Organic & Supramolecular Chemistry

Facile Synthesis of Dihydroquinolines via Palladium Catalyzed Sequential Amination and Cyclisation of Morita-Baylis-Hillman Alcohols

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Quinolines and its derivatives are significant class of heterocyclic compounds which are identified as the key component in many natural products and biologically important molecules. We describe herein a facile method for the synthesis of quinoline derivatives from Morita-Baylis-Hillman (MBH) Alcohols *via* Palladium Catalyzed intramolecular aryl amination followed by allylic amination pathway. The reaction between a series of MBH alcohols and amino compounds (Tosyl, aliphatic and aromatic amines) under optimized reaction conditions with Pd $(PPh_3)_2Cl_2$/DPPP catalyst system, afforded the corresponding 1,2-dihydroquinolines upto 95% isolated yield.

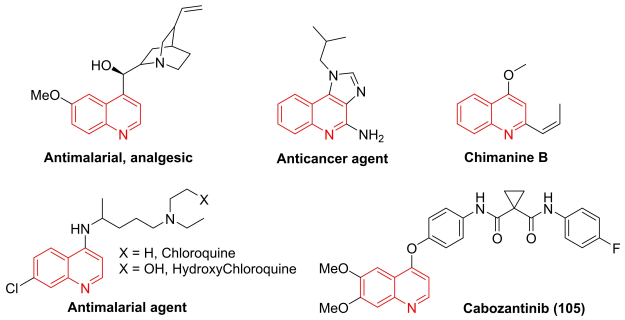

Figure 1. Biologically significant compounds containing Quinoline Skeleton.

Quinolines (also known as 1-azanaphthalene, 1-benzazine or benzo[b]pyridine) are very important class of nitrogen containing heterocyclic compounds having significant role in diverse fields such as natural product synthesis, medicinal chemistry, material science etc.[1] Quinoline derivatives are usually being used for antiseptics, antiviral, antitumor, hypnotics, anticonvulsants, antineoplastics, antihistaminics, anti-inflammatory and antibacterial applications (Figure 1).[2] It is noteworthy that, recently hydroxychloroquines (HCQ), a quinoline based antimalarial drug has been the center of attention during the context of Covid-19 pandemic.[3] Moreover, the fully or partially hydrogenated derivatives of quinolines (*eg.* Dihydroquinolines) are very important as they form key structural units in large number of natural products and bioactive molecules.[4] Consequently, large number of methods have been developed for the synthesis of these classes of compounds.

The classical reactions including Knorr,[5] Friedlander,[6] Combes, [7] Skraup,[8] Niementowski,[9] Pfitzinger[10] and Deobner-von Miller[11] reactions have been frequently used for the preparation of Quinoline backbone. In spite of these methods, various transition metal (Fe,[12] Cu,[13] Rh,[14] Pd[15] and Au[16] etc) mediated annulations approaches are also been utilized towards the synthesis of this particular class of heterocyclic compounds. Among these, base catalyzed and/or transition metal catalyzed cyclizations of easily accessible Morita-Baylis-Hillman (MBH) adducts/acetates have received special attention in recent years. In this regard, a number of works have been carried out by exploring the amination/intramolecular cyclization of MBH adducts as an efficient synthetic strategy for dihydroquinoline synthesis (Figure 2).[17] For example, N. J. Kim and coworkers reported the synthesis of quinoline derivatives from Morita-Baylis-Hillman acetates on reaction with amines[18] and N-tosylimines[19] *via* nucleophilic substitution reaction. Same group have also utilized the N-tosylamide derivatives of MBH acetates for dihydroquinoline synthesis *via* I_2/PhI$(OAc)_2$ catalyzed oxidative cyclization of corresponding amidyl radicals.[20] Napoleon and Manheri described an interesting synthetic route to N-substituted 1, 2-dihydroquinolines by adopting a tandem S_N2-S_NAr cyclization of MBH acetates in presence of alkyl or aryl amines.[21] Moreover, Palladium catalyzed synthesis of dihydroquinolines from MBH acetates by following substitution/CN coupling reaction,[22] Heck type reaction[23] and domino Heck reaction-cyclization pathways[24–26] are also described.

Despite of these studies, Palladium catalyzed synthesis of 1, 2 dihydroquinoline directly from MBH alcohols are rarely explored. In this regard, G. Poli and coworkers have documented a palladium catalyzed domino synthesis of dihydroquinoline derivatives by the reaction between MBH alcohols and

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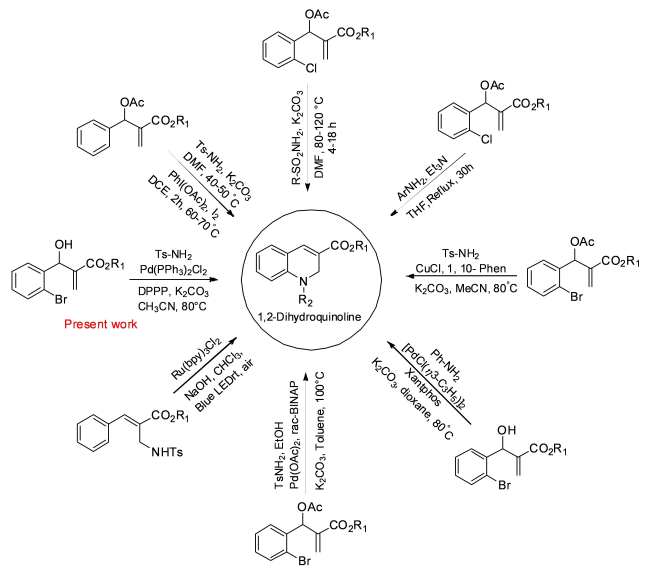
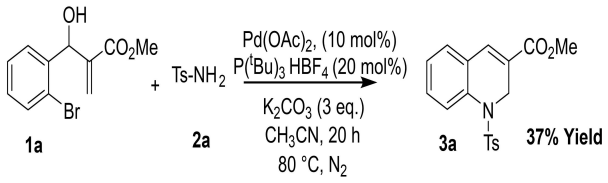


Figure 2. Dihydroquinoline synthesis from MBH adducts.

amines.[27] However this approach demands the use of expensive palladium catalyst $[PdCl(\eta^3-C_3H_5)]_2$ and specific ligand (Xantphos). Therefore, due to the larger significance and wide spread applications of these class of compounds, there remains a continued demand for developing more efficient and milder strategies for synthesizing Quinoline derivatives from easily available starting materials. In this context, as part of our continuing interest on the transition metal mediated synthesis of carbo/heterocyclic compounds,[28] we here in describe an efficient synthetic pathway to 1,2-dihydroquinolines *via* palladium catalyzed sequential arylic/allylic amination of Morita-Baylis-Hillman Alcohols.



Scheme 1. Palladium catalyzed dihydroquinoline synthesis from MBH alcohol.

Baylis-Hillman adducts used in this study are synthesized by following the literature procedure[29] and characterized using spectroscopic analysis. Our present studies commenced with the palladium catalyzed reaction of *o*-bromo substituted Baylis-Hillman alcohols **1a** with Tosyl amine **2a**. The initial trial with $Pd(OAc)/P(^tBu)_3HBF_4$ catalytic system in presence of K_2CO_3 base under nitrogen atmosphere in acetonitrile solvent at 80 °C resulted in the formation of 1,2-dihydroquinoline **3a** in 37% yield (Scheme 1).

The structure of the product **3a** was confirmed based on ^{1}HNMR, ^{13}CNMR, FTIR and HRMS analyses and also in comparison with the literature data. After that, detailed optimization studies were performed to explore the best suitable condition for this reaction. As part of the initial optimizations, the effect of different palladium sources has been screened out. The reaction with $PdCl_2$ catalyst gave only 26% product yield (Table 1, entry 2); while Pd/C failed to deliver the reaction (Table 1, entry 3). However, when reaction performed using $Pd(PPh_3)_2Cl_2$, the product **3a** was isolated in 62% yield (Table 1, entry 4). Among the various ligands tested with $Pd(PPh_3)_2Cl_2$ catalyst, better result was obtained with the bidentate ligand, DPPP [1, 3-Bis(dipenylphosphino) propane] to give the product in 73% isolated yield (Table 1, entry 10). Other ligands were less effective than DPPP (Table 1, entry 5–9) and therefore further optimization studies were performed using DPPP as ligand with $Pd(PPh_3)_2Cl_2$ catalyst. Even though, the exact role of PPh_3 and/or DPPP in promoting the reaction is not clear, the increased efficiency of bidentate ligands in similar reactions are observed in literature.[27] Therefore, DPPP might be favorably assisting the *insitu* formation of the active Pd(0) species from $Pd(PPh_3)_2Cl_2$ during the reaction.[30]

Next, we have investigated the effect of other parameters including base, solvents, additive, temperature, time etc for promoting this reaction. These studies revealed that, bases such as $^tBuCO_2K$, $^tBuCO_2Na$, Na_2CO_3, Cs_2CO_3 are less effective than K_2CO_3 (Table 2, entry 3–6) and only K_3PO_4 gave comparable result (Table 2, entry 2). Similarly, among the various solvents tried, acetonitrile provided higher product yield than

Table 1. Screening of Catalyst and Ligand.[a]

Entry	Catalyst	Ligand	Yield(%)[b]
1	$Pd(OAc)_2$	$P^t(Bu)_3HBF_4$	37
2	$PdCl_2$	$P^t(Bu)_3HBF_4$	26
3	Pd/C	$P^t(Bu)_3HBF_4$	nd
4	$Pd(PPh_3)_2Cl_2$	$P^t(Bu)_3HBF_4$	62
5	$Pd(PPh_3)_2Cl_2$	$P^t(Bu)_3$	33
6	$Pd(PPh_3)_2Cl_2$	$P(Bu)_3$	25
7	$Pd(PPh_3)_2Cl_2$	$P(Ph)_3$	trace
8	$Pd(PPh_3)_2Cl_2$	$P(o\text{-}Tol)_3$	24
9	$Pd(PPh_3)_2Cl_2$	$P(Cy)_3$	13
10	$Pd(PPh_3)_2Cl_2$	DPPP	73
11	$Pd(PPh_3)_2Cl_2$	DPPE	56

[a] Reaction conditions: **1a** (1 eq.), **2a** (1.2 eq.), Catalyst (10 mol%), ligand (20 mol%), K_2CO_3 (3 eq.), CH_3CN (2 ml), N_2 atm., 80 °C, 20 h.
[b] Isolated Yield.

Table 2. Screening of Base and Solvent.[a]

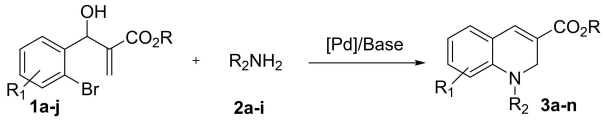
Entry	Solvent	Base	Yield(%)[b]
1	CH_3CN	K_2CO_3	73
2	CH_3CN	K_3PO_4	71
3	CH_3CN	$^tBuCO_2K$	27
4	CH_3CN	$^tBuCO_2Na$	21
5	CH_3CN	Na_2CO_3	35
6	CH_3CN	Cs_2CO_3	11
7	1,4 Dioxane	K_2CO_3	59
8	DMF	K_2CO_3	13
9	DMSO	K_2CO_3	trace
10	Toluene	K_2CO_3	nd
11	Ethanol	K_2CO_3	nd
12	CH_3CN	K_2CO_3	90[c]
13[c]	CH_3CN	K_2CO_3	Nd[d]/trace[e]
14[c]	CH_3CN	K_2CO_3	49[f]/67[g]
15[c]	CH_3CN	K_2CO_3	73[h]/80[i]

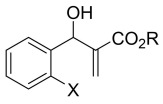
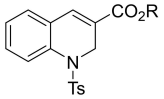
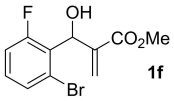
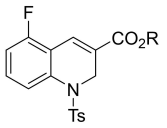
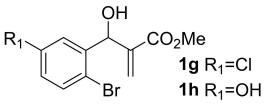
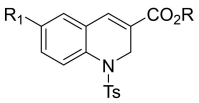
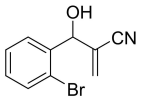
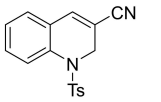
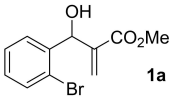
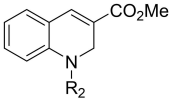
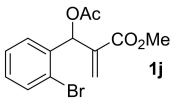
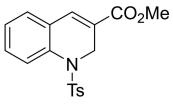
[a] Reaction conditions: **1a** (1 eq.) **2a** (1.2 eq.), $Pd(PPh_3)_2Cl_2$ (10 mol%), DPPP (20 mol%), Base (3 eq.), Solvent (2 ml), N_2 atm., 80 °C, 20 h.
[b] Isolated Yield.
[c] Reaction in presence of Bezoquinone(1 eq.).
[d] Reaction without catalyst or base.
[e] Reaction without ligand or N_2 atm.
[f] Reaction with $Pd(PPh_3)_2Cl_2$ (5 mol%), DPPP (10 mol%).
[g] Reaction with $Pd(PPh_3)_2Cl_2$(10 mol%), DPPP (10 mol%).
[h] Reaction with $Pd(PPh_3)_2Cl_2$ (5 mol%), 100 °C, 20 h.
[i] Reaction with $Pd(PPh_3)_2Cl_2$(5 mol%), 80 °C, 36 h.

other solvents such as 1, 4 Dioxane, DMF, DMSO (Table 2, entry 7–9). No product formation was observed in the case of Toluene and Ethanol (Table 2, entry 10–11). Based on these screening studies, K_2CO_3 and Acetonitrile were selected as base and solvent, respectively for further reactions. After optimizing these parameters, the effect of incorporation of an additive into the reaction was considered. Interestingly, when the reaction was repeated in presence of Benzoquinone (BQ); the product yield was increased to 90% (Table 2, entry 12). It is of note that, the influence of BQ in Palladium catalyzed reactions for accelerating the alkene coordination, by serving as π-acid ligands and by decreasing the electron density at the palladium center has been proposed earlier.[31] The control experiments in the absence of any one of the parameters such as catalyst, ligand, base or nitrogen atmosphere evidenced the indispensible role of these components for the formation of **3a** (Table 2, entry 13). In the final phase of optimization studies, we have evaluated the effect of changing the catalyst/ligand stoichiometry and increasing the reaction temperature/time under lower catalyst loadings. Attempts to lower the amounts of catalyst and/or ligand loadings resulted in lower yields of product formation (Table 2, entry 14). When reaction was repeated at higher temperature (100 °C) or for longer reaction time (36 hr) with 5 mol% of the catalyst, resulted the formation of **3a** in 73% and 80% yields, respectively (Table 2, entry 15). Therefore, the optimized reaction condition was identified as $Pd(PPh_3)_2Cl_2$ (10 mol%), DPPP (20 mol%) and K_2CO_3 (3 eq.) in CH_3CN (2 ml) solvent under N_2 atmosphere at 80 °C, for 20 h.

After establishing the optimized reaction conditions, the generality and scope of the transformation using a variety of substituted Morita-Baylis-Hillman alcohols and amines were disclosed. This reaction seems to be general over a wide range of substrates and among which *o*-bromo substituted MBH alcohols converted into the corresponding Quinoline derivatives in good yields. Similarly, *o*-Iodo (**1b)** substituted MBH alcohols reacted well to afford **3a** in 95% yield; while corresponding chloro analogue (**1c)** gave only 17% yield. (Table 3, entry 2 and 3). Various substrates having electron donating or withdrawing groups including methyl, methoxy, chloro, fluro and nitro substituents could tolerate under the reaction conditions. MBH adduct with ethylester (**1d)** also showed good reactivity to form the product **3b** in good yield (Table 3, entry 4). Interestingly, no product formation was detected with the reaction of non *ortho*-substituted BH alcohol (**1e)** (Table 3, entry 5). For dihalo substituted substrates **1f**–**g**, the corresponding dihydroquinoline **3c**–**d** was obtained in moderate to good yields (Table 3, entry 6–7). However, the reaction of hydroxyl substituted adduct (**1h)** resulted only in trace amount of product formation (Table 3, entry 8) and acrylonitrile derived adduct (**1i)** failed to deliver the reaction (Table 3, entry 9). In the next set of experiments, we have explored the reaction of **1a** with a number of substituted amines/sulphonamides (**2b**–**2i**). Reaction of **1a** with *p*-chloro substituted tosylamine (**2b)** offered **3g** in 85% yield (Table 3, entry 10). Amination/cyclization of **1a** with aryl amines (**2c**–**f)** also worked well forming the corresponding products **3h**–**l** in moderate to good yields (Table 3, entry 11–15). However, the reactions using aliphatic amines **2h** and **2i** gave poor results (Table 3, entry 16–17). Finally, for better understanding of the reaction pathway, Baylis-Hillman Acetate (**1j**) was subjected to reaction under the optimized conditions and as expected this substrate was found to be more reactive than corresponding alcohols (Table 3, entry 18). A plausible mechanism for the formation of 1, 2-dihydroquinoline from Baylis-Hillman alcohols

Table 3. Generality of the Reaction.[a]



Entry	MBH adduct	Amine	Product		Yield(%)[b]
1	 **1a** X=Br, R=Me	**2a** R_2 =Ts		**3a**	90
2	**1b** X=I, R=Me			**3a**	95
3	**1c** X=Cl, R=Me			**3a**	17
4	**1d** X=Br, R=Et			**3b**	75
5	**1e** X=H, R=Me			**3a**	nd
6	 **1f**	**2a**		**3c**	73
7	 **1g** R_1=Cl	**2a**		**3d**	54
8	**1h** R_1=OH	**2a**		**3e**	Trace
9	 **1i**	**2a**		**3f**	nd
10		**2b** R_2= 4Cl-Ts		**3g**	85
11		**2c** R_2= Ph		**3h**	65
12	 **1a**	**2d** R_2= 4Me-Ph		**3i**	43
13		**2e** R_2= 4OMe-Ph		**3j**	35
14		**2f** R_2= 4NO_2-Ph		**3k**	38
15		**2g** R_2= Benzylamine		**3l**	35
16		**2h** R_2= Cyclohexylamine		**3m**	Trace
17		**2i** R_2= Isopropylamine		**3n**	Trace
18	 **1j**	**2a**		**3a**	95

[a]Reaction conditions: **1a–j** (1 eq.) **2a–i** (1.2 eq.), $Pd(PPh_3)_2Cl_2$(10 mol%), DPPP (20 mol%), BQ (1 eq.), K_2CO_3 (3 eq.), CH_3CN (2 ml), 80 °C, 20 h, N_2 atmosphere, [b]Isolated Yield.

under palladium catalysis is available in the literature[27,32] which is explained as two sequential catalytic cycles involving Buchwald type intermolecular aryl amination followed by intramolecular allylic amination.

In conclusion, we have described a facile method for efficient synthesis of 1,2-dihydroquinolines by the direct use of Morita-Baylis-Hillman alcohols by adopting a palladium catalyzed Buchwald type intermolecular C–N coupling followed by an intramolecular allylic amination reaction. The reaction of a series of MBH alcohols with amino compounds including tosyl amine derivative, aliphatic and aromatic amines in presence of $Pd(PPh_3)_2Cl_2$ (10 mol%), DPPP (20 mol%) and K_2CO_3 (3 eq.) in CH_3CN (2 ml) solvent under N_2 atmosphere at 80 °C, for 20 h resulted in the formation of corresponding dihydroquinolines up to 95% isolated yields. This methodology is highly efficient in terms of simple reaction protocol, easily available starting materials, broad substrate scope and good reaction yields. The efforts to utilize the synthesized products towards the design of various molecular skeletons with biological and pharmaceutical significance are in progress and will be reported in due course.

Supporting Information Summary

Experimental procedures for the synthesis of (**1a–j** and **3a–n**), spectroscopic data for (**1a–j** and **3a–l**) along with ^{1}H and ^{13}CNMR spectra of (**1a–j** and **3a–l**) are presented in this part.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Allylicamination · Cyclization · Morita-Baylis-Hillman · Palladium · Quinoline

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