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Synthesis of Substituted Quinolines via Allylic Amination and Intramolecular Heck-Coupling

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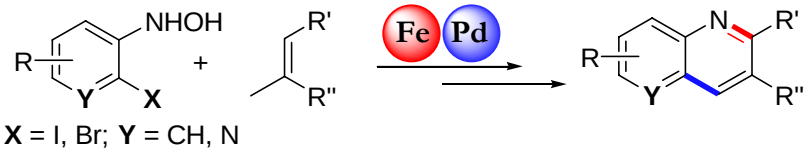
Abstract



X = I, Br; **Y** = CH, N

A new catalytic approach for the synthesis of substituted quinolines via C-N and C-C bond formation using 2-haloaryl hydroxylamines and allylic C-H substrates is described. Fe-catalyzed allylic C-H amination followed by Pd-catalyzed intramolecular Heck-coupling and aerobic dehydrogenation deliver the valuable quinoline and napthyridine heterocycles in good to excellent overall yields. In this process, $Pd(OAc)_2$ plays a dual role in catalyzing Heck coupling as well as aerobic dehydrogenation of dihydroquinolines.

Introduction

Quinolines and their derivatives are an important class of heterocycles that are often found in many natural products, biologically active, and pharmaceutically useful compounds.[1] Medicinal chemistry applications of such compounds include Piavastatin, a tri-substituted quinoline, as a HMG-CoA reductase inhibitor,[2a] 3-aryl quinolines as PDGF receptor tyrosine kinase inhibitor,[2b] 3-triazolo quinolines as antimicrobial agents,[2c] and other quinoline derivatives used as antiretroviral agents, potent HIV-1 integrase inhibitors,[3a] LTD receptor antagonists,[3b] antimalarial agents,[3c] and anti-inflammatory,[3d] anticancer,[3e] antibiotic,[3f] and antihypertensive drugs.[3g] On the other hand, substituted quinolines are valuable synthons for the preparation of nano- and mesostructures with enhanced electronic and photonic properties.[4] As a result, various synthetic methods are reported in the literature for the synthesis of substituted quinoline derivatives.[5–7] Traditionally, 3-substituted quinoline derivatives are prepared by the Skraup,[5a] Döebner-von Miller,[5b] Friedländer,[5c] and Combes[5d] methods and other catalytic methods using molecular-iodine,[6a] $In(OTf)_3$,[6b] CAN,[6c] $RuCl_2(PPh_3)_3$,[6d] $[Cp^*RhCl_2]_2$[6e] etc. However, many of these procedures suffer from harsh reaction conditions and the use of relatively expensive catalysts.[5,6] Moreover, substituted quinolines have also been synthesized using Baylis–Hillman(BH) adducts and/or pre-

functionalized olefin substrates.[7] Kim et al. reported synthesis of 3-substituted quinolines using BH acetates and ortho-halo anilines (**i**) as shown in Figure 1,[7a] but the first step requires seven days for completion. Alternatively, another approach by the same group was reported using ortho-halo aryl BH acetates with tosyl amides (**ii**).[7b] Nicholas et al. reported a reductive cyclization method (**iii**),[7c] whereas Larock et al. used allylic alcohols with 2-haloanilines (**iv**).[7d] Recently, Lee et al. described another method using ortho-amino aryl ketones and alkynes to make quinoline 3-carboxylates (**v**)[7e]. Other recent approaches utilized ortho-nitrogenated functional arenes for the synthesis of 3-substituted quinolines,[8] however the major limitation of these methods is requirement of complex or pre-functionalized substrates which limits the scope of their synthetic utility.

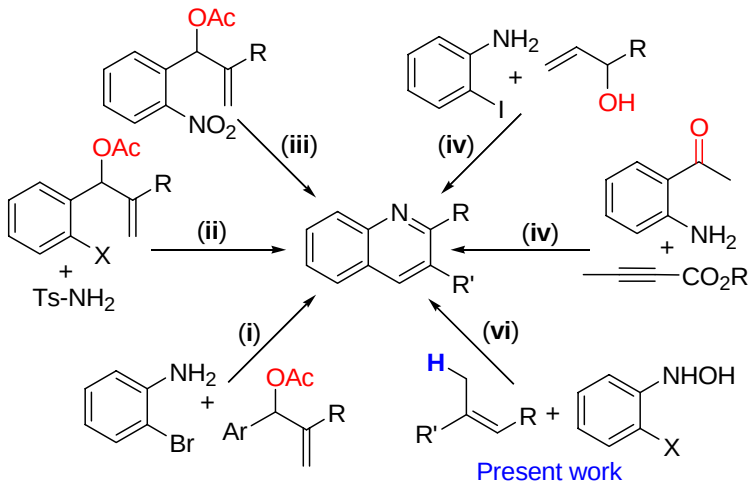
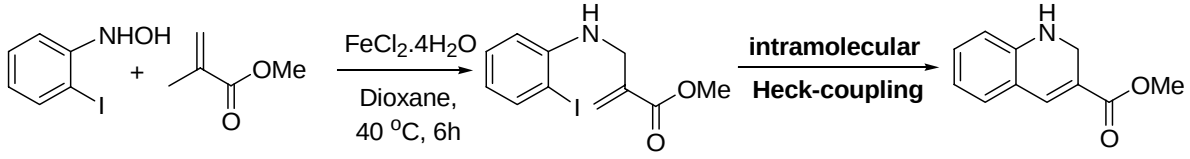


Figure 1. Existing synthetic routes for substituted quinolines and our approach

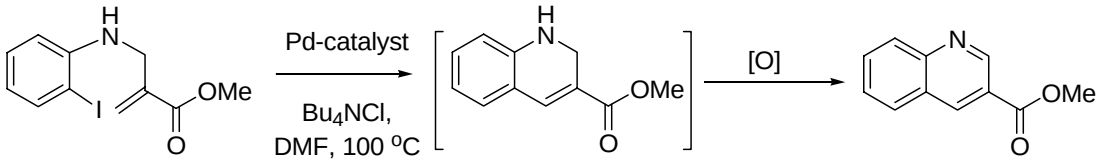
Results and Discussion

In recent years, the development of sustainable, environmentally friendly, and low cost catalytic C–C and C–heteroatom bond forming protocols have attracted much attention in synthetic organic chemistry. In continuation of our ongoing efforts on catalytic synthesis of organo nitrogen molecules[9] and heterocycles[10], we recently reported a direct method to access novel β-alkyl N-aryl aza Baylis-Hillman (ABH) adducts which cannot be prepared by traditional aza Baylis-Hillman reactions.[9e] Considering the feasibility, we envisaged that an allylic amination of ortho-halo N-arylhydroxylamines followed by intra-molecular Heck-coupling could lead to highly substituted dihydroquinolines (Scheme 1).



Scheme 1. Catalytic synthesis of 3-substituted quinoline via ABH adduct formation

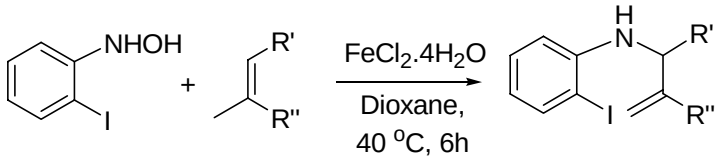
Initially we have synthesized an ABH adduct, starting from methyl methacrylate and 2-iodophenyl hydroxylamine, which we chose as our model substrate to study intramolecular Heck-coupling reaction. We tested the intra-molecular coupling reaction using standard Heck-coupling conditions using $PdCl_2$, Na_2CO_3, nBu_4NCl, DMF at 100 ^oC. Interestingly, ring aromatization (aerobic dehydrogenation) was observed along with Heck-coupling that led to yield quinoline in 41 % accompanied by a small amount of dihydroquinoline (<5 %) along with other decomposed products (Scheme 2). In this reaction, $PdCl_2$ played a dual role in catalyzing Heck-coupling as well as ring-aromatization. Some Pd-catalysts are known to catalyze aerobic dehydrogenation reactions and ring annulations.[11] In order to improve the catalytic system, we screened a set of Pd-catalysts [$PdCl_2$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$] for Heck-coupling while keeping other parameters the same such as, nBu_4NCl, Na_2CO_3, DMF at 100 ^oC for overnight. $Pd(OAc)_2$ turned out to be more efficient than other catalysts to give quinoline in 64 % yield. Further optimization, including the amount of catalyst, presence and absence of additives [nBu_4NCl, nBu_4NBr, nBu_4NI], bases [$NaHCO_3$, Na_2CO_3, DBU, Et_3N] and solvents [DMSO, DMF, DMA, MeCN, THF], allowed us to find the optimum reaction conditions to be $Pd(OAc)_2$ (5 mol%), nBu_4NI (1 equiv.), $NaHCO_3$ (1.2 equiv.) in DMF solvent at 90 ^oC to give exclusively quinoline in 82 % isolated yield.

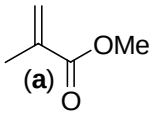
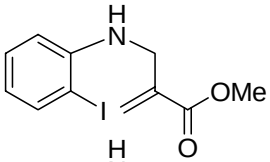
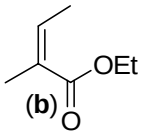
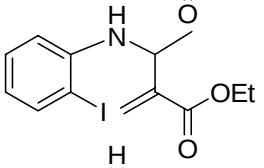
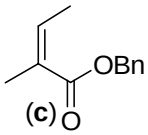
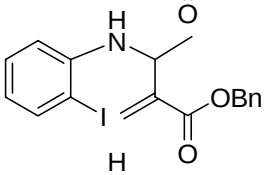
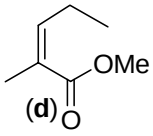
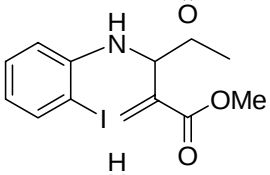
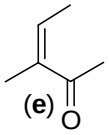
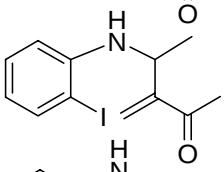
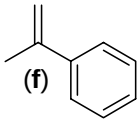
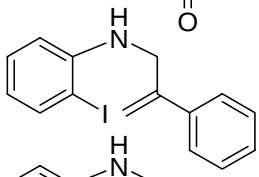
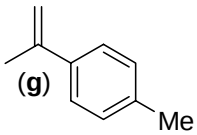
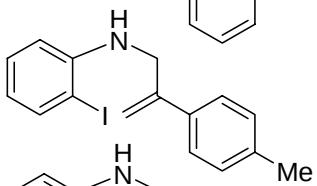
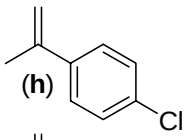
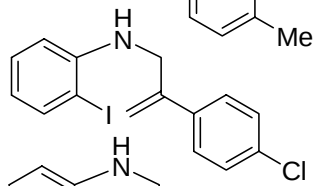
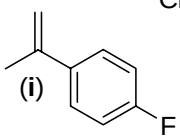
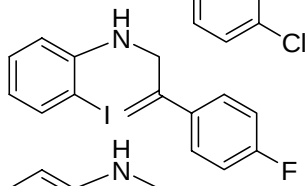
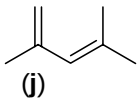
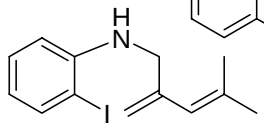
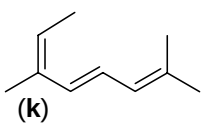
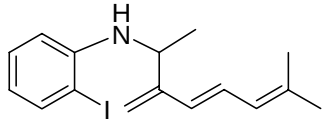


Scheme 2. Pd-catalyzed intramolecular Heck-coupling and concomitant aerobic dehydrogenation

With the optimized reaction conditions in hand, we have synthesized several ortho-haloaryl ABH adducts and allyl amines (Tables 1 and 2) that could be employed for Heck-coupling reaction to access highly substituted quinolines. We have previously reported **1b** and **2b,** but all other ABH adducts as well as allyl amines are new and characterized the same by GC, NMR and IR analysis. ABH adducts **1a-1e** were produced in high yields by treating 2-iodophenyl hydroxylamine with methyl methacrylate (**a**), tiglate esters (**b-d**) and 3-methyl-3-penten-2-one (**e**). When α-methyl styrene was treated with 2-iodophenyl hydroxylamine at 40 ^oC, the corresponding allyl amine was obtained only in 52 % yield. However the yield was improved up to 66 % by raising the temperature to 70 ^oC. At this temperature, various other α-methyl styrenes were treated with 2-iodophenyl hydroxylamine which afforded allyl amines **1f-1i** in very good yields. We have also synthesized 2-haloaryl allyl amines of diene and triene (**1j-1k**) following our recent report.[9f]

Table 1. Fe-catalyzed synthesis of ABH adducts and allyl amines using 2-iodoaryl hydroxylamines.[a]

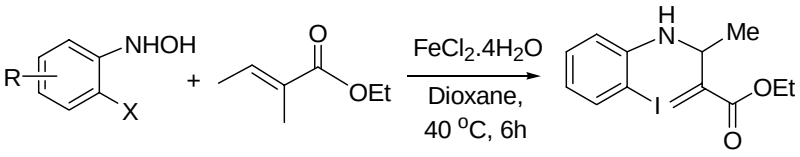


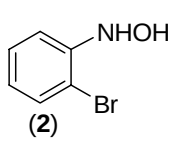
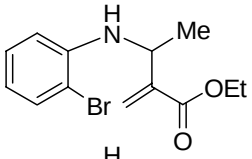
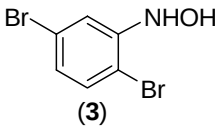
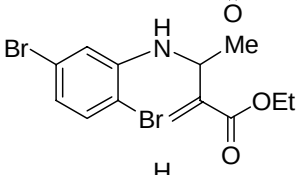
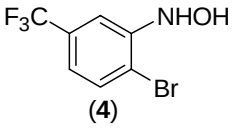
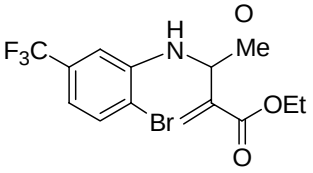
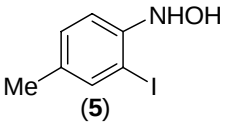
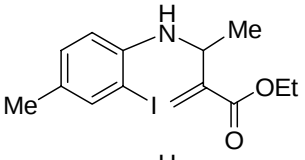
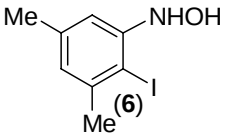
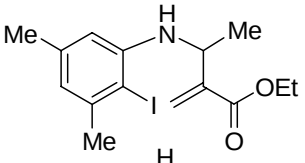
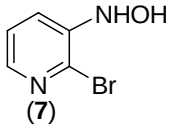
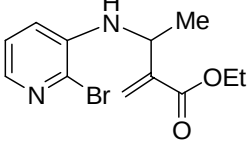
Substrate	ABH adduct / Allyl amine	% Yield[b]
 (a)		**1a,** 86 %
 (b)		**1b,** 84 %
 (c)		**1c,** 79 %
 (d)		**1d,** 85 %
 (e)		**1e,** 73 %
 (f)		**1f,** 66 %[c]
 (g)		**1g,** 62 %[c]
 (h)		**1h,** 68 %[c]
 (i)		**1i,** 74 %[c]
 (j)		**1j,** 69 %[d]
 (k)		**1k,** 75 %[d]

[a] All reactions were performed at 40 °C with 1:3 substrate ratio (ArNHOH: substrate). [b] Isolated yields . [c] Reactions performed at 70 °C. [d] Reactions performed at 60 °C.

We have used substituted aryl hydroxylamines (**2**-**7**) to afford the corresponding ABH adducts **2b**-**7b** in excellent yields (Table 2) which could provide diverse substitutions on quinoline nuclei in later steps. Relatively low yields were obtained with di-substituted hydroxylamine substrates (**3**, **4** and **6**). Iodo-substituted hydroxyl amines (**5** and **6**) worked well in comparison to the bromo-substituted ones (**2**, **3** and **4**). Surprisingly 2-bromo-pyridyl-3-hydroxylmine (**7**) was found to be an excellent aminating agent which produced the corresponding ABH adduct in 93% yield. It should be mentioned here that these substituted ABH adducts have never been reported previously and they might serve as good intermediates for other synthetic applications[12] in the future.

Table 2. Fe-catalyzed synthesis of ABH adducts using substituted 2-haloaryl hydroxylamines[a]

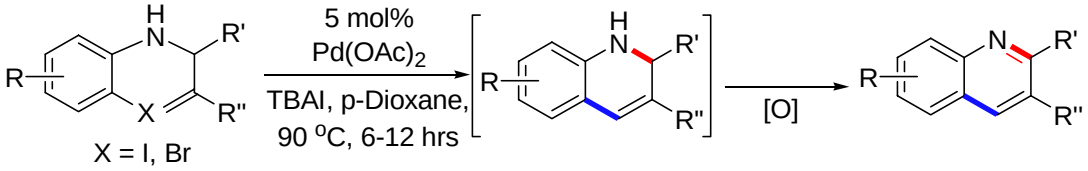


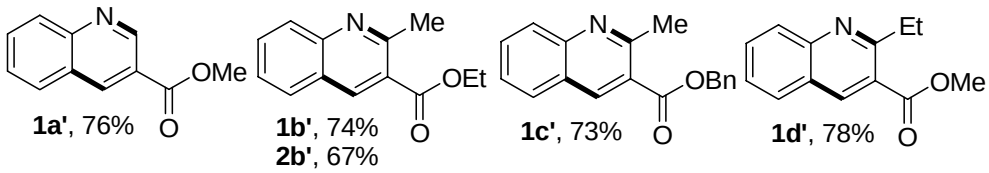
Substrate	ABH adduct	% Yield[b]
 (**2**)		**2b**, 79 %
 (**3**)		**3b**, 73 %
 (**4**)		**4b**, 68 %
 (**5**)		**5b**, 82 %
 (**6**)		**6b**, 76 %
 (**7**)		**7b**, 93 %

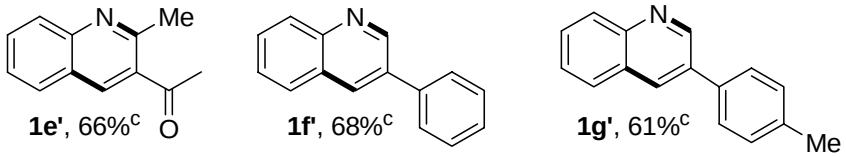
[a] All reactions were performed at 40 °C with 1:3 substrate ratio (ArNHOH: substrate). [b] Isolated yields .

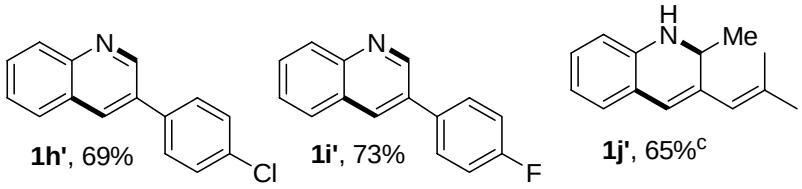
With a diverse set of ABH adducts and allylamines in hand, we started exploring the intra-molecular Heck-coupling using the optimized conditions (*vide supra*). Under the present catalytic conditions, ABH adducts **1b**–**1e** produced the corresponding di-substituted quinolines (**1b'**–**1e'**) in excellent yields (Table 3) via Heck-coupling and concomitant aerobic dehydrogenation (annulation). Functionalized quinolines **1a'-1d'** and **1d'-7b'** are the potential compounds to obtain corresponding quinoline 3-carboxylic acids which are useful for medicinal chemistry applications.[13]

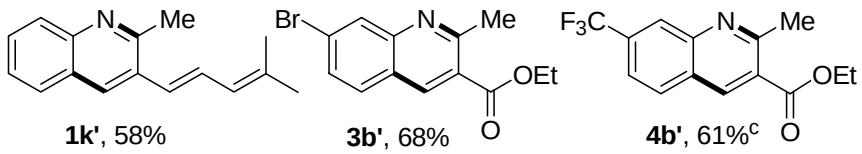
Table 3. Pd-catalyzed synthesis of substituted quinolines via concomitant aerobic oxidation of dihydroquinolines.[a,b]

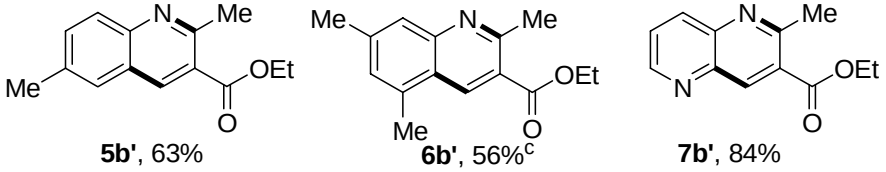












[a] All reactions were performed at 90 °C. [b] Isolated yields . [c] additional 5 mol% $Pd(OAc)_2$ used.

Treatment of allyl amines **1f-1i** under the same conditions led to their corresponding quinolines **1f'-1i'** in good yields, but the formation of small amounts (5-10 %) of indolines[14] (five membered heterocycles) was observed (GC-MS analysis) as well. Lesser amounts of side product were observed in the case of allyl amines **1h** and **1i**, which bear electron withdrawing substituents (p-Cl and p-F) on their α-methyl styrene counter part, compared to the allyl amines **1f** and **1g** (p-H and p-Me). This indicates the contribution of electronic effect in determining the side product formation. It is noteworthy that the same catalytic approach could be extended to allylamines of diene (**1j**) and triene (**1k**) which afforded the corresponding vinyl dihydroquinoline (**1j'**) and di-enyl quinoline (**1k'**) in good yields. The presence of olefinic groups on quinoline rings **1j'** and **1k'** facilitates further functionalization if desired. We have also confirmed that iodo-substituent (**1b**) works well compared to bromo substituted allyl amine (**2b**) which is consistent with previous observation by Hegedus et al.[14]

Later we moved on to other ABH adducts (**3b**-**7b**) in order to access multi-substituted quinolines (**3b'**-**7b'**). Under the palladium-catalyzed conditions, treatment of dibromo allyl amine (**3b**) afforded the quinoline product (**3b'**) exclusively where C-2 bromo substituent involved in coupling while leaving the C-5 bromo-substituent unaffected. Interestingly, the 7-bromo quinoline product (**3b'**) can undergo further coupling reactions for the elaboration of complex compounds.[7e,15] This coupling reaction is also extended to methyl and trifluoromethyl substituted ABH adducts to access the substituted quinolines **4b'**, **5b'** and **6b'**. It should be noted here that trifluoromethyl is an important moiety for optimizing the properties of pharmaceutical lead compounds, often improving bioavailability, bioactivity, and metabolic stability.[16] Heterocyclic ABH adduct **7b** afforded an interesting bis-heterocyclic product i.e. substituted 1,5-napthyridine (**7b'**). 1,5-napthyridines are used as a TGF (transforming growth factor) inhibitors for the treatment of cancer and fibrotic diseases.[17] All the allylic amination and Heck-coupling reactions are reasonably versatile and provided a wide variety of quinolines. An interesting feature of this approach is that the Pd catalyst plays a dual role in catalyzing both Heck-coupling as well as aerobic oxidation of the dihydroquinoline ring.

Conclusion

In summary, we have devised a new catalytic route to the diverse set of substituted quinolines starting from 2-haloaryl hydroxylamines and olefins. This two-step approach involves allylic C-H amination and intramolecular Heck coupling, where the former step involves C-N bond formation and the latter involves C-C bond formation. A wide variety of

new ABH adducts and allyl amines were synthesized and efficiently assembled into the valuable quinoline heterocycles in good to excellent yields. This procedure is operationally simple and there is no requirement of pre-functionalized olefins for the allylic amination step.

Experimental Procedures

General Procedure for the Preparation of Aza Baylis-Hillman Adducts and Allyl Amines: To the solution of $FeCl_2.4H_2O$ (10 mg, 0.05 mmol), Olefin (1.50 mmol) in dioxane (5 mL), was added the phenylhydroxylamine (0.5 mmol) solution slowly in dioxane (5 mL) via syringe pump over 4 hours at 40 ^oC (70 ^oC for styrenes). Reactions were allowed to continue for two more hours to get complete consumption of phenylhydroxylamine. After that the mixture was filtered through celite and the filtrate was concentrated to dryness. The crude product was purified over a short column of silica gel (hexane/ethylacetate eluents) to give the corresponding ABH adduct/Allylamine which was then directly analyzed by GC-MS, NMR and IR analysis.

General Procedure for the Intramolecular Heck-coupling of Aza Baylis-Hillman Adducts and Allyl Amines: ABH adduct/Allylamine (0.25 mmol), tetrabutyl ammoniumiodide (TBAI) (0.25 mmol) and $Pd(OAc)_2$ (0.025 mmol) were combined in a round-bottom flask. DMF (4 mL) was added to the same flask and kept for heating on a sand bath at 90 ^oC for 6-12 hours while stirring. Once the reaction is completed (monitored by TLC and GC-MS), the mixture was filtered through celite and the filtrate was concentrated to dryness. The crude product was purified over a short column of silica gel (hexane/ethylacetate eluents) to isolate substituted quinolines which were then directly analyzed by GC-MS, NMR and IR analysis.

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