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Metal-Free Synthesis of Alkenylazaarenes and 2-Aminoquinolines through Base-Mediated Aerobic Oxidative Dehydrogenation of Benzyl Alcohols

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A metal-free, base-mediated, and atom-efficient oxidative dehydrogenative coupling of substituted phenylmethanols (benzyl alcohols) with methyl azaarenes or phenylacetonitriles to afford substituted alkenylazaarenes or 2-aminoquinolines, respectively is described. $CsOH.H_2O$ was discovered to be the base of choice for obtaining optimal yields of the title compounds, although the reaction could proceed with KOH as well. The protocol that works efficiently in the presence of air is amenable over broad range of substrates.

Introduction

The oxidative dehydrogenative coupling of alcohols has emerged as an attractive option for the synthesis of a variety of functionalized organic molecules and synthesis of variety of *N*-heterocycles.[1] Extrusion of hydrogen and water as the by-product, atom economy and sustainability due to ready availability of alcohols from several industrial processes or renewable resources are the key attributes, which have contributed to the growth of such transformations. From initial focus on the use of precious and toxic noble-metal-based catalysts,[2] currently more acceptable earth-abundant Mn, Fe, Co, Ni or Cu-based catalysts are effective options for executing such coupling reactions.[3] During our program to discover compounds to treat Visceral Leishmaniasis,[4] we became interested in performing α-olefination of 2-methylquinolines as analogous compounds were reported to display antileishmanial activity (Figure 1).[5] Given the significance of aryl-substituted olefins, bearing *N*-heteroarene unit in various natural products, drug molecules and materials,[6] engineering new strategies for its synthesis has been a topic of continued research.[7] In particular, there has been a spurt of papers related to dehydrogenative coupling of alcohols for realizing α-olefinations of *N*-heteroarenes under a variety of metal-based and metal-free conditions during the last few years. Appraisal of these protocols revealed that most of the metal-mediated reactions were performed under strongly basic conditions

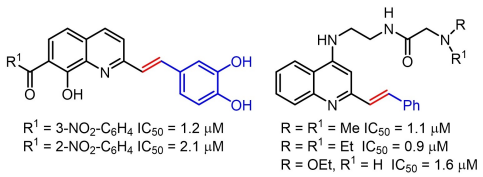

Figure 1. 2-Styrylquinolines as antileishmanial agents against *L. donovani*.[5a]

(Figure 2). For example, Kempe et al.[8] used 40% KOH whereas Maji et al.[9] used 1.0 equiv. of KO^{t}Bu together with Mn complexes for carrying out the α-olefinations of *N*-heteroarenes with alcohols. Likewise, coupling reactions with Ni, Co and Fe-based catalysts were also carried out in the presence of KO^{t}Bu (1.0 equiv).[10] Instead, the metal-free dehydrogenative couplings for α-olefinations of azaarenes invariably used the oxidant with catalytic amount of base.[11] Strategically in such reactions the alcohol is oxidized to aldehyde or ketone, which is the reactive intermediate that condenses with the acidic methyl of azaarenes. Earlier, Wolfson et al. reported high catalytic activity and full selectivity of alkali metal hydroxides for aerobic oxidation of phenylmethanols in a nonpolar medium (Figure 3).[12] Even the synthesis of aldimine via reaction between

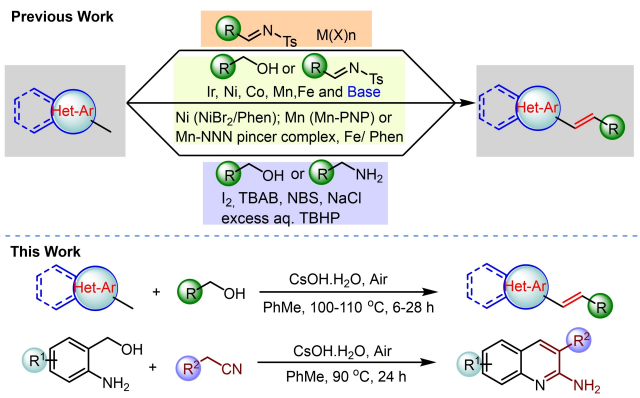

Figure 2. Different routes to the synthesis of alkenyl azaarene.[7–10]

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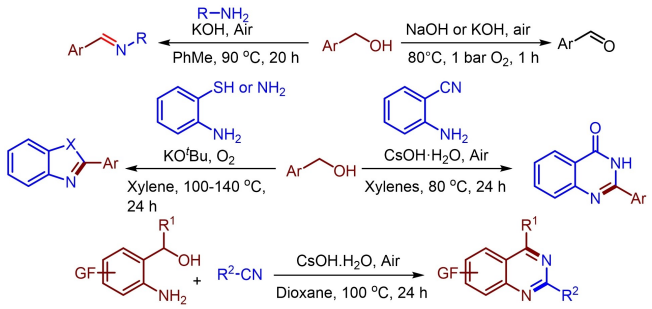


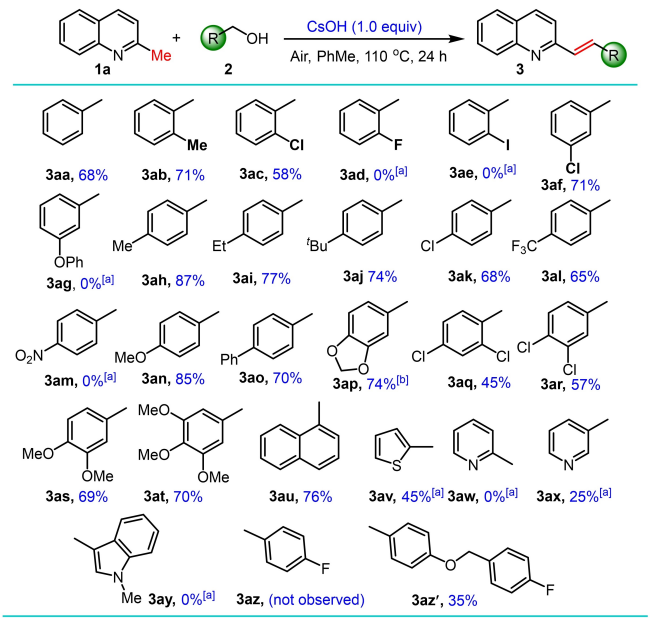
Figure 3. Reactions encompassing aerobic oxidative dehydrogenation reactions of alcohols in the presence of base exclusively.[11–13]

benzylamine and phenylmethanol in the presence of KOH in toluene under heating in air was reported earlier.[13] Moreover, there are citations, which describe the synthesis of heterocycles via oxidation of phenylmethanols in the presence of base exclusively.[14] However, the literature lacks report on the synthesis of alkenyl azaarenes via dehydrogenative coupling of alcohols with methyl azaarenes using base exclusively. Therefore, we were impelled to investigate α-olefination of 2-methylquinoline via dehydrogenative coupling of phenyl methanol in the presence of a base only with the notion that this would allow a metal-free and sustainable route to 2-alkenyl azaarenes. Herein, we disclose the results of our investigations toward a metal-free base-mediated direct olefination of methyl-substituted azaarenes with aryl methanols. We expanded the scope of the protocol to the synthesis of substituted 2-aminoquinolines via reaction between (2-aminophenyl)methanol and phenylacetonitriles. Notably during the writing of this work, Maji et al. disclosed another Mn-based catalyzed C-alkylation of methyl *N*-heteroarenes with primary alcohols wherein it was claimed that trace product was formed in the presence of KO^{t}Bu exclusively.[15]

Results and Discussion

In a pilot reaction in the Schlenk tube fitted with air balloon, 2-methylquinoline (**1a**) and (4-methylphenyl)methanol (**2h**) were heated at 120 °C in the presence of ^{t}BuOK (1.0 equiv) in xylenes for 24 h. We were pleased to discover that the desired 2-styrylquinoline **3ah** was obtained in 30% yield together with the starting substrate **1a** and *p*-tolualdehyde. Encouraged by the results, we examined different base including ^{t}BuONa, NaOH, KOH and CsOH.H_2O and found CsOH.H_2O to be the superior reagent for this reaction. The reaction in dioxane gave moderate yield of **3ah** but yields were inferior in DMF, DMSO or MeCN. We found that in most cases, the starting material **1a** was recovered and therefore we screened the reaction with enhanced amount of **2h** and found that 1.2 equiv. was suited for optimal yield. In addition, the reaction was discovered to work efficiently when performed in the presence of air together with the use of freshly distilled toluene (refer to Table S1, Supporting Information). Thus, the optimized condition that produced best yield of **3ah** was heating 1.0 equiv. of **1a** with 1.2 equiv. of **2h** in toluene at 110 °C under air.

With the optimized conditions in hand, we tested the scope of the strategy with different 2-methyl quinolines and arylmethanols. In first set of reactions, 2-methyl quinoline **1a** was treated with many arylmethanols (**2a–z**) under the standardized conditions. We discovered that yields of products **3** varied between 45 to 87% for the alcohols to which the methodology was compatible (Scheme 1). It is worth mentioning that for most cases the column chromatographic purification was not required as the removal of solvent and addition of water furnished the pure solid products. It was found that whereas (2-chlorophenyl)methanol **2c** afforded the product **3ac** in 58% yield, (2-flourophenyl) and (2-iodophenyl)methanols (**2d** and **2e**) failed to yield the products **3ad** and **3ae**, respectively and **1a** was recovered unreacted. The (3-chlophenyl)methanol **2f** was attuned to the protocol to offer the 2-styrylquinoline **3af** in 71% yield but the reaction of (3-phenoxyphenyl)methanol **2g** was unsuccessful. Except for the (4-nitrophenyl)methanol **(2m)**, the reactions with all other (4-substitutedphenyl)methanols were successful to afford the products **3ah–3al**, **3an–3ao** in 65–87% yields. The reactions with (di- or tri-substituted phenyl) methanols (**2p–2t**) too furnished the corresponding styryl derivatives **3ap–at** in 45–70% yields. For the alcohol **2p**, optimal yield of the product **3ap** was achieved by performing the reaction for 48 h in the presence of 2.0 equiv. of alcohol. It is highlighted that **3ap** is the starting material for preparing antimalarial natural compound (±)-Galipinine.[16] The reaction of (1-naphthyl)methanol **2u** also smoothly gave the product **3au** in 76% yield. Amongst the heterocyclic methanols investigated during the study, (thiophene-2-yl)methanol **2v** and (pyridine-3-yl)methanol **2x** gave the respective product **3av** and **3ax**, whereas alcohols **2w** and **2y** were found to be unsuited. When



Scheme 1. Scope of the synthesis of 2-Styrylquinolines.[a] **1a** was recovered from the reaction.[b] 2.0 equiv. of **2a** was used.

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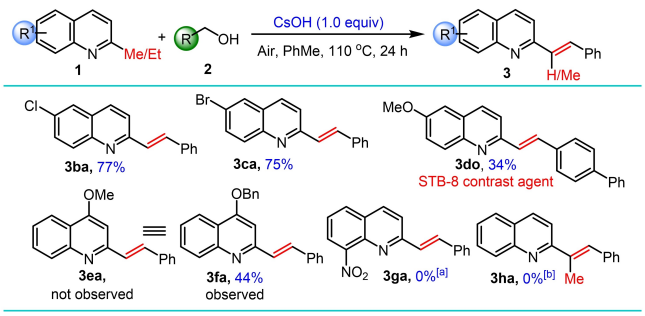
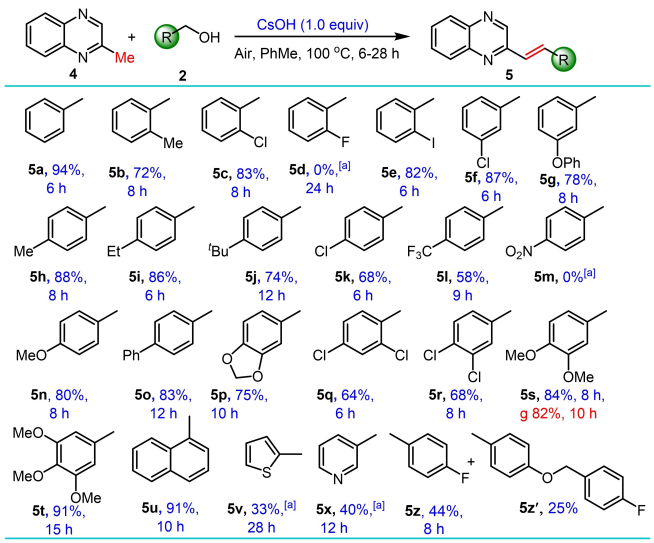
checked independently, we found that the transformation of (2-pyridyl)methanol **2w** to the corresponding pyridine-2-aldehyde under the influence of base was unsuccessful. Moreover, direct reaction of pyridine-2-aldehyde with **1a** in the presence of CsOH.H_2O to obtain **3aw** was unproductive too.

Interestingly, the (4-fluorophenyl)methanol **2z** instead of the expected **3az** afforded **3az′** in 35% yield. Perhaps the fluoro-group of the aldehyde being electrophilic in nature undergoes nucleophilic aromatic substitution by the alcohol in the presence of a base.

In the next set of reactions, we investigated the protocol by reacting differently substituted 2-alkylquinolines with substituted phenylmethanols **2**. The reaction of 6-chloro and 6-bromo-2-methylquinoline (**3b–c**) with **2a** gave the respective 2-styryl quinolones **3ba** and **3ca** in 75–77% yield (Scheme 2). The STB-8 reagent[6h] i.e. a (*E*)-2-(2-([1,1′-biphenyl]-4-yl)vinyl)-6-methoxyquinoline (**3do**) was prepared in 35% yield by reacting 6-methoxy-2-methylquinoline **1d** with [1,1′-biphenyl]-4-ylmethanol (**2o**) under the optimized conditions. Isolation of aldehyde in the reaction accounted for lower yield of **3do**. Conversely,



Scheme 2. Scope of the reaction with different substituted 2-alkylquinolines.[a]complex reaction mixture was observed.[b] **1h** and benzaldehyde were recovered and no coupling product was observed even after prolonged reaction time.

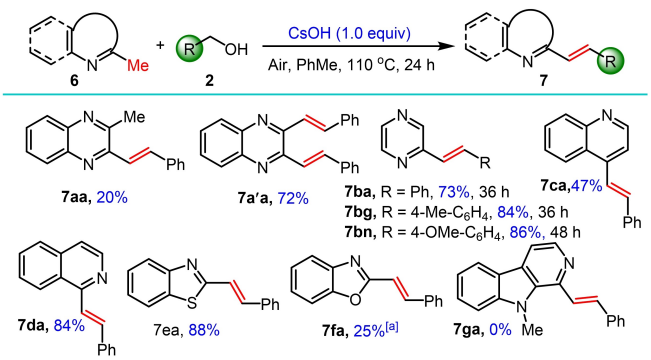


Scheme 3. Scope of the protocol with 1,4-quinoxalines. Yields are based on the substrate **4**.[a]Starting material **4** was recovered.

the reaction of 4-methoxy-2-methylquinoline (**1e**) with **2a** instead of the expected 4-methoxy-2-styrylquinoline (**3ea**) resulted in 4-benzyloxy-2-styrylquinoline (**3fa**) in 44% yield. However, reactions of **2a** with 2-methyl-8-nitro-quinoline (**1g**) or 2-ethylquinoline (**1h**) were unsuccessful to afford **3ga** or **3ha**, respectively.

Towards broadening the scope of the strategy, next we investigated reactions with 2-methylquinoxaline **4**, which is more nucleophilic as compared to /2-methylquinoline. Accordingly, **4** was treated with **2a** under the optimized condition and we were delighted to discover reaction was completed in 6 h to afford the product **5a** in 94% yield (Scheme 3). Subsequently, reactions of **4** with different arylmethanols (**2b–s**) were evaluated and in all cases except for (2-fluorophenyl)methanol **2d** and (4-nitrophenyl)methanol **2m**, the required products (**5b–c**, **5e–l**, **5n–5s**) were obtained in 64–91% yields. Although the time required for the reaction varied between 6–15 h, unlike 2-styrylquinolines, here the chromatographic purification was essential to obtain pure products. We found that (3-phenoxypheny)methanol **2g** which was inert to 2-methylquinoline reacted with **4** to afford the corresponding product **5g**. For assessing the scalability, gram scale reaction **2s** with **4** was performed to isolate the product **5s** without diminution of yield though time consumed for completion of reaction was relatively higher. Notably, reactions of heterocyclic alcohols **2v** and **2x** furnished the respective products **5v** and **5x** in 33% and 40% yields only and the time consumed for reaction of **2v** was 28 h. Unlike 2-methylquinoline, here the reaction of **4** with **2z** gave the styryl product **5z** in 44% yield together with the ether derivative **5z′** in 25% yield.

These results made it apparent that base alone is sufficient to perform the oxidation of the alcohol to aldehyde under aerobic conditions, which in turn reacts with methyl of the azaarenes to afford 2-styrylazaarene. Thus, we considered investigating the scope further with other methyl-azaarene systems. In this context, 2,3-dimethylquinoxaline **6a** was treated with 1.0 equiv. of **2a** in toluene under heating at 110 °C for 24 h. The reaction resulted in the formation of a mixture of products from which we could isolate 2-styrylquinoxaline **7aa** in 20% yield together with 2,3-bisstyrylquinoxaline **7a′a** in trace amount (Scheme 4). Nonetheless, increasing the amount of the



Scheme 4. Scope of the protocol with different 2-methylazarenes.[a]-Unreacted starting material was recovered.

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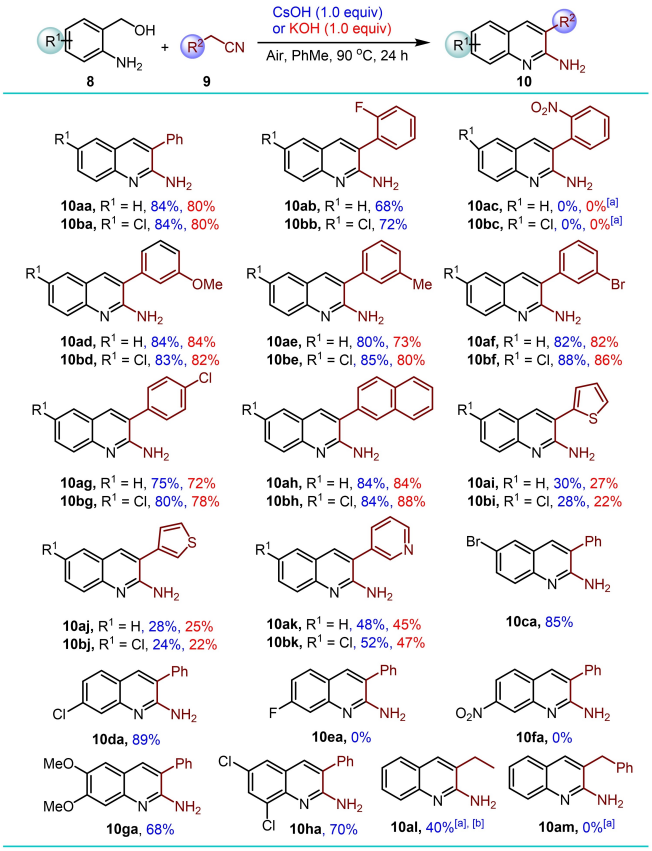
2a to 4.0 equiv. produced **7a′a** in 72% yield. Subjecting 2-methylpyrazine **6b** to reaction with alcohols **2a**, **2h** or **2n** afforded the corresponding 2-styrylpyrazines **7ba**, **7bh** or **7bn** in 73–86% yields. We also investigated the reaction of **2a** with 4-methylquinoline **6c**, 1-methyliosquinoline **6d**, 2-methylbenzothioazole **6e**, and 2-methylbenzoxazole **6f** and it was satisfying to discover that the protocol was amenable for all substrates though yield of **7ca**, **7da**, **7ea** and **7fa** varied. For **6f**, we recovered the unreacted starting material together with benzaldehyde in the reaction mixture.

However, even increasing the amount of alcohol or reaction time the yields of **7fa** did not improve. Conversely, the reaction of **2a** with 1,9-dimethyl-9*H*-β-carboline **6g** under the optimised conditions was unsuccessful to offer product **7ga**.

Successful implementation of the protocol provided the impetus to study the fate of reaction between (2-aminophenyl) methanol and phenylacetonitriles under the optimized condition as it may offer 2-aminoquinolines. Although several strategies for the synthesis of 2-aminoquinolines are known,[17] to the best of our knowledge metal-free synthesis of 2-aminoquinolines from (2-aminophenyl)methanol is not reported. Therefore, (2-aminophenyl)methanol **8a** was treated with phenylacetonitrile **9a** in the presence of $CsOH.H_2O$ in toluene at 110 °C and we were pleased to isolate the desired 2-aminoquinoline **10aa** in 56% yield together with amide **11** (see Table S2, Supporting Information). Assuming that high temperature may induce hydrolysis of phenylacetonitrile by the water released during the process, we considered optimizing the reaction for the base and temperature. Interestingly, we discovered that the reaction was successful in the presence of $CsOH.H_2O$ as well as KOH and unlike for 2-methylquinoline **(1)**, herein only 1.0 equiv. of either base was required (see Supporting Information). In addition, the superior yields of **10aa** was obtained by use of 1.2 equiv. of phenylacetonitrile. Thus the conditions which offered the optimal yield of the 3-phenyl-2-aminoquinoline **10aa** were (2-aminophenyl)methanol (1.0 equiv) and phenylacetonitrile (1.2 equiv) in the presence of $CsOH.H_2O$ (1.0 equiv) or KOH (1.0 equiv) under heating at 90 °C for 24 h.

With the optimized conditions in hand, we investigated the scope with a variety of (2-aminophenyl)methanol (**8a–h**) and arylacetonitriles (**9a–l**) in the presence of $CsOH.H_2O$ and KOH and the results are presented in Scheme 5. In the first set of experiments methanol **8a** and **8b** were treated with several phenyl acetonitriles (**9a–h**) and except for the nitro group bearing phenylacetonitrile **9c**, all substrates offered the desired products **10aa–10ab**, **10ad–10ah**, **10ba–10bb**, **10bd–bh** in 68–88% yields. It was observed that reactions performed in the presence of $CsOH.H_2O$ gave relatively better yields of products than the ones pursued in KOH. Next, we investigated the protocol by reacting heteroarylacetonitriles (**9i–k**) with **8a** and **8b**, which gave the products **10ai**, **10bi**, **10aj**, **10bj**, **10ak**, **10bk** in low yields. Perhaps recovery of the starting material explained the low yields. Subsequently, the scope of the reaction was evaluated with different (substituted-2-aminophenyl)methanols (**8c–h**). We observed that except for the methanols bearing 4-fluoro and 4-nitrophenyl substitution (**8e–f**), all other substrates afforded the products (**10ca–10da**, **10ga–10ha**) in 68–89% yields. The suitability of the method was also studied with aliphatic nitriles such as butyronitrile **9l** and phenylpropionitrile **9m** and it was found that whereas butyronitrile afforded the product **10al** in 40% yield, the reaction with the latter was unsuccessful. Notably, the reaction between **8a** and **9l** was performed with 4.0 equiv. of **9l** to obtain the product.



Scheme 5. Scope of the formation of 2-aminopyridine derivatives in the presence of base only.[a] Starting substrate was recovered,[b] 4.0 equiv. of **9l** was used.

We extended the study to include the use of secondary alcohol in the reaction. Accordingly, when (2-aminophenyl)(phenyl)methanol **12** was subjected to reaction with **9a** in the presence of $CsOH.H_2O$, we isolated acridin-9(10*H*)-one **13** as the major product in 30% yield (Scheme 6). Literature cites the formation of such product oxidative C–H amination of 2-aminobenzophenone in the presence of KO^{t}Bu and DMSO.[18]

However, when the same reaction was performed in the presence of KOH, we isolated the required 2-amino-3,4,–diphenylquinoline **14** in 25% yield together with the 2-aminobenzophenone **15** but with no trace of acridin-9(10*H*)-one.

Finally, to exemplify the utility of the 2-aminoquinoline derivatives, in a representative reaction compound **10aa** was treated with acetophenone in the presence of $Cu(OAc)_2$ and ZnI in dichlorobenzene to produce 2,4-diphenylimidazo[1,2-*a*]

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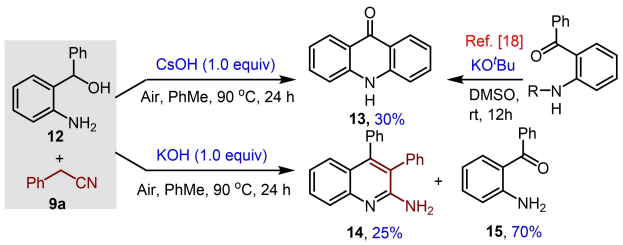

Scheme 6. Reaction with secondary alcohol.

quinolone 16 in 32% yield together with the recovery of starting material (58%) (Scheme 7).[19]

Conclusion

In summary, we have developed a base-mediated facile, practical and atom-efficient method for preparing the alkenyl azaarenes and 2-aminoquinolines utilizing (substitutedaryl) methanols or substituted (2-aminophenyl)methanols, respectively. The protocol scores over the reported methodologies as it does not requires the use of a metal catalyst or ligand and is tenable in the presence of air only. Comparatively, the $CsOH.H_2O$ was found more efficient than KOH, speculatively due to Cesium effect.[20] This method tolerates wide range methyl azaarenes and arylmethanols. The protocol was successfully extended for the synthesis of 2-aminoquinolines from (2-aminophenyl)methanol and phenylacetonitriles via aerobic oxidative cyclocondensation.

Experimental Section

General Information- Unless otherwise stated, all reactions were performed in non-dry glassware under an air atmosphere and were monitored by analytical thin layer chromatography (TLC). TLC was performed on pre-coated silica gel plates. After elution, plate was visualized under UV illumination at 254 nm for UV active materials. Further visualization was achieved either via Iodine or $KMnO_4$ solution. The melting points were recorded on a hot stage apparatus and are uncorrected. IR spectra were recorded using a FTIR spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on 400 or 500 MHz NMR spectrometers with $CDCl_3$ or DMSO-d^6 as solvent, using TMS as an internal standard (chemical shifts in δ). Peak multiplicities of ^1H-NMR signals were designated as s (singlet), brs (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet), m (multiplet) etc. Coupling constants (J) are in Hz. The ESI-MS and HRMS were recorded on triple quadrupole Mass spectrometer and orbitrap velos pro mass spectrometer. Column chromatography was performed using silica gel (100–200 mesh) or neutral alumina. Analytical grade solvents for the column chromatography were used as received.

General procedure for the synthesis of alkenylazaarenes (**3 aa**–**3 az** and **3 ba**, **3 ca**, **3 do**, **3 fa**, **7 aa**–**7 fa**) as exemplified for **3 ah**.

Method A. To a two way 50 mL round-bottom flask equipped with a stirring bar and condenser (attached with an air balloon on the top) was added 2-methylquinoline **1 a** (0.20 g, 1.40 mmol), (4-tolyl) methanol **2 h** (0.20 g, 1.68 mmol), and $CsOH.H_2O$ (0.21 g, 1.39 mmol) in toluene (3 mL) and the mixture was heated at 110 °C under stirring. The reaction was continued for 24 h and on completion (as monitored by TLC), the solvent was removed completely under the reduced pressure. The residue thus obtained was triturated with H_2O (10 mL) to furnish **3 ah** as a yellow solid product that was filtered and dried in vacuum.

Method B. For the products where solid was not obtained, the residue was extracted with H_2O (25 mL) and EtOAc (3×20 mL). The combined organic layers was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to furnish the crude product. Purification by silica gel column chromatography using hexanes/ EtOAc (9 : 1, v/v) as the eluent, to yield the product.

General procedure for the synthesis of 2-Styrylquinoxalines (**5 a**–**5 z**) as exemplified by the synthesis of **5 a**.

To a round-bottom flask fitted with condenser (having an air balloon) was added 2-methyl quinoxaline **4** (0.20 g, 1.39 mmol), phenyl methanol **2 a** (0.18 g, 1.66 mmol), and $CsOH.H_2O$ (0.21 g, 1.39 mmol) in toluene (3 mL) was heated at 100 °C. The reaction progress was monitored by TLC. After completion, the solvent was removed under vacuum and the residue was directly adsorbed on silica. Purification by column chromatography on silica gel using hexanes/ EtOAc (9 : 1, v/v) as eluent afforded the product **5 a**.

General procedure for the synthesis of 3-Phenylquinolin-2-amines (**10 aa**–**10 am**, **10 ba**–**10 bk**, **10 ca**–**10 ha**, **14**) as exemplified for **10 aa**.

A round-bottom flask equipped with a stirring bar, condenser (attached with an air balloon on the top) was charged with 2-(aminophenyl)methanol **8 a** (0.20 g, 1.62 mmol), phenylacetonitrile **9 a** (0.23 g, 1.94 mmol), and the base ($CsOH.H_2O$: 0.24 g or KOH: 0.090 g, 1.62 mmol) in toluene (6 mL) and heated at 90 °C for 24 h under vigorous stirring. On completion, the solvent was removed from the reaction mixture and the residue was directly adsorbed on neutral alumina for column chromatography. Purification using hexanes/ EtOAc (7 : 3, v/v) as eluent afforded the product **10 aa** as a white solid.

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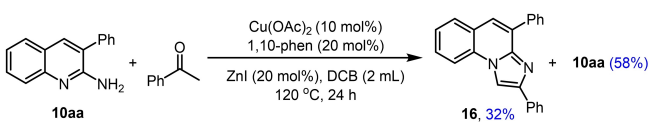
Conflict of Interest

The authors declare no conflict of interest.



Scheme 7. Utility of 2-aminoquinoline.

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Keywords: Alkenyl azaarene · 2-Aminoquinoline · Benzylalcohol · Nitrogen heterocycles · Oxidative dehydrogenation

[1] a) C. Gunanathan, D. Milstein, *Science* **2013**, *341*, 1229712–1229714; b) A. Corma, J. Navas, M. J. Sabater, *Chem. Rev.* **2018**, *118*, 1410–1459; c) T. Irrgang, R. Kempe, *Chem. Rev.* **2019**, *119*, 2524–2549; d) A. Mukherjee, D. Milstein, *ACS Catal.* **2018**, *8*, 11435–11469.

[2] a) D. Benito-Garagorri, K. Kirchner, *Acc. Chem. Res.* **2008**, *41*, 201–213; b) J. Choi, A. H. R. MacArthur, M. Brookhart, A. S. Goldman, *Chem. Rev.* **2011**, *111*, 1761–1779; c) N. Selander, K. J. Szabo, *Chem. Rev.* **2011**, *111*, 2048–2076; d) C. Gunanathan, D. Milstein, *Chem. Rev.* **2014**, *114*, 12024–12087.

[3] a) J. Miao, H. Ge, *Eur. J. Org. Chem.* **2015**, 7859–7868; b) S. Chakraborty, U. K. Das, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2017**, *139*, 11710–11713; c) M. Garbe, K. Junge, M. Beller, *Eur. J. Org. Chem.* **2017**, 4344–4362; d) M. Mastalir, M. Glatz, E. Pittenauer, G. Allmaier, K. Kirchner, *J. Am. Chem. Soc.* **2016**, *138*, 15543–15546; e) N. A. Espinosa-Jalapa, A. Kumar, G. Leitus, Y. Diskin-Posner, D. Milstein, *J. Am. Chem. Soc.* **2017**, *139*, 11722–11725; f) B. Maji, M. K. Barman, *Synthesis* **2017**, *49*, 3377–3393; g) F. Kallmeier, R. Kempe, *Angew. Chem. Int. Ed.* **2018**, *57*, 46–60; *Angew. Chem.* **2018**, *130*, 48–63.

[4] a) S. Mukhopadhyay, D. S. Barak, R. Karthik, S. K Verma, R. S. Bhatta, N. Goyal, S Batra, *RSC Med. Chem.* **2020**, *11*, 1053–1062; b) S. Gangwar, M. S. Baig, P. Shah, S. Biswas, S. Batra, M. I. Siddiqi, N. Goyal, *Chem. Biol. Drug Des.* **2012**, *79*, 149–156.

[5] a) P. M. Loiseau, S. Gupta, A. Verma, S. Srivastava, S. K. Puri, F. Sliman, M. Normand-Bayle, D. Desmaele, *Antimicrob. Agents Chemother.* **2011**, *55*, 1777–1780; b) A. Luczywo, I. P. Sauter, T. C. da S Ferreira, M. Cortez, G. P. Romanelli, G. Sathicq, S. E. Asís, *J. Heterocycl. Chem.* **2021**, doi.org/10.1002/jhet.4217.

[6] Representative examples only a) T. Endo, M. Tsuda, T. Okada, S. Mitsuhashi, H. Shima, K. Kikuchi, Y. Mikami, J. Fromont, J. Kobayashi, *J. Nat. Prod.* **2004**, *67*, 1262–1267; b) S. Blanchard, A. D. William, A. C.-H. Lee, A. Poulsen, E. L. Teo, W. Deng, N. Tu, E. Tan, K. L. Goh, W. C. Ong, C. P. Ng, K. C. Goh, Z. Bonday, E. T. Sun, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2443–2447; c) J. Dai, Z.-Q. Liu, X.-Q. Wang, J. Lin, P.-F. Yao, S.-L. Huang, T.-M. Ou, J.-H. Tan, D. Li, L.-H. Gu, Z.-S. Huang, *J. Med. Chem.* **2015**, *58*, 3875–3891; d) G. Huang, C. M. Solano, J. Melendez, J. Shaw, J. Collins, R. Banks, A. K. Arshadi, R. Boonhok, H. Min, J. Miao, D. Chakrabarti, Y. Yuan, *J. Med. Chem.* **2020**, *63*, 11756–11785; e) Q. Li, J. S. Lee, C. Ha, C. B. Park, G. Yang, W. B. Gan, Y. T. Chang, *Angew. Chem. Int. Ed.* **2004**, *43*, 6331–6335; *Angew. Chem.* **2004**, *116*, 6491–6495; f) S. Wang, Y.-T. Chang, *Chem. Commun.* **2008**, 1173–1175; g) N.-Y. Kang, H.-H. Ha, S.-W. Yun, Y. H. Yu, Y.-T. Chang, *Chem. Soc. Rev.* **2011**, *40*, 3613–3626; h) R. K. Mittal, P. Purohit, *Anti-Cancer Agents Med. Chem.* **2020**, *20* 1981–1991; i) Q. Li, J. Min, Y.-H. Ahn, J. Namm, E. M. Kim, R. Lui, H. Y. Kim, Y. Ji, H. Wu, T. Wisniewski, Y.-T. Chang, *ChemBioChem* **2007**, *8*, 1679–1687; j) J. H. Burroughes, D. D. C. Bradley, A. R. Brown, R. N. Marks, K. Mackay, R. H. Friend, P. L. Burns, A. B. Holmes, *Nature* **1990**, *347*, 539–541.

[7] Some selected citations only, a) B. Qian, P. Xie, Y. Xie, H Huang, *Org. Lett.* **2011**, *13*, 2580–2583; b) J. Liu, Q. Ren, X. Zhang, H. Gong, *Angew.Chem. Int. Ed.* **2016**, *55*, 15544–5548; *Angew. Chem.* **2016**, *128*, 15773–15777; c) J. Xiao, J. Yang, T. Chen, L.-B. Han, *Chem. Commun.* **2016**, *52*, 2157–2160; d) Q.-Q. Li, Z. Shah, J.-P. Qu, Y.-B. Kang, *J. Org. Chem.* **2018**, *83*, 296–302; e) S. Prameela, F.-R. N. Khan, *Eur. J. Org. Chem.* **2020**, 5394–5410; f) W. Li, J. Tang, S. Li, X. Zheng, M. Yuan, B. Xu, W. Jiang, H. Fu, R. Li, H. Chen, *Org. Lett.* **2020**, *22*, 7814–7819; g) L. Wang, Z. Yu, **2020**, CN 111253305; *Chem. Abstr.* 173: 370956.

[8] G. Zhang, T. Irrgang, T. Dietel, F. Kallmeier, R. Kempe, *Angew. Chem. Int. Ed.* **2018**, *57*, 9131–9135; *Angew. Chem.* **2018**, *130*, 9269–9273.

[9] M. K. Barman, S. Waiba, B. Maji, *Angew. Chem. Int. Ed.* **2018**, *57*, 9126–9130; *Angew. Chem.* **2018**, *130*, 9264–9268.

[10] a) J. Rana, R. Babu, M. Subaramanian, E. Balarama, *Org. Chem. Front.* **2018**, *5*, 3250–3255; b) B. M. Ramalingam, I. Ramakrishna, M. Baidya, *J. Org. Chem.* **2019**, *84*, 9819–982; c) J. Das, M. Vellakkaran, Sk. Motahar, D. Banerjee, *Org. Lett.* **2019**, *21*, 7514–7581.

[11] S. Hazra, V. Tiwari, A. Verma, P. Dolui, A. J. Elias, *Org. Lett.* **2020**, *22*, 5496–5501.

[12] a) K. Ben-Harush, A. Wolfson, M. Herskowitz, *Lett. Org. Chem.* **2006**, *3*, 664–667; b) A. Wolfson, K. Ben-Harush, M. Herskowitz, *Kinet. Catal.* **2010**, *51*, 63–68.

[13] J. Xu, R. Zhuang, L. Bao, G. Tang, Y. Zhao, *Green Chem.* **2012**, *14*, 2384–2387.

[14] a) S. Yao, K. Zhou, J. Wang, H. Cao, L. Yu, J. Wu, P. Qiu, Q. Xu, *Green Chem.* **2017**, *19*, 2945–2951; b) X. Shi, J. Guo, J. Liu, M. Ye, Q. Xu, *Chem. Eur. J.* **2015**, *21*, 9988–9993; c) Q. Wang, M. Lv, J. Liu, Y. Li, H. Cao, X. Zhang, Q. Xu, *ChemSusChem* **2019**, *12*, 3043–3048.

[15] A. Jana, A. Kumar, B. Maji, *Chem. Commun.* **2021**, DOI: 10.1039/d1 cc00181 g.

[16] a) I. Jacquemond-Collet, F. Benoit-Vical, A. Valentin, E. Stanislas, M. Mallié, I. Fourasté, *Planta Medica* **2002**, *68*, 68–69; b) S. G. Davies, A. M. Fletcher, P. M. Roberts, J. E. Thomson, *Eur. J. Org. Chem.* **2019**, 5093–5119.

[17] Representative examples only: a) W. Lv, B. Xiong, H. Jiang, M. Zhang, *Adv. Synth. Catal.* **2017**, *359*, 1202–1207; b) G. Chakraborty, R. Sikari, S. Das, R. Mondal, S. Sinha, S. Banerjee, N. D. Paul, *J. Org. Chem.* **2019**, *84*, 2626–2641; c) K. Das, A. Mondal, D. Pal, D. Srimani, *Org. Lett.* **2019**, *21*, 3223–3227.

[18] W.-T. Wei, J.-F. Sheng, H. Mian, X. Luo, X.-H. Song, M. Yan, Y. Zou, *Adv. Synth. Catal.* **2018**, *360*, 2101–2106.

[19] L. Zhang, L. Zheng, B. Guo, R. Hua, *J. Org. Chem.* **2014**, *79*, 11541–11548.

[20] a) G. Dijkstra, W. H. Kruizinga, R. M. Kellogg, *J. Org. Chem.* **1987**, *52*, 4230–4234; b) C. Galli, *Org. Prep. Proced. Int.* **1992**, *24*, 285–307.

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