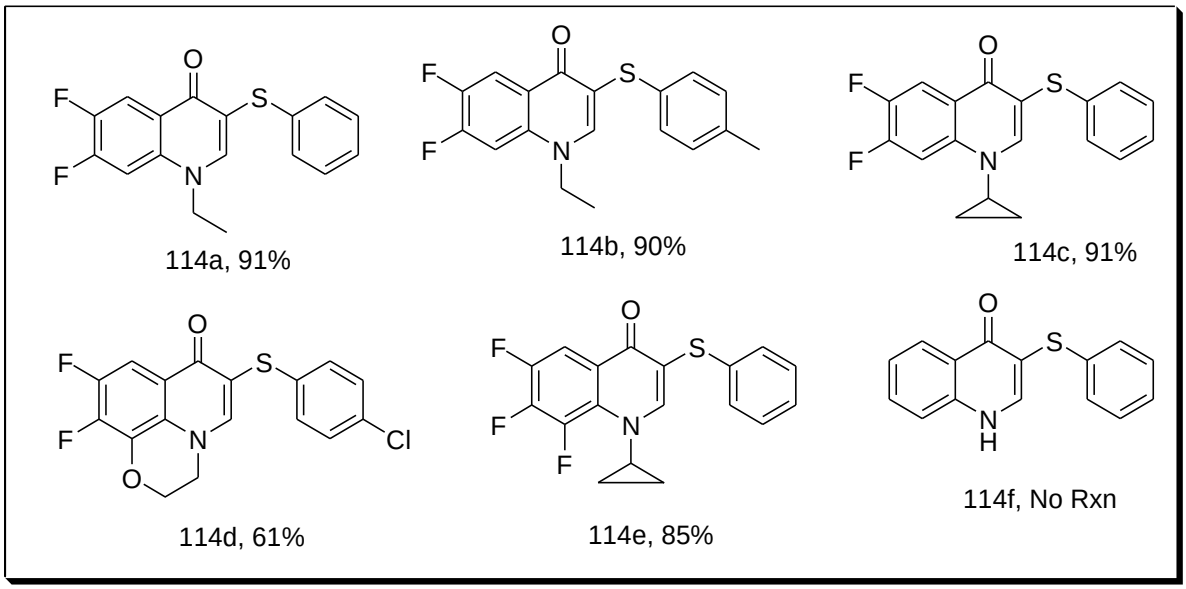
Palladium catalysed direct thioetherification of quinolone derivatives with diaryl disulfides was firstly reported by Zhang and his coworkers. They have inserted the –SPh group into the scaffold *via* decarboxylation technique in the presence of $Pd(OAc)_2$ and Ag_2CO_3 in DMSO.[58] The yield of the product was high in case of diaryl disulfides bearing an electron-donating

group such as diphenyl disulfide, *p*-tolyldisulfide, and bis(4-methoxyphenyl)disulfide whereas bis(4-chlorophenyl)disulfide substituted with an electron-withdrawing group gave a lower yield. However, the prime requirement of the protocol was the quinolone carboxylic acids containing a halogen substituent.

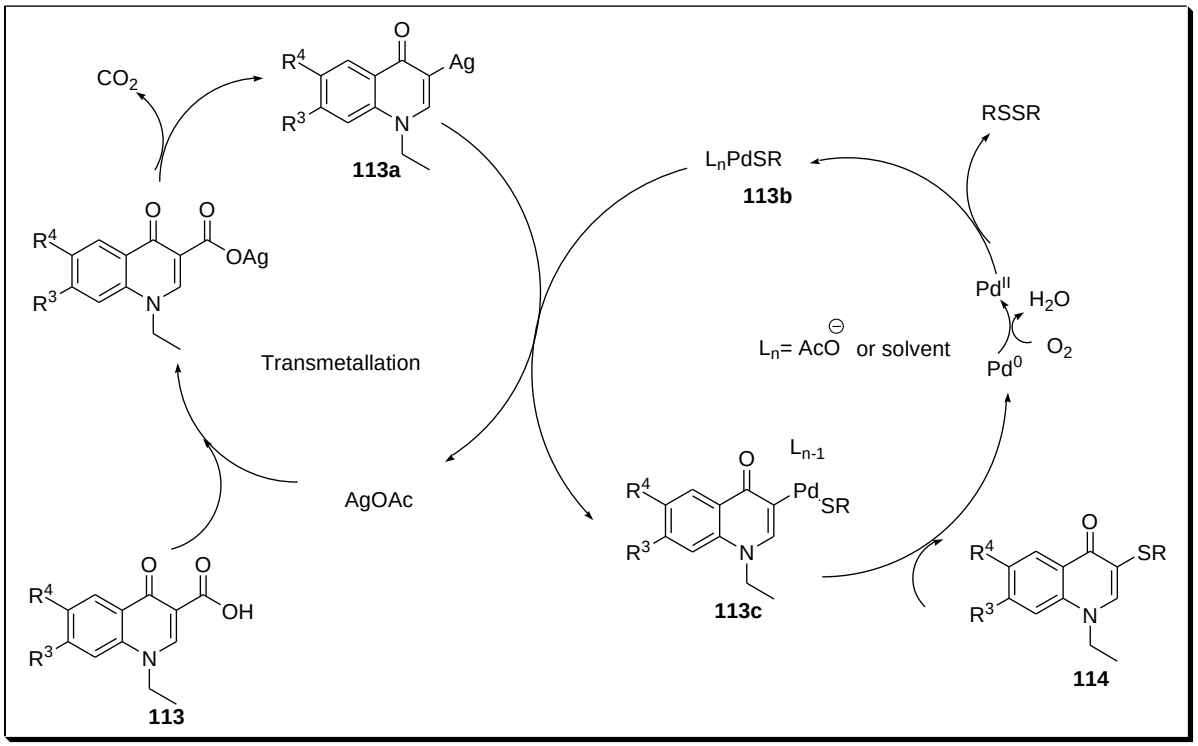


Scheme–I.38. Palladium catalyzed thioetherification of quinolones *via* C-S coupling

Selected examples

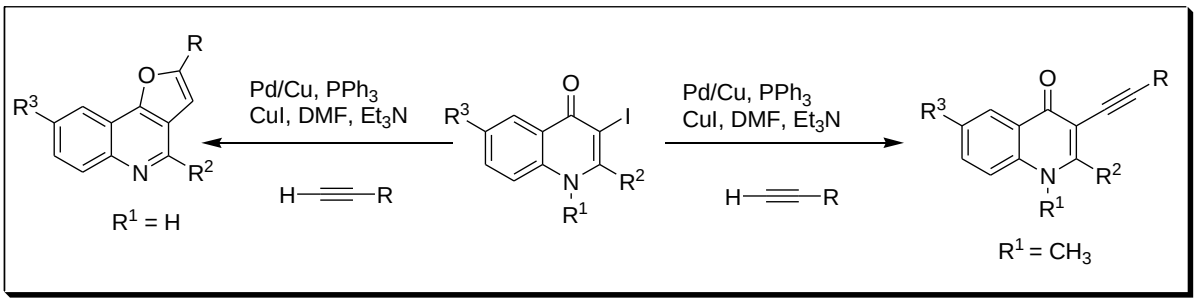


Plausible mechanism



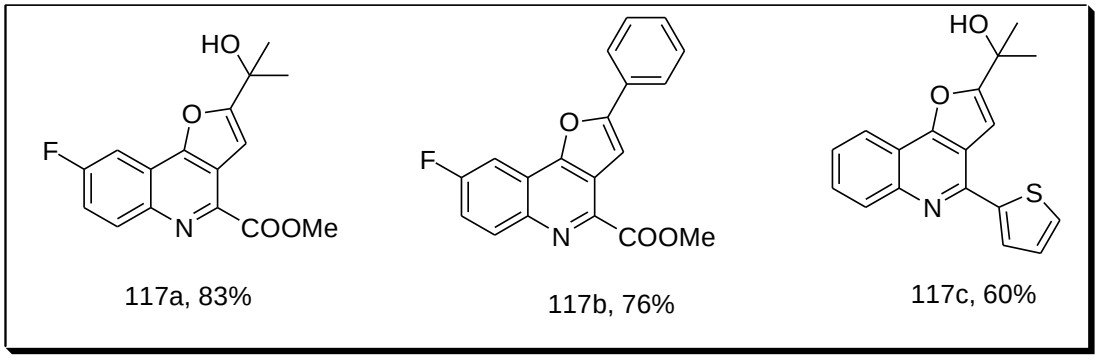
I.B.3. Sonogashira coupling reaction

Pal *et al.* synthesized of 2-substituted furo[3,2-c]quinolines *via* tandem sonogashira coupling–cyclization under Pd/C-copper catalysis. These reactions underwent under mild conditions and formed the furo[3,2-c]quinolines with significant regioselectivity . Rather, the reaction became irrespective of the nature of the substituent present at C-2 of the starting quinolone.[59]

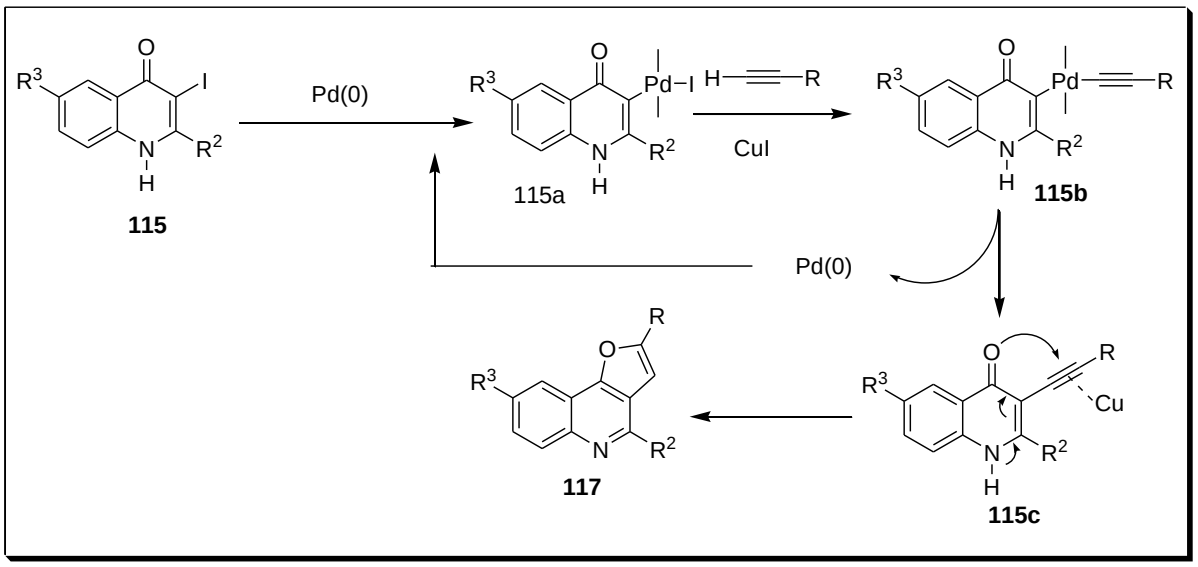


Scheme-I.39. Pd/C-copper catalysed One-pot synthesis of 2-substituted furo[3,2-c]quinolones

Selected Examples



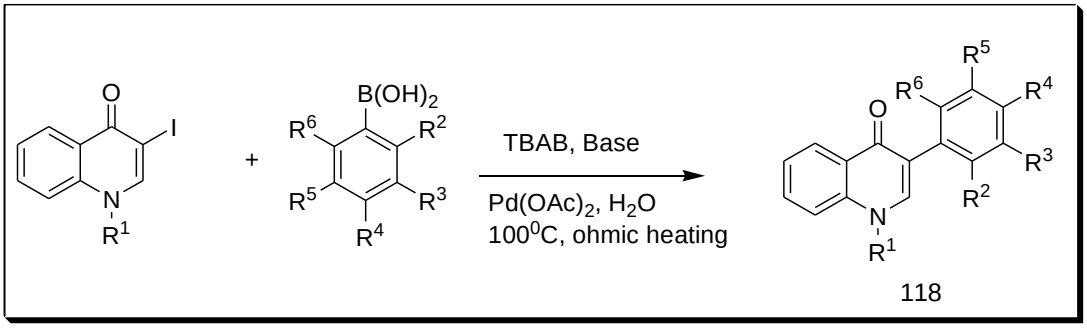
Plausible mechanism



The main highlight of this tandem coupling–cyclization process was the formation of furoquinoline. Initially, palladium metal-mediated activation of the triple bond of the 3-alkynyl quinoline generated *insitu* followed by an intramolecular attack of the oxygen on the activated triple bond with subsequent proton transfer and release of the metal ion to give the desired product. The –NH group of the quinolone ring played a crutial role in the cyclization step and perhaps facilitated the preferential participation of the C-4 quinoline oxygen. N-methylated quinolones afforded only the sonogashira coupled product instead of forming the fused cyclic product.

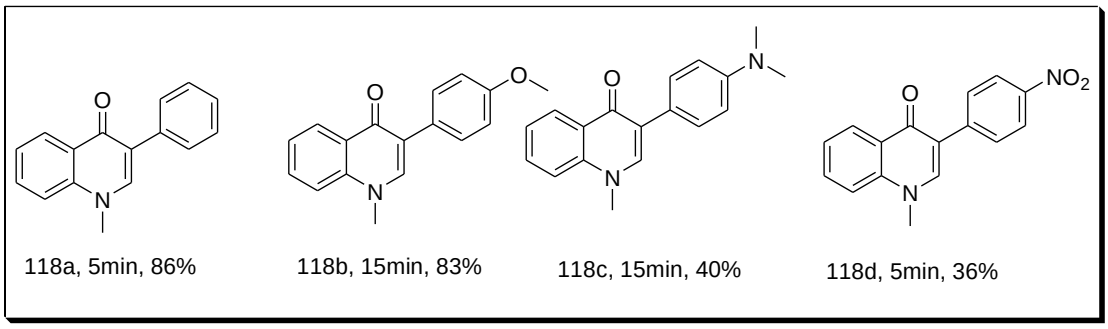
I.B.4. Suzuki cross coupling

Potential bioactive 3-arylquinolin-4(1H)-ones were synthesized under ohmic heating using an efficient, reusable, and ligand-free protocol *via* the Suzuki−Miyaura coupling of 1-substituted-3-iodoquinolin-4(1H)-ones with several boronic acids in water using $Pd(OAc)_2$ as a catalyst and tetrabutylammonium bromide (TBAB) as the phase transfer catalyst.[60]



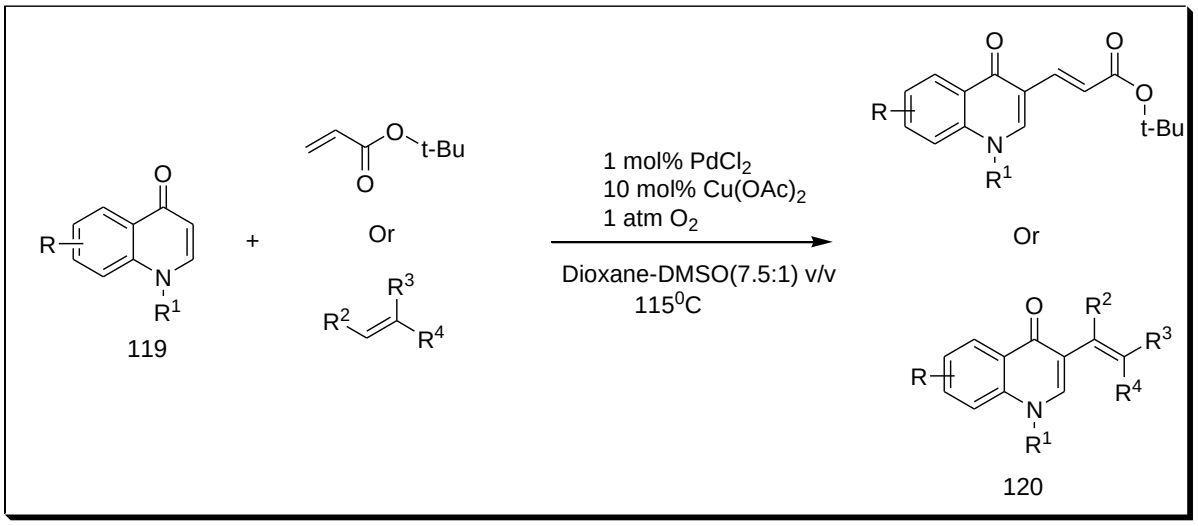
Scheme-I.40. Ohmic heating induced Suzuki cross coupling reaction

Selected Examples



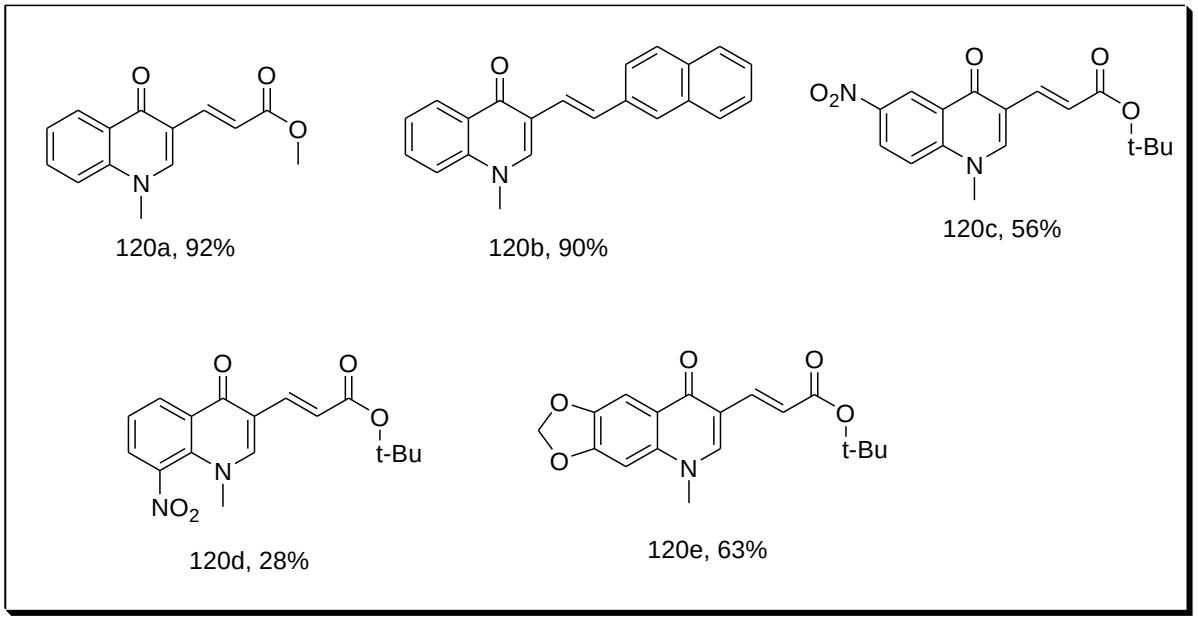
I.B.5 Alkenylation coupling

Herein, Ge and his coworker successfully developed an unprecedented Pd catalysed C-3 alkenylation of 4-quinolones with low catalyst loading. [61]



Scheme-I.41. Pd catalysed C-3 alkenylation of 4-quinolones

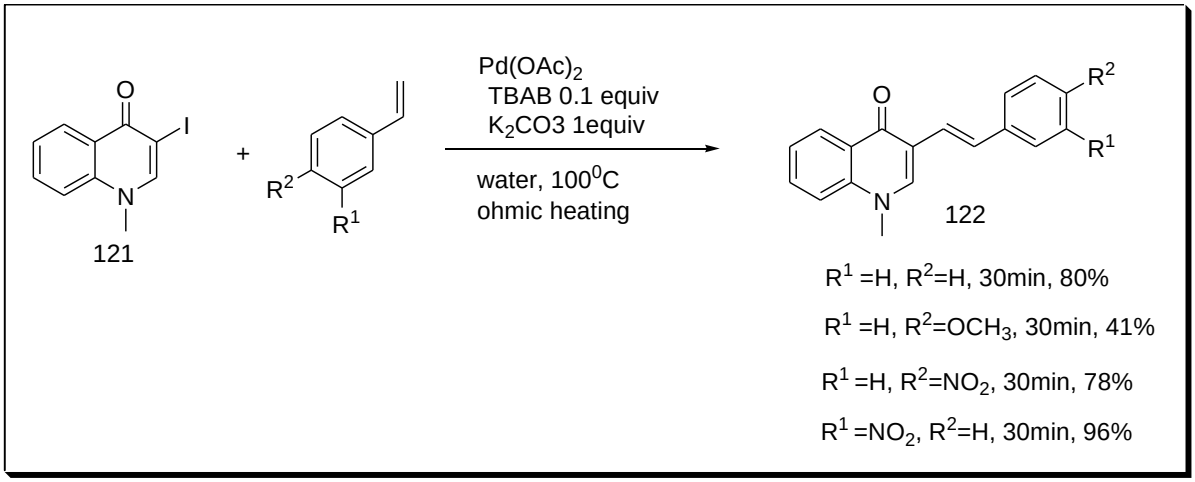
Selected Examples



It has been found that all terminal acrylates, sterically hindered acrylates both undergo the reaction smoothly. Rather, the reaction did not proceed well in the presence of electron releasing group at C-6 position on the quinolone ring. Steric factor also prevents the reaction in C-8 substituted 4-quinolones to give the high yield of the product. Most importantly, -NH protection was essential requirement for this reaction.

I.B.6. Heck Coupling

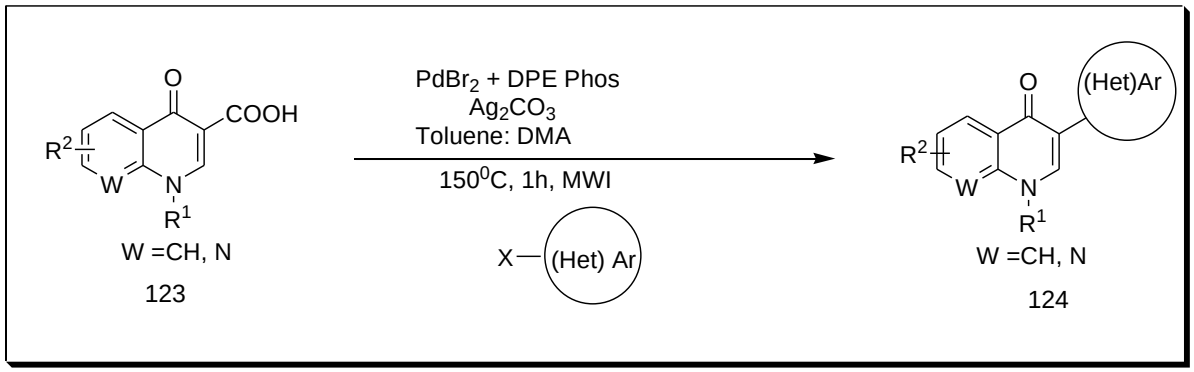
In 2016, Silva *et al.* reported the synthesis of (E)-3-Styrylquinolin-4(1H)-ones by heck coupling reaction in water from 3-iodo substituted 4-Quinolones. The reaction was performed in the presence of ohmic heating, [$Pd(OAc)_2$ as a catalyst, TBAB as a Phase Transfer catalyst] instead of classical heating procedure.[62] They have mentioned several advantages to this method, such as use of universal solvent water instead of other toxic solvent, avoid of additional ligands, more rapid reaction and short span of time .Moreover, ΩH (ohmic heating) resulted the better yields in comparison to previous method in the literature.



Scheme-I.42. Ohmic heating induced Heck cross-coupling reaction

I.B.7. Decarboxylative cross coupling

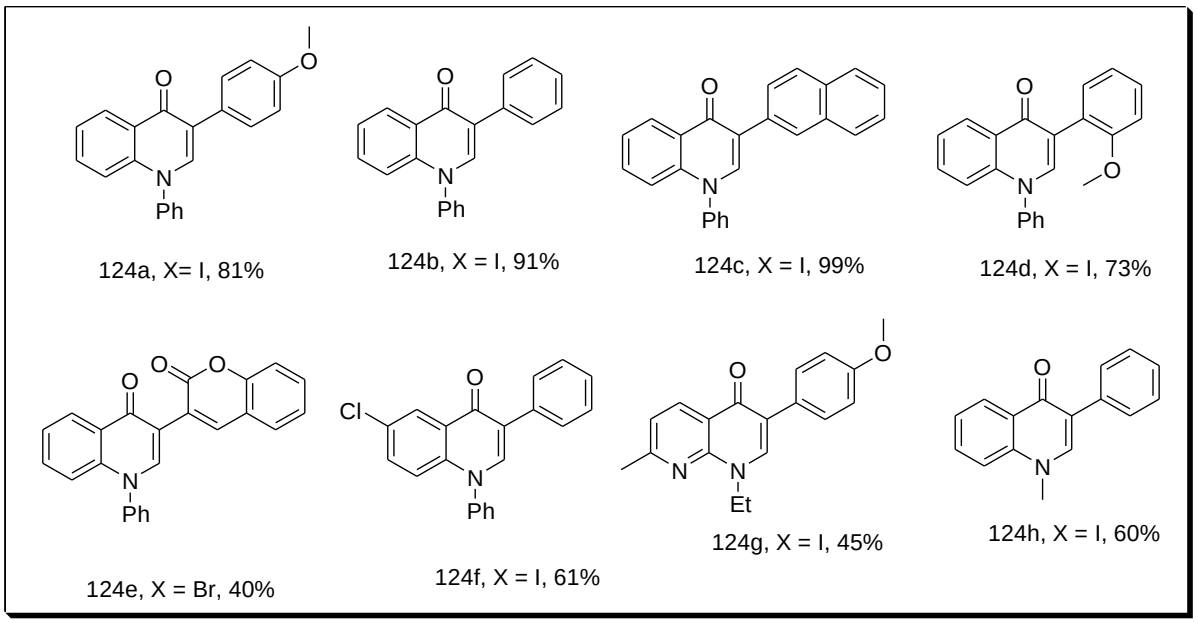
In 2012, an efficient and practical decarboxylative cross-coupling reaction of quinolin-4(1H)-one 3-carboxylic acids with (hetero)aryl halides has been established by using a bimetallic system of $PdBr_2$ and silver carbonate. [63]



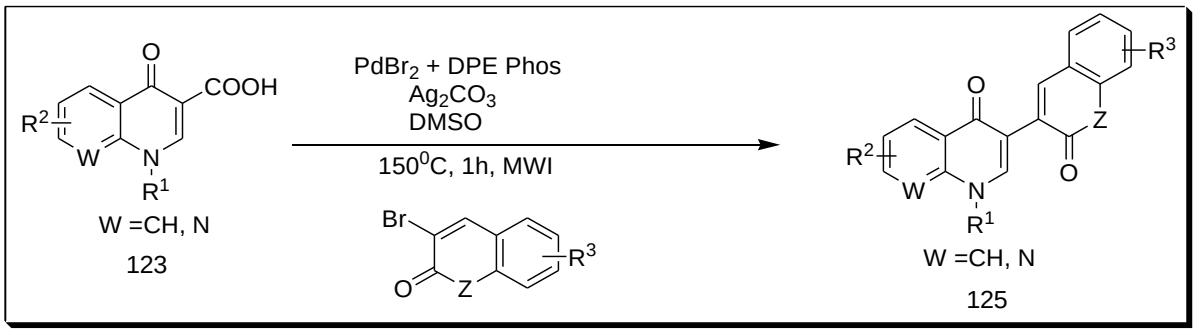
Scheme-I.43. Pd/Ag catalysed decarboxylative cross-coupling reaction of aryl halides with 4-quinolones

They attempted to choose microwave irradiation to enhance the reaction rate and to reduce the reaction time as well as to increase the yield of the product. Many screening had been done by using various Pd catalyst, ligand, solvent, base and temperature. The combination of $PdBr_2$ and Ag_2CO_3 along with DPEPhos served the promising result. Both aryl iodide and bromide participated in the reaction well. Aryl chloride became less effective as a coupling partner. Steric factor did not influence the decarboxylation reaction so well. Electron-donating or -withdrawing groups substituted N-alkyl- and N-arylquinolin4 (1H)-one 3-carboxylic acids converted into the corresponding product in good yields.

Selected Examples



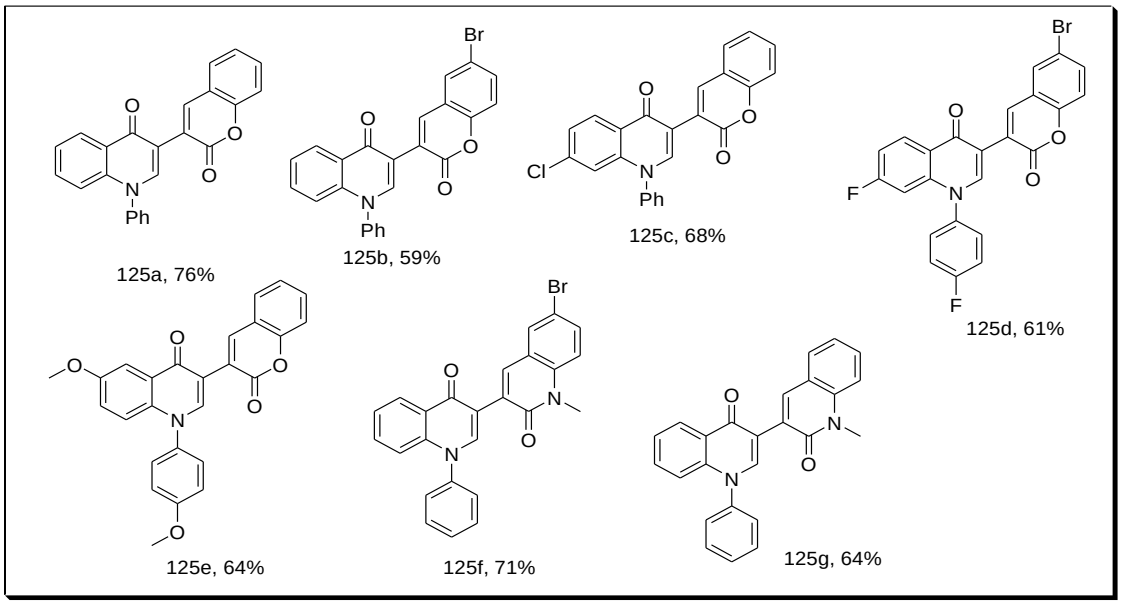
Following the procedures of the above development, the same research group discovered the the similar type of Pd catalysed decarboxylative coupling reaction of heterocyclic carboxylic acids with heterocyclic halides.[64]



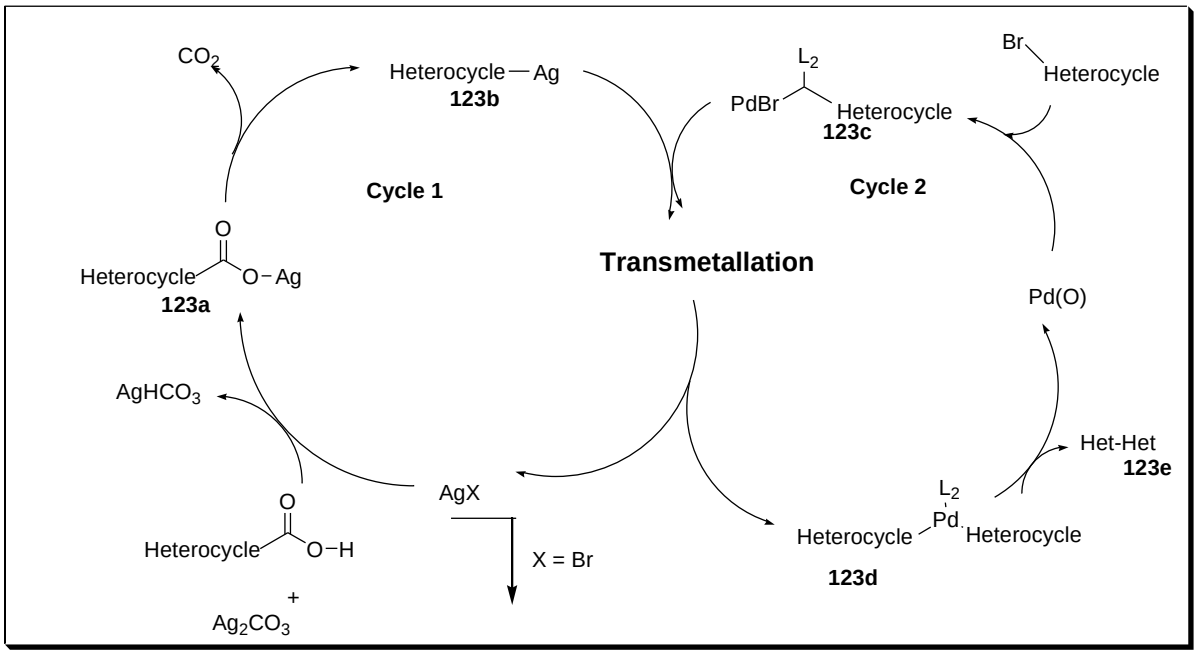
Scheme-I.44. Pd catalysed decarboxylative of 4-quinolone with heterocyclic halides cross coupling reaction

They performed the reaction by using their previously reported procedure [$PdBr_2$ (5 mol %), DPEphos (10 mol %); Ag_2CO_3 (1 equiv) in toluene/DMA] at 150°C for 1 h under microwave irradiation], but it resulted poor yield of the desired product. By optimizing several conditions, they had found that DMSO was the optimal solvent for this decarboxylative coupling. They investigated the scope of the Pd-catalyzed decarboxylative coupling of various substituted quinolin-4-ones 3-carboxylic acids with 3-bromocoumarins and 3-bromoquinolin-2-ones possessing different steric and electronic properties. Gratifyingly, all the couplings proceeded cleanly and selectively in good to excellent yields regardless of the nature of the substituents on the aromatic ring of the quinolin-4-one 3-carboxylic acid .

Selected Examples

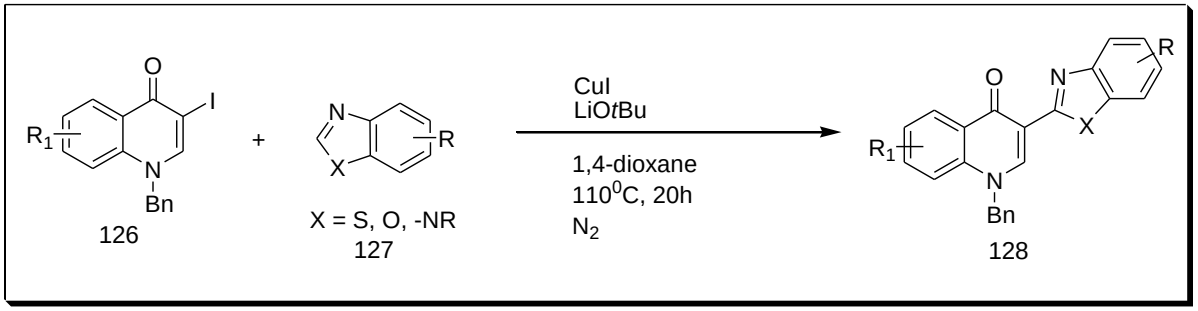


Mechanistic pathway



I.B.8. C-H bond activation

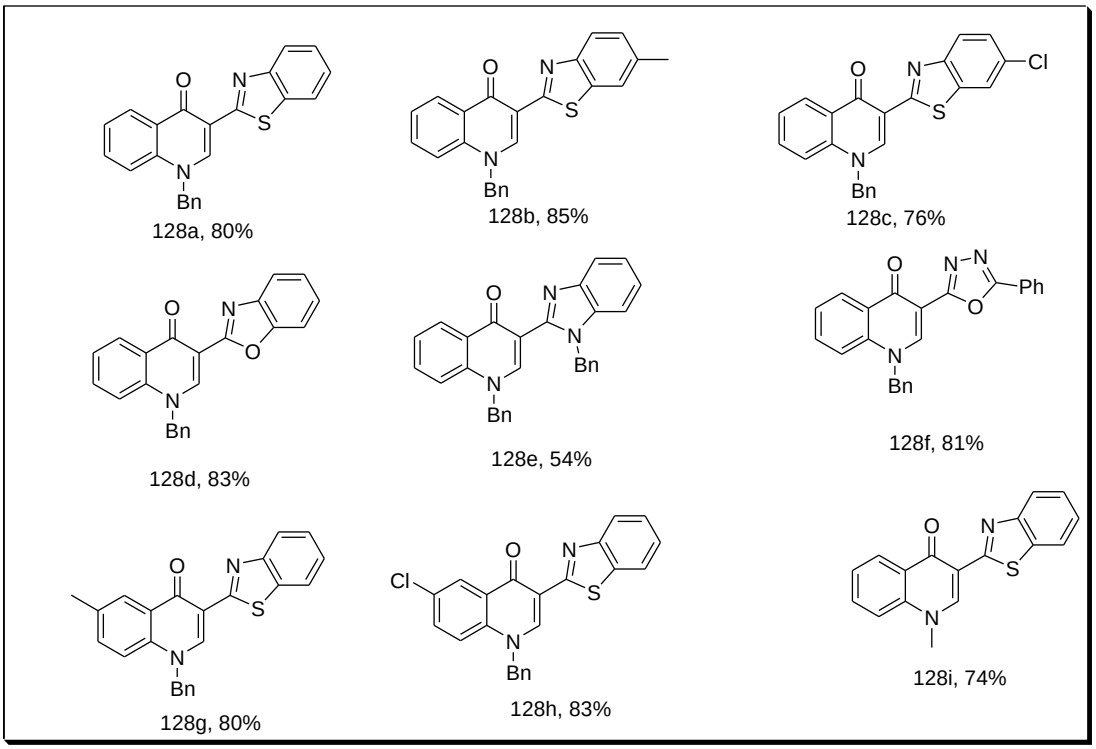
Hong and his coworkers developed an efficient and practical method for the direct insertion of azoles into the 4-quinolones via C–H functionalization in presence of copper catalyst. [65]



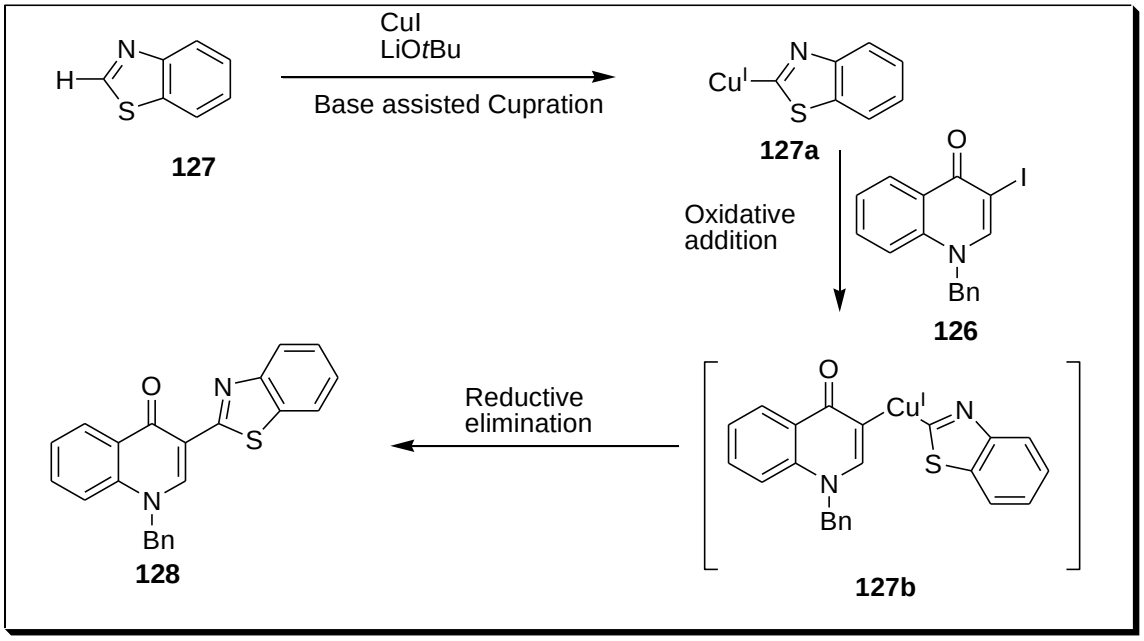
Scheme-I.45. Cu catalysed C-H functionalisation of azoles with 4-quinolones.

Interestingly, Pd catalyst and KO*t*Bu have no such promising effect for the formation as well as the product yield. Rather, the combination of CuI and LiO*t*Bu showed the better efficacy for such C-H bond functionalisation. A broad array of azoles, including variously substituted benzothiazoles, benzoxazoles, and imidazole were efficiently coupled with quinolone to prepare the diverse coupling products in moderate to good yields.

Selected Examples



Plausible Mechanism

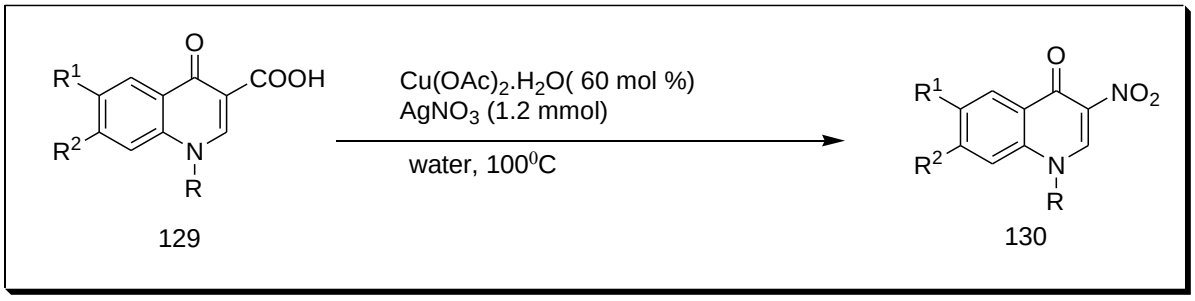


They proposed a plausible mechanism for the C-H bond functionalizing of azoles with N-benzyl-quinolone. Base-assisted cupration of benzothiazole took place at the first stage. Then, Cu species 127a would undergo the oxidative addition to provide the

copper species of higher oxidation state. Subsequently, reductive elimination of intermediate 127b yielded the desired coupled product.

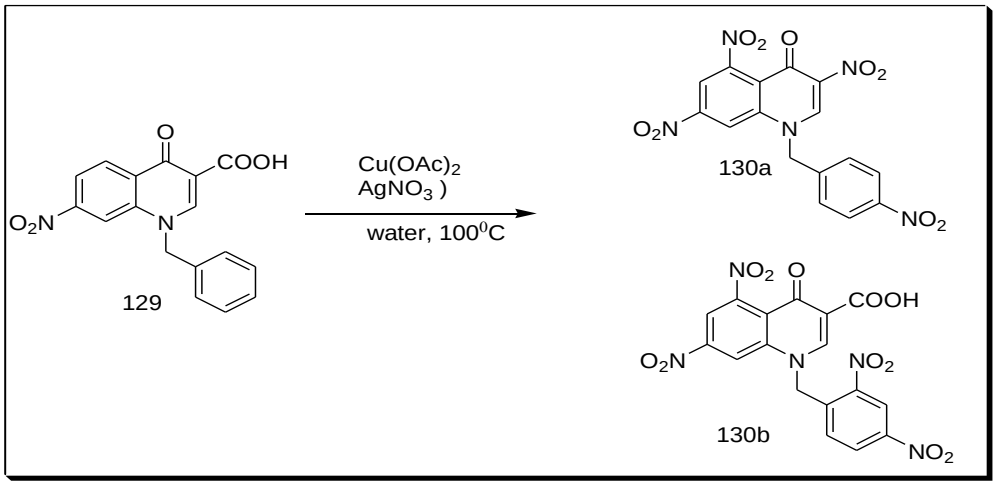
I.B.9. Decarboxylative ipso nitration

In 2015, Saxena *et al.* successfully developed a methodology to convert the 3-carboxy-4-quinolones to 3-nitro-4-quinolones using silver nitrate as a nitrating agent in presence of copper acetate.[66]

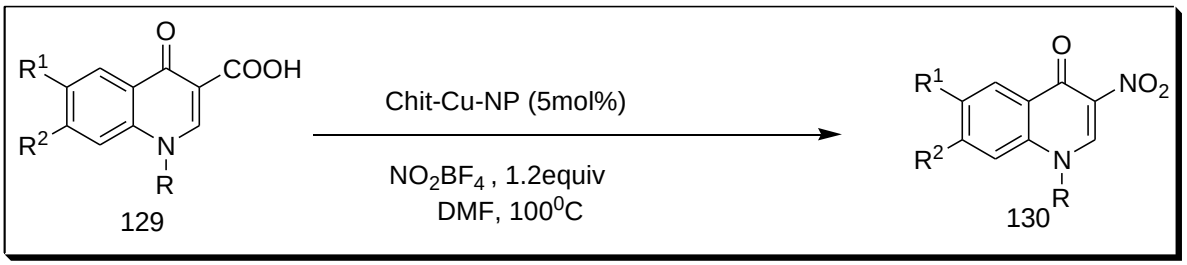


Scheme-I.46. Cu/Ag catalysed decarboxylative ipso nitration of 4-Quinolones

Selected Example



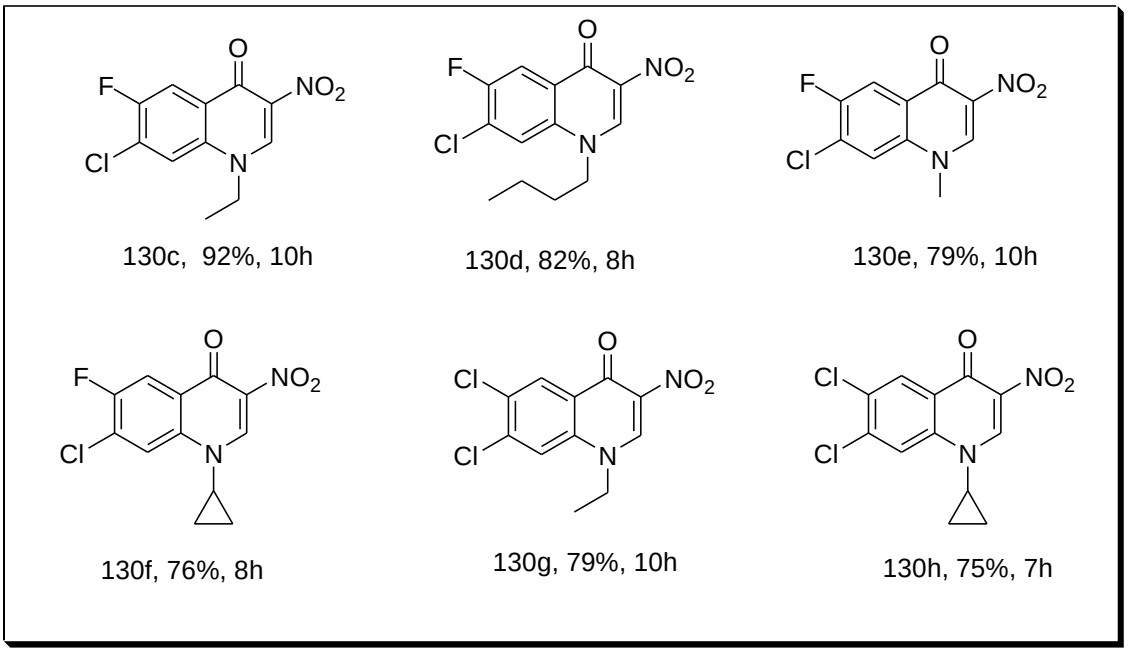
Recently, Narula and his co worker demonstrated the ipso nitration of 3-carboxy-4-quinolones in aid of NTFB via decarboxylative nitration using polysaccharide supported copper nanoparticles.[67]



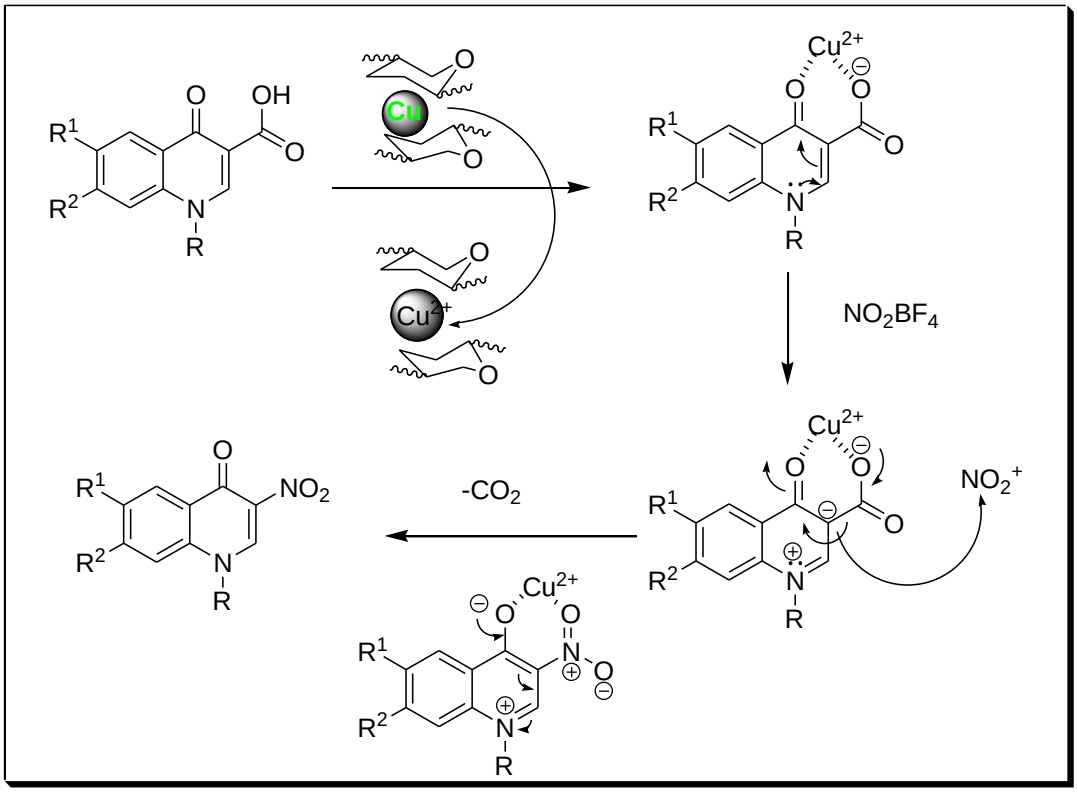
Scheme-I.47. Chitosan Cu-NP catalysed ipso nitration of 4-Quinolones.

The bi-functional groups such as hydroxyl and amine in chitosan are responsible for providing the excellent stability to the metal nanopartcles. In catalysis, it has shown its versatile potential. The high stoichiometric ratio of chit-Cu-NP (30 mol %) did not provide the profound impact on the yield. Many metal nitrates were employed but NO_2BF_4 which generated NO_2^+ in the reaction medium, is responsible for the nitration to give modest yield.

Selected Examples



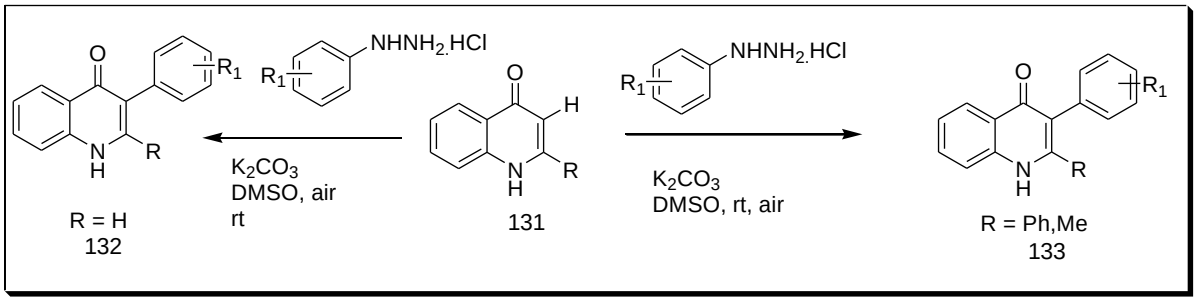
Plausible Mechanism



A plausible reaction mechanism was explained for the copper-nano particle decarboxylative nitration of the quinolones (Scheme above). -mediated chelation of β-keto acid assisted. Initially the Cu oxidized to Cu^{2+} in the presence of atmospheric oxygen. Then the two carbonyl groups of the quinolones chelated with Cu^{2+} ions through oxygen. The decarboxylative nitration proceeded through a concerted step, in which NO_2^+ from nitronium tetrafluoroborate attacks on the C-3 carbon. Simultaneously, decarboxylation takes place which leads to product formation.

I.B.10. Transitional metal free C-3 arylation reaction

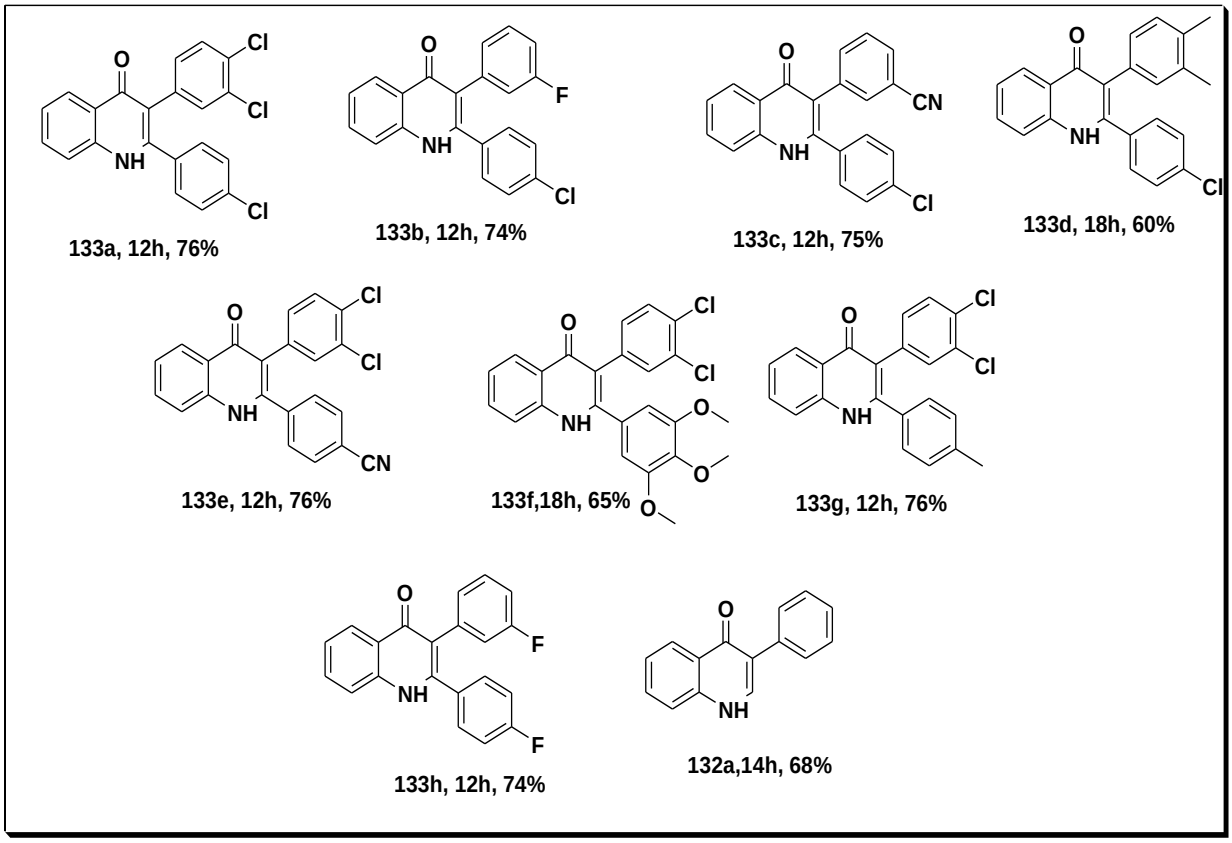
Yadav and his coworkers described the transition-metal-free C-3-arylation of quinolin-4-ones in the presence of base by using arylhydrazines as aryl radical source and air as oxidant. The reaction proceeds smoothly at room temperature and does not require any prefunctionalization and N-protection of quinoline-4-ones.[68]



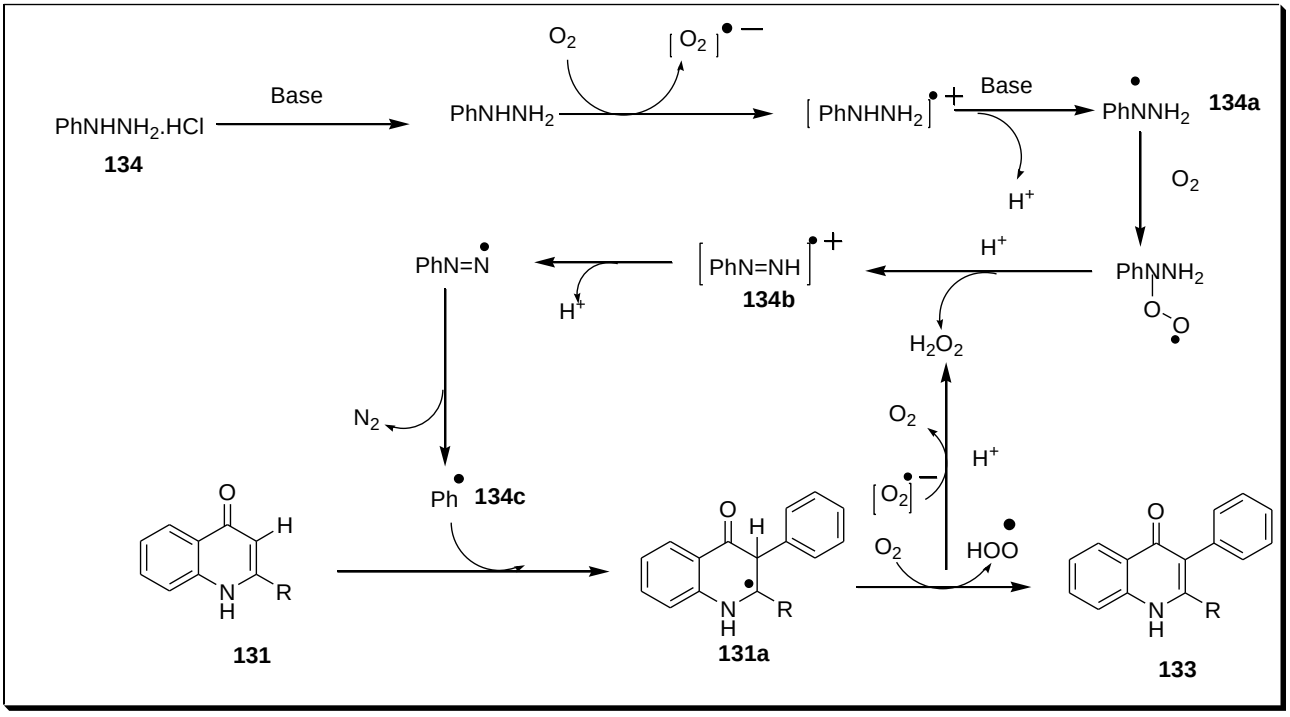
Scheme-I.48. Metal free C-3 arylation of 4-quinolones.

Phenylhydrazines bearing electron-withdrawing groups such as chloro, fluoro, cyano underwent the reaction smoothly to result the 3-arylated product in good yields. Moreover hydrazines having electron-releasing groups such as methoxy and dimethyl were well tolerated. Both the electron withdrawing and electron-donating groups on 2-phenyl ring were participated in arylation in quite well.

Selected Examples



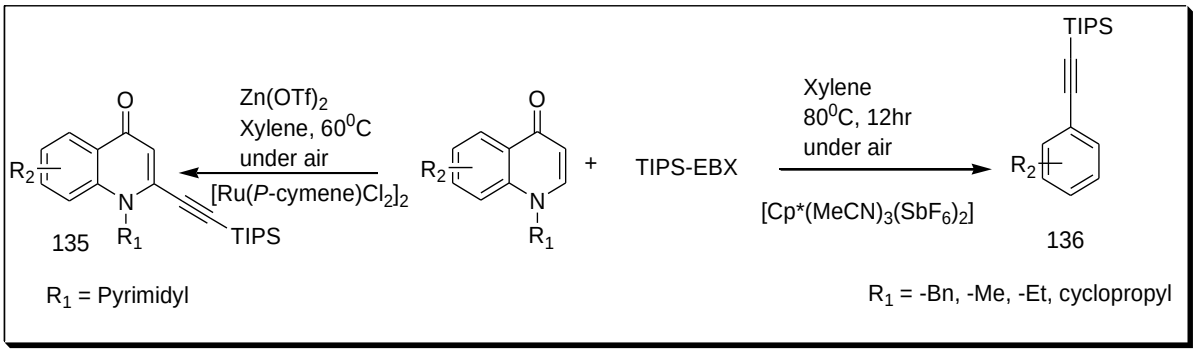
Plausible Mechanism



The group had proposed a plausible mechanism in which the free phenylhydrazine formed from its hydrochloride salt (134) in the presence of base at the initial stage. In presence of air/oxygen, it underwent single electron transfer[69] to generate the phenylhydrazine cation radical intermediate. Simultaneously, it lost H^+ in the presence of base which leads to phenylhydrazyl radical [134a]. Then, the radical [134a] converted into cation radical of phenyldiazene [134b] and hydrogen peroxide via passing through radical peroxide intermediate.[70] Due to unstable nature of the phenyl cation radical intermediate, it rapidly transformed into aryl radical [134c] and N_2 by losing the H^+. Later the aryl radical reacted with the quinoline-4-ones (131) to give the intermediate [131a] which afforded the desired product upon oxidation.[71]

I.B.11. Alkynylation of 4-quinolones

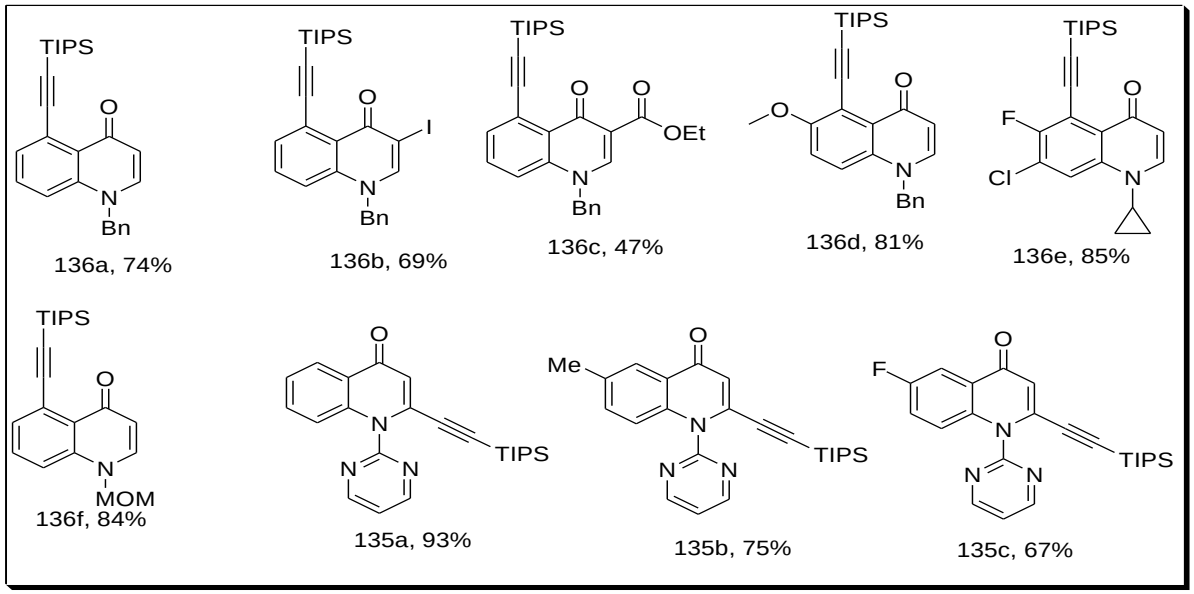
Hong *et.al* reported the two different efficient strategies for site selective C-5 alkynylation of 4-quinolones directed by the weakly coordinating carbonyl group and Ru(II) catalyzed C-2 selective alkynylation via N-pyrimidyl directing group using TIPS-EBX (an alkylating agent)[72]



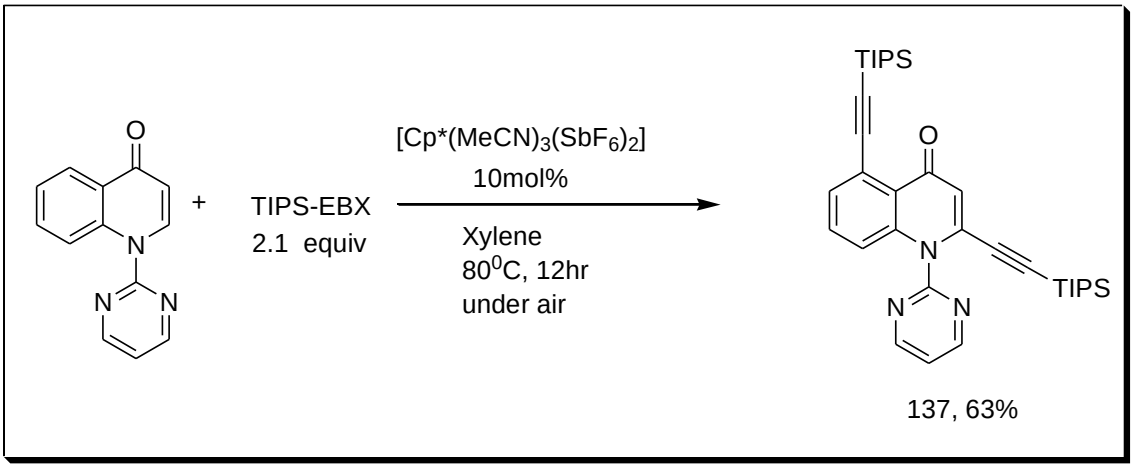
Scheme-I.49. Ru (II) catalysed site selective alkynylation of 4-Quinolones

Generally, N-Benzyl 4-quinolones containing bromo, iodo, ester and imide groups at the C-3 position smoothly participated to afford the corresponding C-5 alkynylated derivatives. Interestingly, the size and electronic properties of the substituents had no significant influence on the reaction efficiency. In addition, benzyl, methyl, ethyl, cyclopropyl, and MOM groups protected N-quinolones were easily underwent the reaction. In case of C-2 alkynylation, N-pyrimidyl group showed the high regioselectivity to the 4-quinolone moiety. Electron releasing group (Me− and OMe−) and electron withdrawing groups (F−, Cl−, Br−, CF_3−, and NO_2) on the 4-quinolone moiety were feasible to provide the C-2 alkynylated products.They had used these strategies in one-pot reaction to achieve both C-2 and C-5 alkynylation on the 4-quinolone scaffold.

Selected Examples

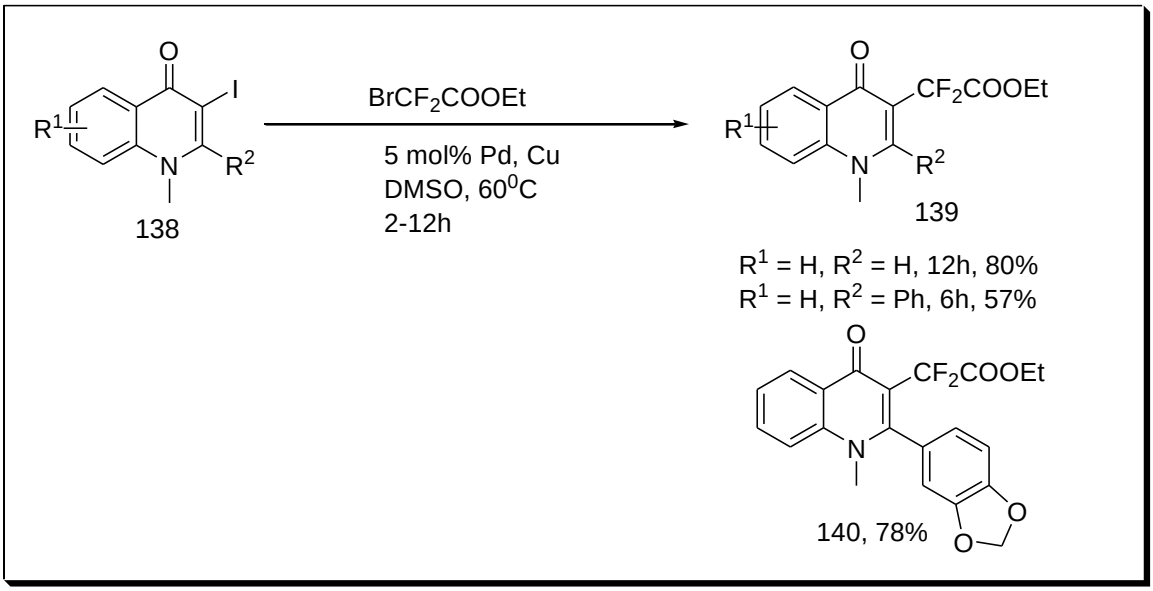


One pot catalytic C-2/C-5 alkynylation of 4-Quinolones



I.B.12. –CF_2 unit insertion of 4-Quinolones

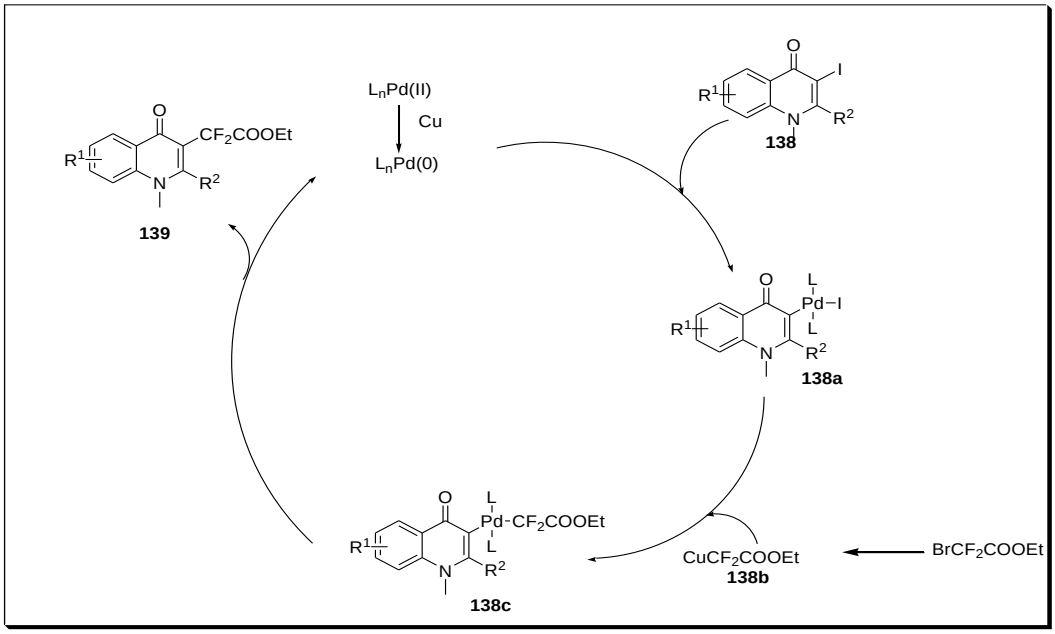
In 2013**,** Yang et al. reported the insertion of –CF_2 unit in the 3-position of 4-quinolone derivatives via palladium catalysed cross coupling in presence of copper mediator. [73]



Scheme-I.50. Pd/Cu catalysed–CF_2 group insertion of 4-Quinolones

Graveolinine, natural quinolone alkaloid[74] isolated from Ruta graveolens have interesting antibacterial, spasmolysis, and antitumor activities. They have inserted the –CF_2 unit into the scaffold via generating the 3-iodo-graveolonine primarily.[75]

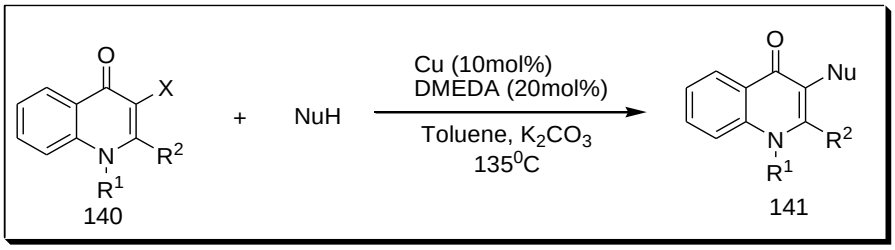
Plausible Mechanism



They have proposed a mechanism in which Pd (II) catalyst may be reduced by copper into an active Pd(0) species initially which then undergo the oxidative addition into the C−I bond of compound 138 to form intermediate 138a. In the meantime, the unstable copper ethyl difluoroacetate complex 138b was easily formed which performed a reaction with the intermediate 138a to form the intermediate 138c rapidly. In last step, the reduction elimination occurred which afforded the desired product 139 via regeneration of Pd(0) catalyst.

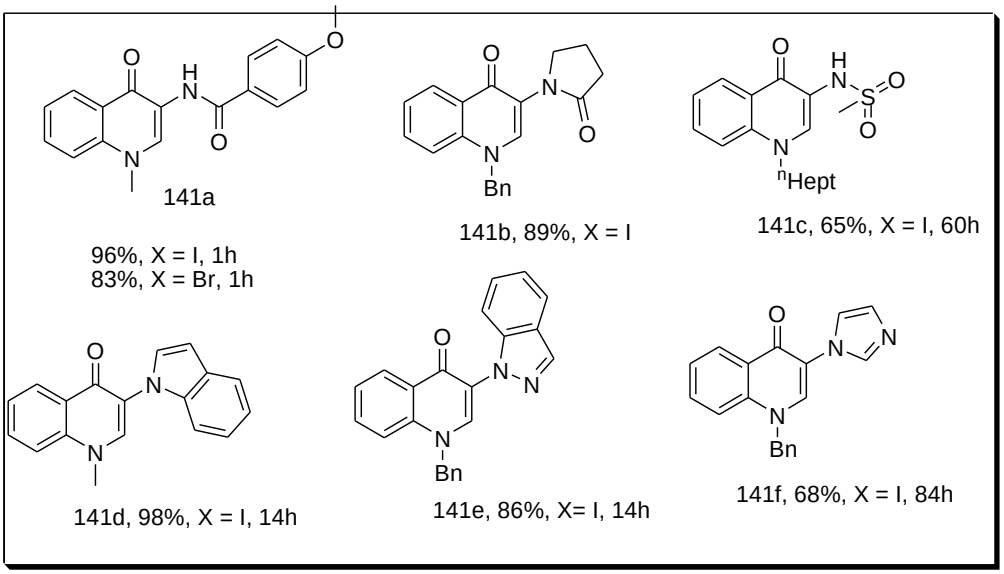
I.B.13. C-N coupling

Mouâd Alami *et al.* first reported the C-N coupling reaction of 3-halo-4(1H)-quinolones with various nucleophiles including amides, lactams, sulfonamides and NH-containing azoles in moderate to good yields. Copper powder, the catalyst plays the pivotal role for this Ullmann C-N bond forming strategy in presence of DMEDA (as a ligand) and K_2CO_3 (as a base) at 135 °C. [76]



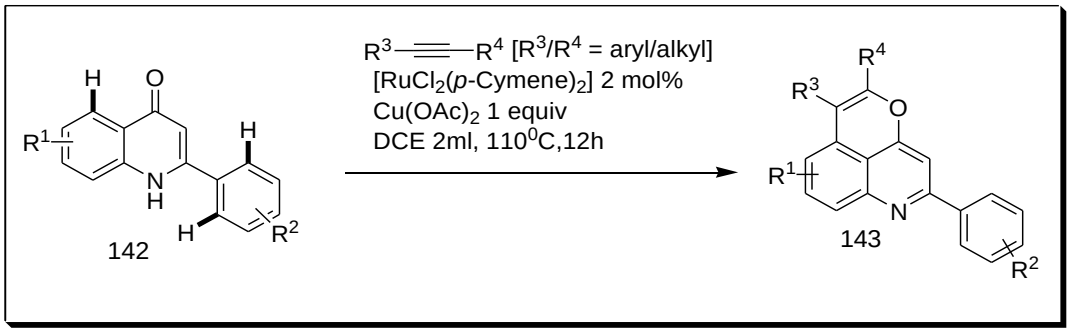
Scheme-I.51. Cu catalysed C-N coupling of 4-quinolones

Selected Examples



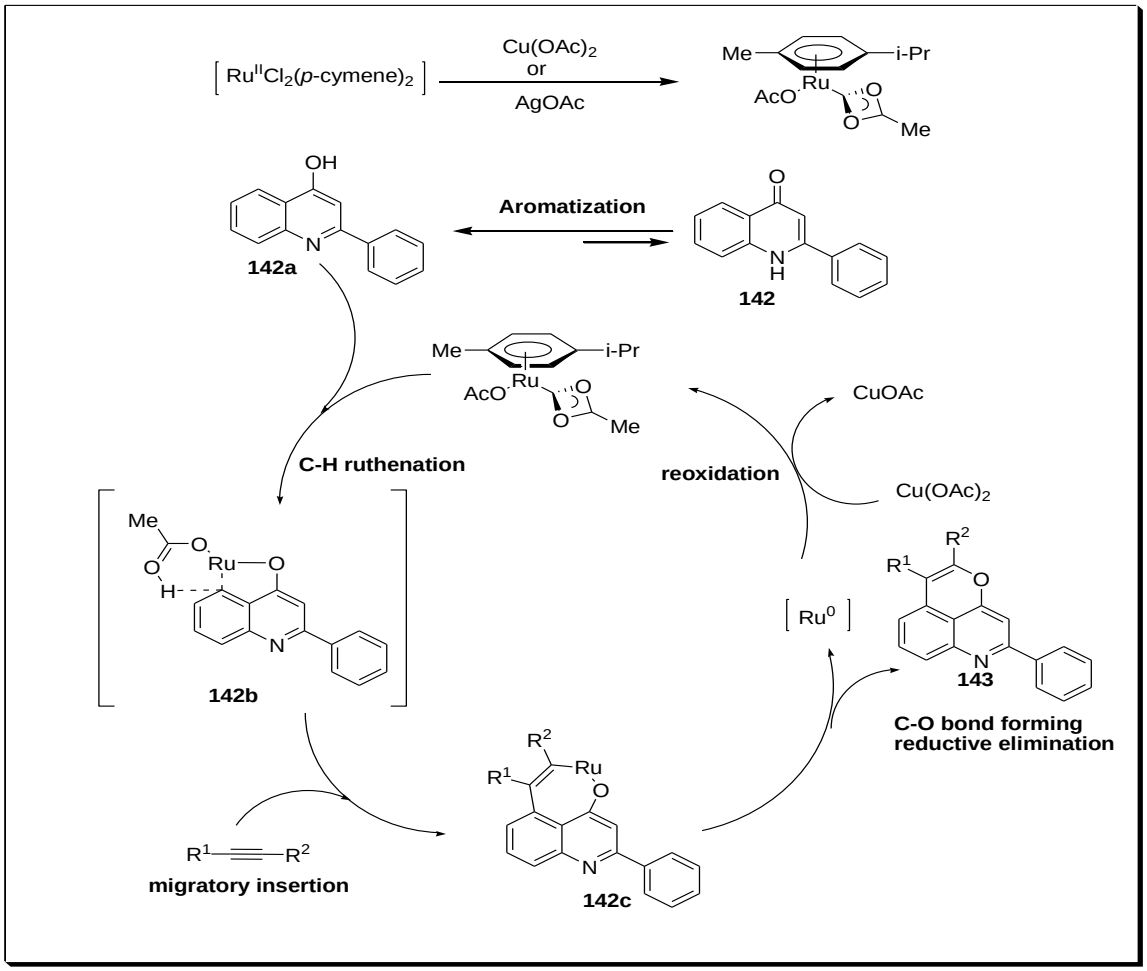
I.B.14. Ru catalysed C-H annulations of 2-arylquinolinone

Patel and his coworkers successfully done the C-H annulations of 2-arylquinolinone with internal alkyne *via* weak coordination in the presence of ruthenium catalyst.[77] electron-donating substituents such as *p*-Me in the 2-aryl ring of Arylquinolinone furnished their expected annulated products in moderate yields whereas Electron-withdrawing groups such as *p*-F and *o*-Cl present in the 2-aryl ring of 2arylquinolinone also provide their annulations products in decent yields.



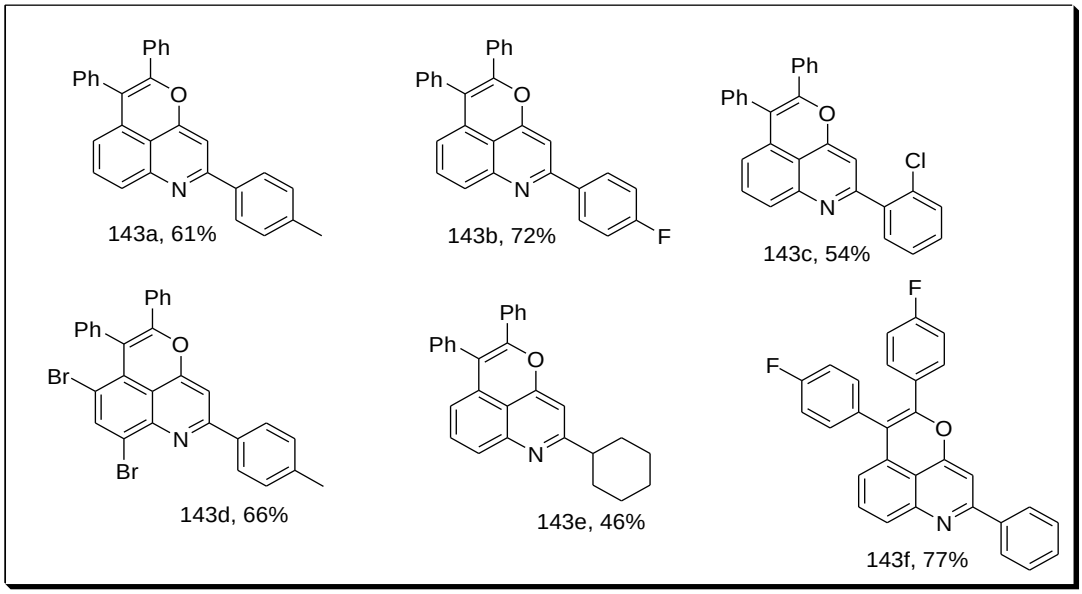
Scheme-I.52. C-H annulations of 2-arylquinolinone with internal alkyne in the presence Ru catalyst

Plausible mechanism



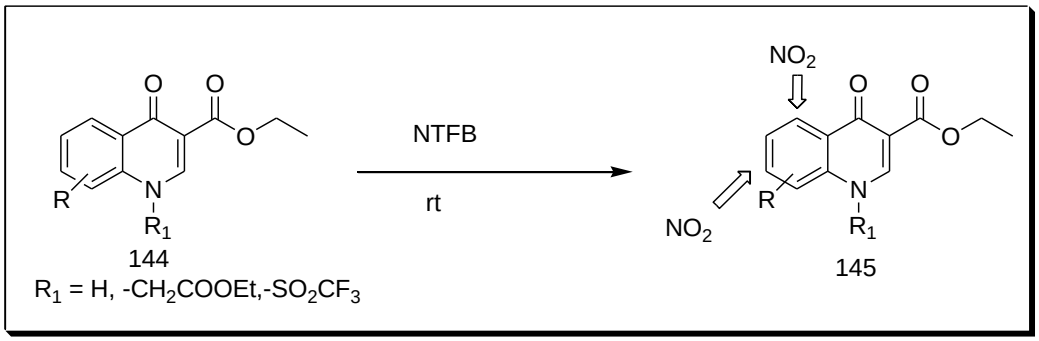
Initially, the chloride ligand of the ruthenium catalyst exchanged via the reactions with an acetate anion either from AgOAc or $Cu(OAc)_2$. Then, aromatization of 2-phenylquinolinone (142) provided the 4-hydroxy-2-phenylquinoline (142a). Afterwards, a five-membered ruthenacycle intermediate (B) is formed from (A). Then, migratory insertion of alkyne took place into the Ru-carbon bond of intermediate (142b) and resulted the intermediate (142c). For unsymmetrical alkynes, the alkyne carbon having higher electron density favoured the insertion into the Ru-carbon bond which accounted for the regioselectivity. Finally, reductive elimination resulted the expected annulated product (143) with the regeneration of catalyst Ru(0) . This Ru(0) is further oxidized to an active Ru(II) catalyst with the aid of oxidant $Cu(OAc)_2$ or by an areal oxidation.

Selected Examples



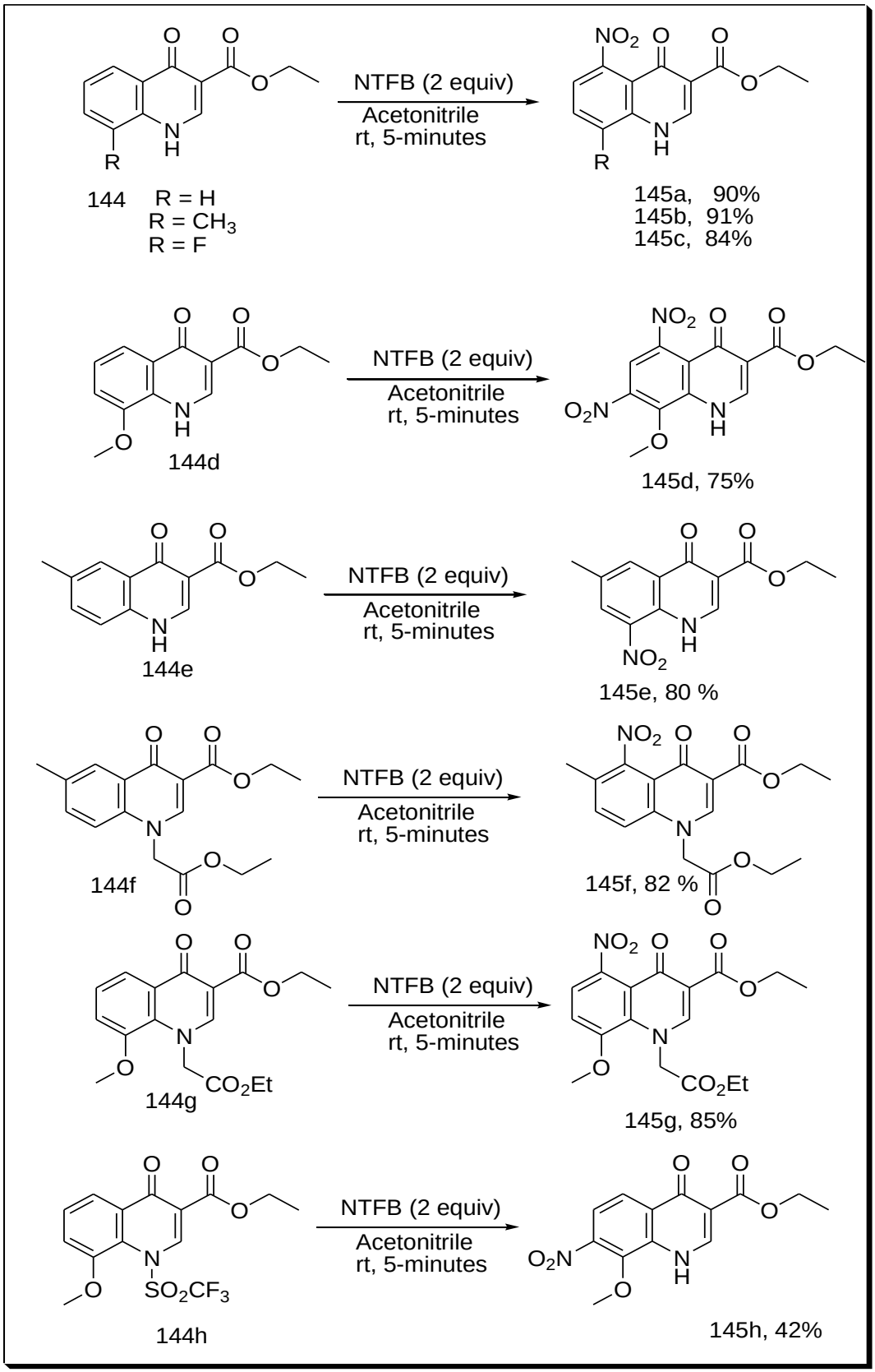
I.B.15. Regiocontrolled nitration of 4-quinolones at ambient temperature

A complete regio-controlled nitration of 4-quinolones at ambient conditions with the aid of NTFB (nitronium tetrafluoroborate) was described. We had tuned the selectivity by the selective functionalization of free N-H group of 4-quinolone. Analyzing the DFT (density functional theory) calculation, the profound impacts of the free N-H and other substituents in the nitration process of 4-quinolones have been screened .Theoretical prediction and experimental observations were well synchronized below this reaction.[78]



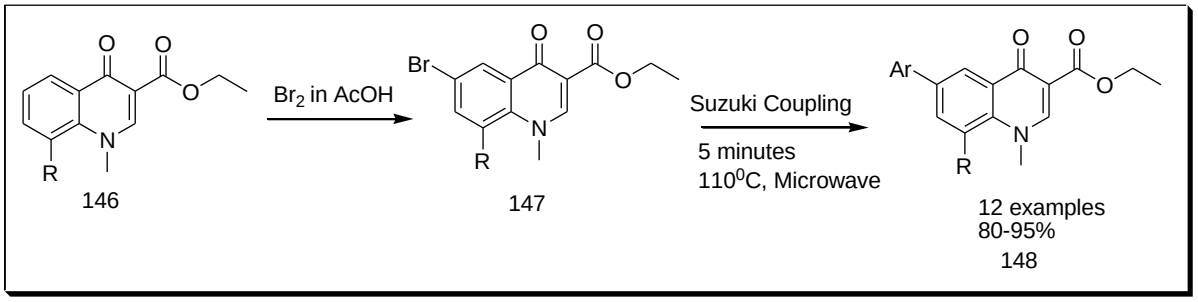
Scheme-I.53. Regiocontrolled nitration of 4-quinolones

Selected Examples



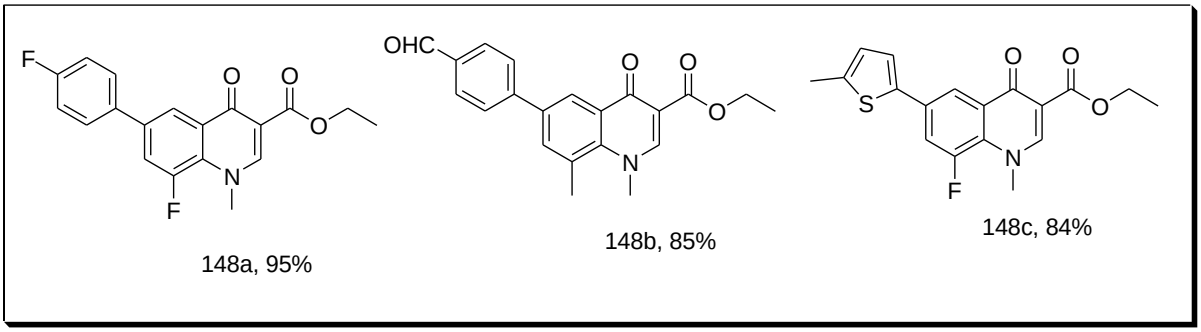
I.B.16. Synthesis of 6-aryl substituted 4-quinolones

Here in, we reported the regioselective bromination at C-6 position and subsequent arylation by Suzuki cross-coupling using Pd-NHC catalyst to prepare a broad array of 6-aryl substituted-4-quinolones. The desired cross-coupled product easily formed in only 10 minutes under microwave irradiation at 110 °C.[79]



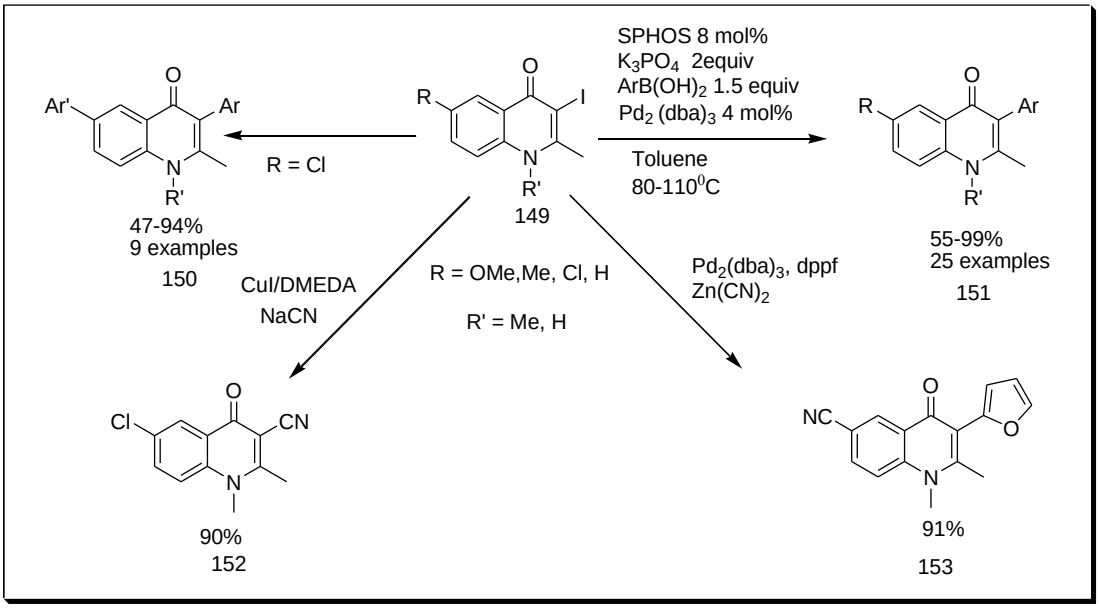
Scheme-I.54. Synthesis of 6-aryl substituted 4-quinolones *via* Suzuki cross coupling

Selected Examples



I.B.17. Suzuki coupling & cyanation

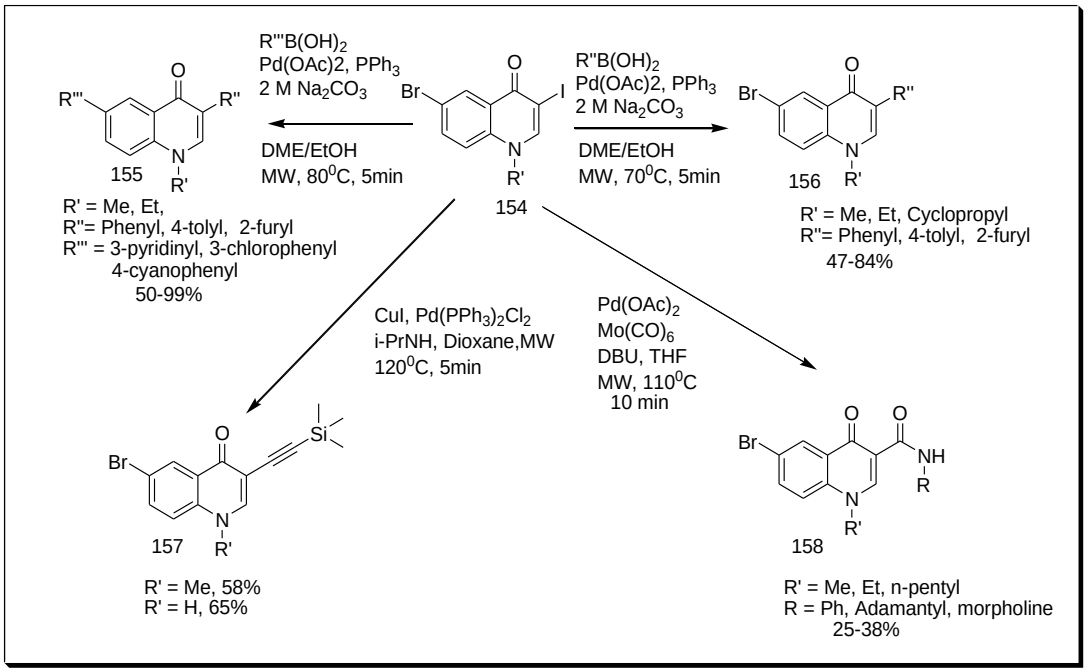
Manetsch *et al.* demonstrated the divergent route to access the structurally diverse 4-Quinolones via sequential Suzuki coupling and cyanation reaction in presence of palladium as well as copper catalyst. A large variety of aryl(Het)boronic acid successfully coupled with 6-chloro-3-iodo substituted 4-quinolone with very good yield. [80]



Scheme-I.55. Synthesis of different substituted 4-Quinolones via Suzuki cross coupling & cyanation reaction.

I.B.18. Regioselective Suzuki, sonogashira & aminocarbonylation reaction

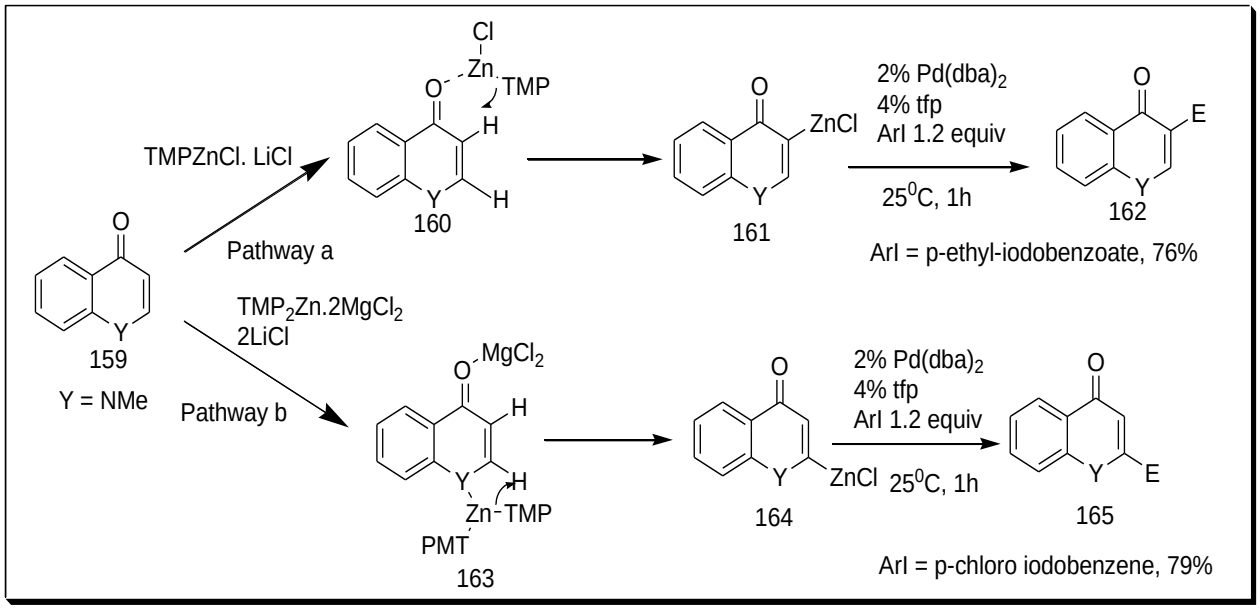
In 2011, Corelli and his coworkers similarly synthesized the1,3,6-trisubstituted quinolin-4(1H)-ones starting from 1-alkyl-6-bromo-3-iodoquinolin-4(1H)-one via regioselective Suzuki coupling, sonogashira coupling and aminocarbonylation reaction. All the reaction proceeded under microwave irradiation in a very short span.[81]



Scheme-I.56. Regioselective Suzuki, sonogashira coupling & aminocarbonylation reaction

I.B.19. Regioselective zincation of C-2 & C-3 position of 4-Quinolones

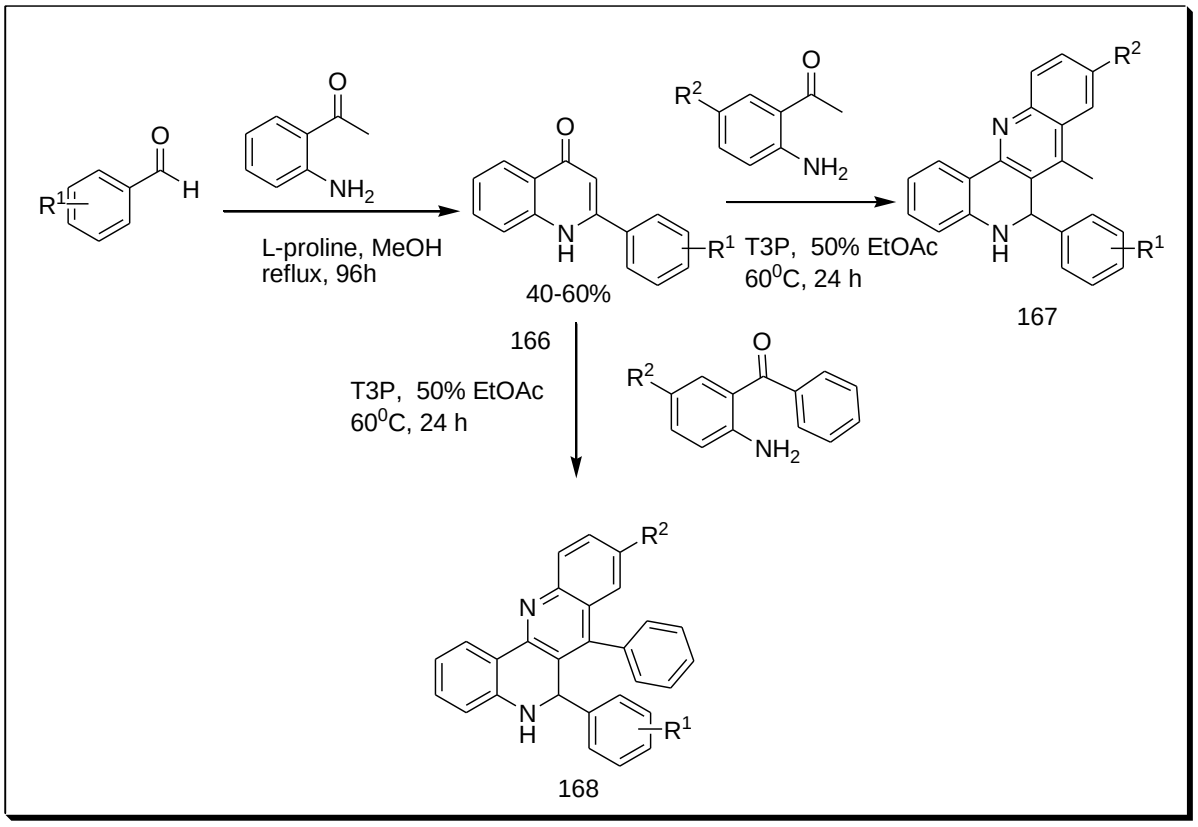
Knochel have employed the regioselective zincation at C-2 and C-3 position of quinolones in presence or absence of $MgCl_2$ lewis acid. For achieving the regioselectivity, they have used highly chemoselective TMP (2,2,6,6-tetramethylpiperidyl) bases such as TMPZnCl.LiCl and $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ by which several quinolone units have been synthesized. [82]



Scheme-I.57. Regioselective electrophile insertion at C-2 & C-3 position of 4-quinolones.

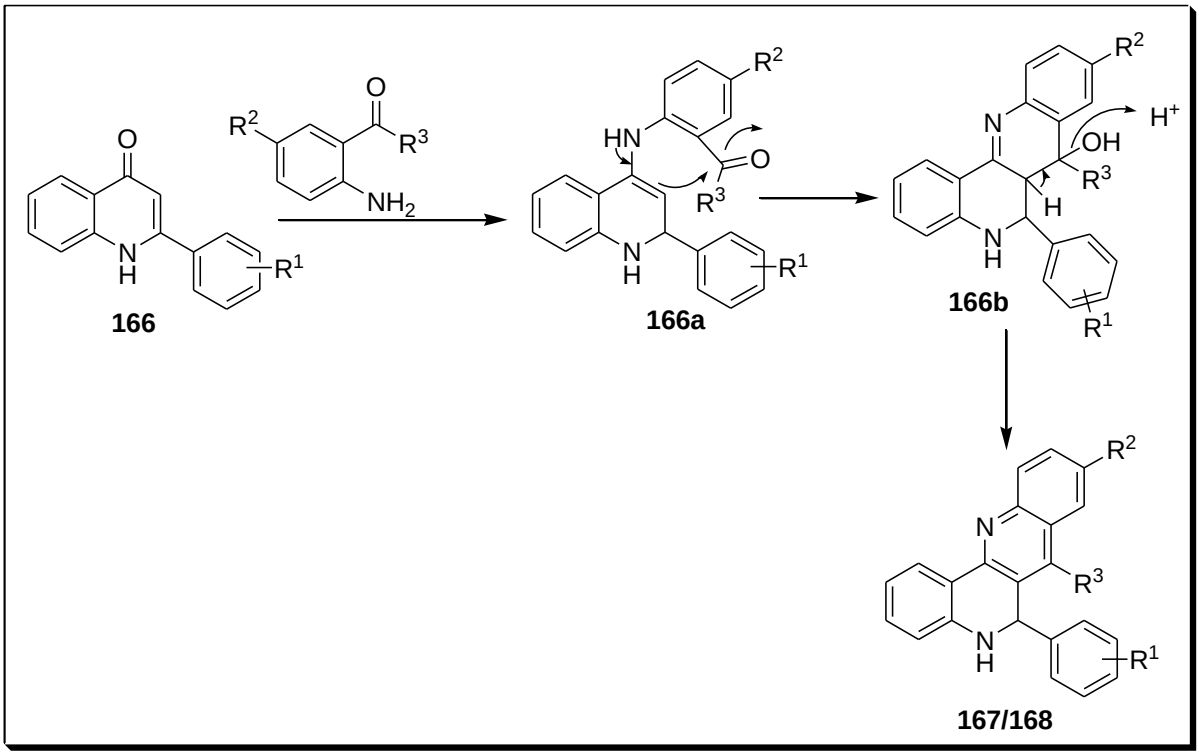
I.C. Miscellaneous reactions of 4-quinolones

More recently, Kumar and his group finished a two step protocol for the synthesis of substituted dibenzo[*b,h*][1,6]naphthyridine derivatives generated from the coupling of 2-aminoacetophenones and 2-aminobenzophenones with dihydroquinolin-4ones using propyl phosphonic anhydride solution as a catalyst (T3P). A diverse analogues of dibenzo[*b,h*][1,6]naphthyridine derivatives was isolated in good yield under expensive catalyst free condition.[83]



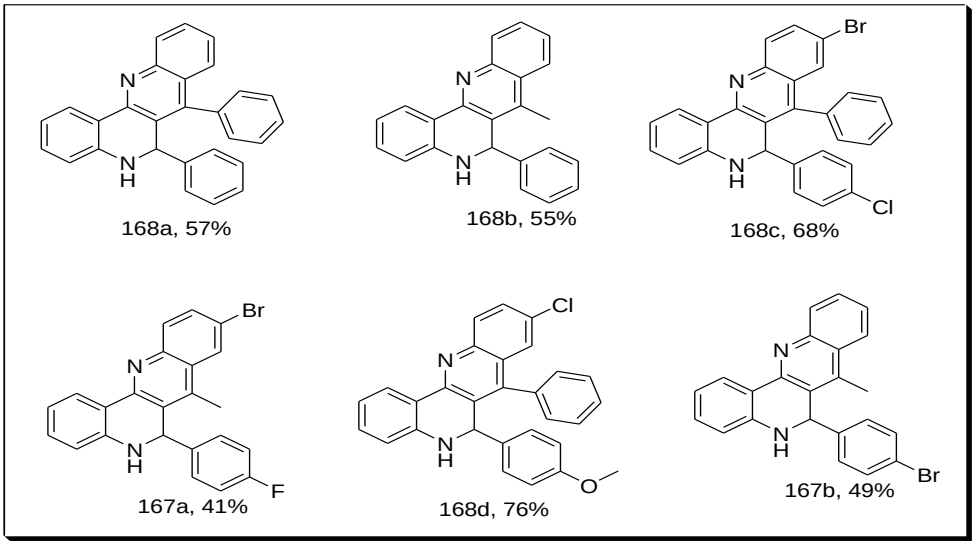
Scheme-I.58. Synthesis of dibenzo[*b*,*h*][1,6]naphthyridine derivatives using T3P as a catalyst

Plausible Mechanism:

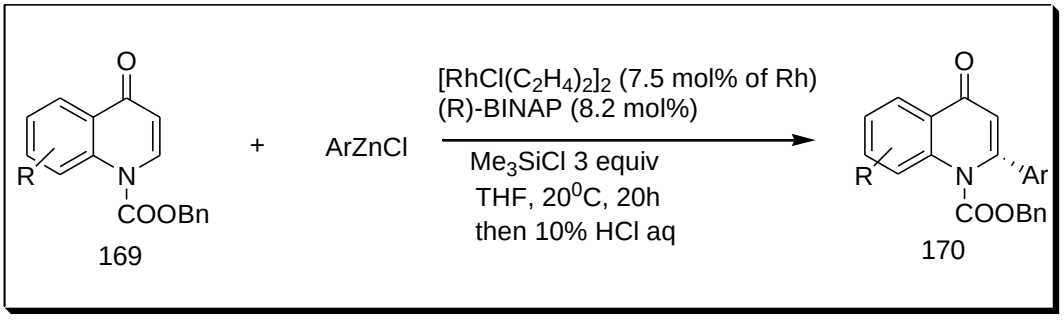


The above reaction proceeded via the formation of 4-acylamino-dihydroquinoline intermediate 166a initially. Then, the enamine group of intermediate 166a attacked the nearby ketone functional group to provide the intermediate 166b. Finally, the desired product generated upon dehydration reaction of intermediate 166b.

Selected Examples

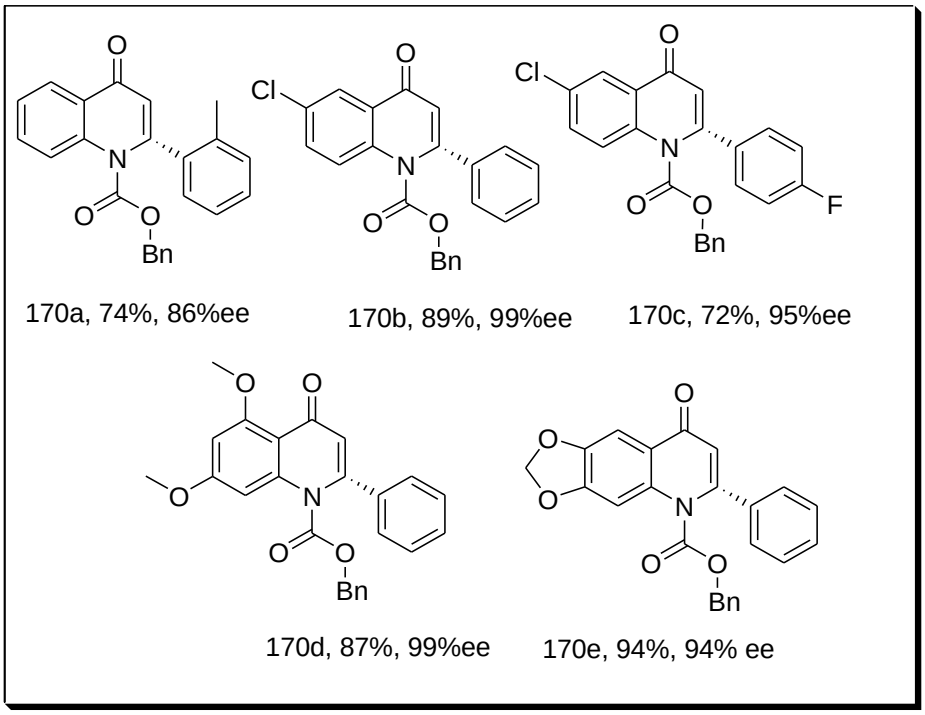


In 2005, Hayashi *et al*. first reported the asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones via rhodium catalysed 1,4-addition of arylzinc reagent to the 4-quinolone moiety with high enantioselectivity. [84]

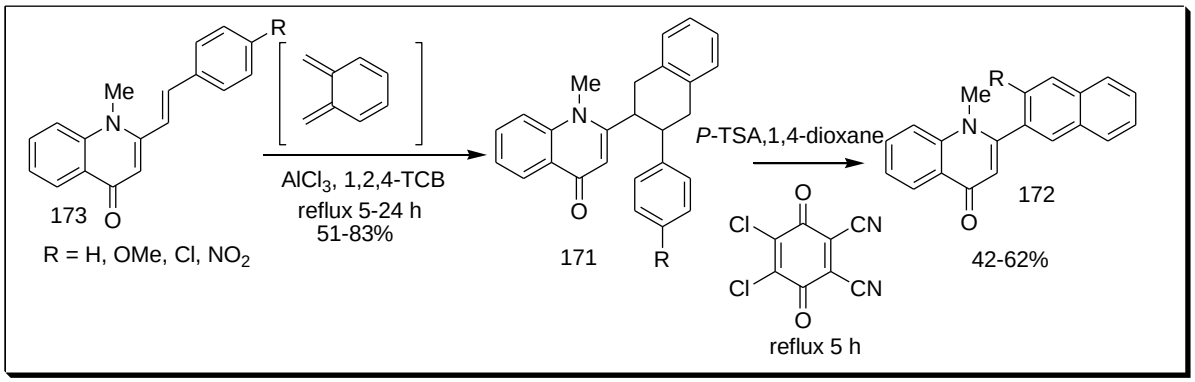


Scheme-I.59. Rh catalysed asymmetric synthesis of 2-aryl-2,3-dihydro-4-quinolones via 1,4-addition of arylzinc reagent

Selected examples



Very recently, Silva *et al.* reported the synthesis of trans-2-(3-aryl-1,2,3,4-tetrahydronaphthalen-2-yl)-1-methylquinolin-*4*(1H)-ones from the cycloaddition reactions in between (E)-1-methyl 2-styrylquinolin-4(1H)-ones and very reactive diene ortho-benzoquinodimethane in presence of lewis acid. Further, they converted this adduct into the 2-(3-arylnaphthalen-2yl)-1-methylquinolin-4(1H)-ones with the aid DDQ in moderate yield.[85]



Scheme-I.60. Lewis Acid Catalyzed Diels–Alder Reactions of (E)-1-Methyl-2-styrylquinolin-4(1H)-ones with ortho-Benzoquinodimethane

The electron donating group (-OMe) decreases the reactivity of of (E)-1-methyl-2-styrylquinolin-4(1*H*)-ones to participate in cycloaddition reaction whereas the electron

withdrawing group showed higher reactivity to afford excellent yield of the desired product.

I.D. Conclusion

In this introduction part, several approaches to the transition metal catalyzed and metal free synthesis of 4-quinolones are briefly discussed. This review also includes various aspect of functionalization of the 4-quinolone precursor *via* C-C coupling (Suzuki, Sonogashira), C-N coupling, nitration, ipso-nitration, decarboxylative C-S coupling, and C-H bond activation etc. The use of these processes has become a lively area of research because 4-quinolone unit is a common structural unit widely encountered in biologically active molecules and natural products. The review describes the latest improvements in the substrate scope, mildness of the procedures, catalyst loading and catalytic cycle in the area of transition metal catalyzed functionalisation.

I.E. References

References of chapter I are given in the Bibliography (pp-223-227)