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FULL PAPER

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Synthesis and structure of arene ruthenium(II) complexes: One-pot catalytic approach to synthesis of bioactive quinolines under mild conditions

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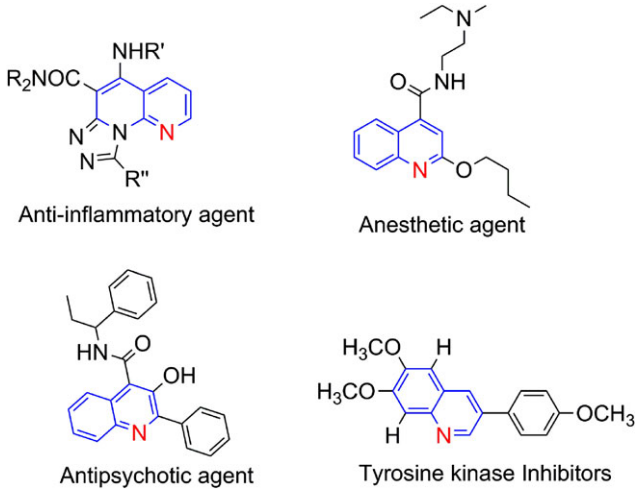
Efficient catalytic one-step synthesis of substituted quinoline derivatives using newly synthesized Ru(II) half-sandwich complexes of the type [Ru(η^6-*p*-cymene)Cl(L)] (L = pyrrole-2-aldehydehydrazones) under mild conditions is described. The synthesized complexes exhibit excellent catalytic activity towards the coupling of 2-amino alcohol with functionalized ketones and secondary alcohols in the optimal conditions and afforded the corresponding quinoline derivatives. The synthetic pathway proceeds with high atom efficiency via a sequence of acceptorless dehydrogenation and condensation steps. The maximum isolated yield of the product obtained was up to 97% using 0.3 mol% of catalyst loading for 5 h. These findings significantly advance the scope of the synthesis of bioactive heterocyclic compounds from readily available starting materials.

KEYWORDS
arene Ru(II) benzhydrazone complexes, mild reaction condition, one-pot synthesis, quinoline derivatives

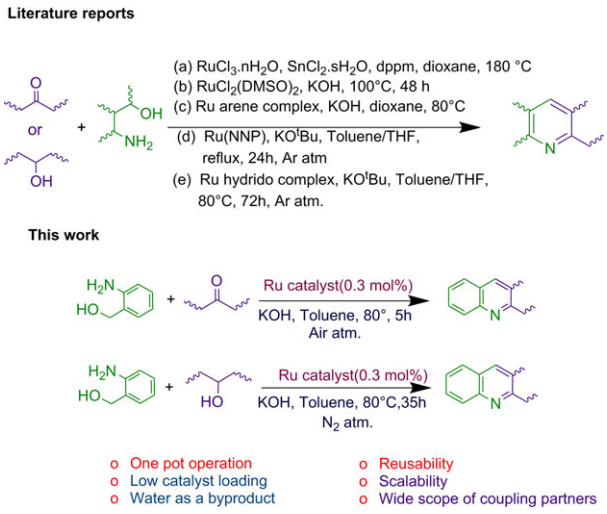
1 | INTRODUCTION

The synthesis of quinolines is the subject of extensive research in synthetic organic chemistry because of the presence of these motifs in many pharmacologically active compounds.[1] Quinolines find many applications in medicinal chemistry, since they are antimalarial,[2]anti-inflammatory,[3] anti-asthmatic,[4] antibacterial,[5] antihypertensive,[6] anaesthetic,[7] antipsychotic[8] and tyrosine kinase inhibitory agents[9] (Scheme 1). Quinoline-based polymers have been reported recently for applications as thermally stable transparent materials in the fields of electronics, optoelectronics and nonlinear optics.[10] In addition, nanostructures and mesostructures with improved electronic and photonic properties have been prepared using various quinolines.[11]

A number of synthetic methods, including the Skraup, Comps, Conrad–Limpach, Gould–Jacobs, Doebner–von Miller and Povarov protocols, have been used to synthesize the quinoline core because of the excellent activities of the quinoline motif.[12] However, harsh reaction conditions, low stereoselectivity, multiple steps and low yields limit the applicability of these methods.[13] It is worth noting that quinolines have been successfully synthesized by the simple and widely used Friedlander method.[14] Further, the use of Pd,[15–18] Ni,[19] Rh,[20,21] Co,[22,23] Ir,[24] Fe[25] and Cu[26] complexes for transition metal-mediated quinoline synthesis has been reported. The Grubbs catalyst has been proposed as one of the best for quinoline synthesis.[27] Shim and co-workers have reported the synthesis of 2,3-disubstituted quinolines from anilines with easily available trialkylamines in the presence of a ruthenium/$SnCl_2$ catalyst at a reaction temperature of 180°C for 20 h (Scheme 2a).[28] Subsequently, the synthesis of polysubstituted quinolines has been reported by Yus



SCHEME 1 Quinoline-based biologically active compounds



SCHEME 2 Synthetic strategies of quinoline synthesis

and co-workers using 2 mol% of $RuCl_2(dmso)_4$ catalyst loading in toluene at 100°C for 48 h (Scheme 2b).[29] Verpoort and co-workers have improved the synthesis of quinolines using ruthenium arene complexes by coupling of alcohols and various ketones using 1 mol% catalyst loading at 80°C (Scheme 2c).[30] One-step synthesis of substituted quinoline derivatives via consecutive C—N and C—C bond formation in 24 h has been described (Scheme 2d) with the help of a bipyridyl-based ruthenium pincer complex.[31] Interestingly, quinoline derivatives were obtained from coupling cyclization of γ-amino alcohols and secondary alcohols using a ruthenium hydride complex in 24 h (Scheme 2e).[32] However, these reported methods show some significant drawbacks such as long reaction time, high loading of catalyst and base, need of additives, harsh reaction conditions as well as workup and recyclability of catalysts. To address the above needs and also as a continuation of our effort in developing Ru catalysts for various reactions,[33] we describe here an efficient one-step synthesis of substituted quinolines from the coupling of amino alcohol and ketones/alcohols catalysed by newly synthesized ruthenium(II) arene benzhydrazone catalysts of 0.3 mol% loading in 5 h.

2 | EXPERIMENTAL

2.1 | Materials and Methods

The complex $[(\eta^6\text{-}p\text{-cymene})RuCl_2(\mu\text{-}Cl)]_2$, benzhydrazide, pyrrole-2-aldehyde and substrates for the quinoline synthesis reaction were purchased from Sigma Aldrich and used without further purification. All other reagents used were purchased from commercial sources and used as received. Pyrrole-2-carboxaldehyde hydrazone ligand was prepared according to a literature procedure.[33b]

Melting points were recorded with a Boetius micro heating table and are uncorrected. The microanalysis of carbon, hydrogen, nitrogen and sulfur was conducted with an Elementar Vario EL III analyser. The infrared (IR) spectra of the complexes were recorded in KBr pellets with a PerkinElmer 597 spectrophotometer in the range 400–4000 cm^{-1}. The electronic spectra of the complexes in acetonitrile solution were recorded with a Cary 300 Bio UV–Vis Varian spectrophotometer in the range 260–800 nm using cuvettes of 1 cm path length. The ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker 400 MHz spectrometer at frequencies of 400, 100 and 160 MHz. Chemical shifts are given in ppm referenced to the deuterated solvents. Electrospray ionization (ESI) mass spectra were recorded with a Thermo Fisher Hybrid Quadrupole-Orbitrap mass spectrometer in positive ion ESI mode.

2.2 | Synthesis of Arene Ruthenium(II) Benzhydrazone Complexes

One equivalent of the starting precursor $[(\eta^6\text{-}p\text{-cymene})RuCl_2(\mu\text{-}Cl)]_2$ was mixed with two equivalents of pyrrole-2-carboxaldehyde benzhydrazone ligand (0.1 mmol) in benzene (20 ml). The reaction mixture was allowed to stir at room temperature for 2 h in the presence of triethylamine (TEA; 0.3 ml). Then, the solution was concentrated to 2 ml and precipitated by the addition of hexane. The reaction was monitored using TLC.

2.2.1 | $[Ru(\eta^6\text{-}p\text{-cymene})Cl(L1)]$ (1)

Yield: 85%; m.p. 148°C. Anal. Calcd (%) for $C_{22}H_{24}N_3OClRu$: C, 54.71; H, 5.00; N, 8.70. Found (%): C, 54.67; H, 5.20; N, 8.66. IR (KBr, cm^{-1}): 2982 $\nu_{(N-H)}$, 1516 $\nu_{(C=N)}$, 1095 $\nu_{(C-O)}$. UV–visible (DMF, λ_{max}, nm (*e*,

$dm^3\ mol^{-1}\ cm^{-1}$)): 365 (976), 303 (4490), 224 (9769). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 11.03 (br, 1H, pyrrole N—H), 8.78 (s, 1H, HC═N), 6.38–8.06 (m, 8H, aromatic), 5.43 (d, 1H, *p*-cym-H), 5.32 (d, 1H, *p*-cym-H), 5.04 (d, 1H, *p*-cym-H), 4.09 (d, 1H, *p*-cym-H), 2.69 (m, 1H, *p*-cym $CH(CH_3)_2$), 2.23 (s, 3H, *p*-cym CCH_3), 1.39 (d, 3H, *p*-cym $CH(CH_3)_2$), 1.19 (d, 3H, *p*-cym $CH(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 172.14, 152.38, 132.41, 128.55, 122.66, 110.98, 81.42, 30.84, 8.85. ESI-MS: *m*/*z* 484.04 $(M + H)^+$ (calcd 483.06).

2.2.2 | [Ru(η⁶-*p*-cymene)Cl(L2)] (2)

Yield: 84%; m.p. 141°C. Anal. Calcd (%) for $C_{23}H_{26}N_3O_2ClRu$: C, 53.84; H, 5.10; N, 8.19. Found (%): C, 53.91; H, 5.29; N, 8.08. IR (KBr, cm^{-1}): 3062 $\nu_{(N—H)}$, 1520 $\nu_{(C═N)}$, 1079 $\nu_{(C—O)}$. UV–visible (DMF, λ_{max}, nm (*e*, $dm^3\ mol^{-1}\ cm^{-1}$): 365 (794), 295 (4527), 252 (7763). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 11.09 (br, 1H, pyrrole N—H), 8.05 (s, 1H, HC═N), 6.27–7.98 (m, 8H, aromatic), 5.23 (d, 1H, *p*-cym-H), 5.08 (d, 1H, *p*-cym-H), 4.26 (d, 1H, *p*-cym-H), 4.25 (d, 1H, *p*-cym-H), 3.74 (s, 3H, OCH_3), 2.50 (m, 1H, *p*-cym $CH(CH_3)_2$), 2.49 (s, 3H, *p*-cym CCH_3), 1.18 (d, 3H, *p*-cym $CH(CH_3)_2$), 0.80 (d, 3H, *p*-cym $CH(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 172. 41, 160. 36, 129. 24, 125. 03, 121.54, 112.17, 109.93, 83.49, 54.30, 43.50, 29.80, 21.34, 17.12, 7. 76. ESI-MS: *m*/*z* 514.08 $(M + H)^+$ (calcd 513.07).

2.2.3 | [Ru(η⁶-*p*-cymene)Cl(L3)] (3)

Yield: 88%; m.p. 143°C. Anal. Calcd (%) for $C_{22}H_{23}Cl_2N_3ORu$: C, 51.06; H, 4.48; N, 8.12. Found (%): C, 51.13; H, 4.55; N, 8.20. IR (KBr, cm^{-1}): 3217 $\nu_{(N—H)}$, 1525 $\nu_{(C═N)}$, 1086 $\nu_{(C—O)}$. UV–visible (DMF, λ_{max}, nm (*e*, $dm^3\ mol^{-1}\ cm^{-1}$): 370 (674), 238 (5245), 232 (6806). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.93 (br, 1H, pyrrole N—H), 8.68 (s, 1H, HC═N), 6.38–7.98 (m, 8H, aromatic), 5.36 (d, 1H, *p*-cym-H), 5.25 (d, 1H, *p*-cym-H), 4.96 (d, 1H, *p*-cym-H), 4.64 (d, 1H, *p*-cym-H), 2.60 (m, 1H, *p*-cym $CH(CH_3)_2$), 2.13 (s, 3H, *p*-cym CCH_3), 1.29 (d, 3H, *p*-cym $CH(CH_3)_2$), 1.19 (d, 3H, *p*-cym $CH(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 172.52, 150.65, 136.18, 130.60, 129.94, 122.85, 111.10, 100.49, 84.50, 46.00, 30.84, 22.35, 22.03, 18.52, 8.75. ESI-MS: *m*/*z* 518.03 $(M + H)^+$ (calcd 517.02).

2.2.4 | [Ru(η⁶-*p*-cymene)Cl(L4)] (4)

Yield: 88%; m.p. 143°C. Anal. Calcd (%) for $C_{22}H_{24}N_3O_2ClRu$: C, 52.92; H, 4.84; N, 8.42. Found (%): C, 52.92; H, 4.84; N, 8.42. IR (KBr, cm^{-1}): 2982 $\nu_{(N—H)}$, 1516 $\nu_{(C═N)}$, 1095 $\nu_{(C—O)}$. UV–visible (DMF, λ_{max}, nm (*e*, $dm^3\ mol^{-1}\ cm^{-1}$): 366 (738), 291 (5893), 235 (9901). ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 11.18 (br, 1H, pyrrole N—H), 9.34 (s, 1H, OH), 8.65 (s, 1H, HC═N), 6.31–7.82 (m, 8H, aromatic), 5.39 (d, 1H, *p*-cym-H), 5.26 (d, 1H, *p*-cym-H), 4.99 (d, 1H, *p*-cym-H), 4.69 (d, 1H, *p*-cym-H), 2.60 (m, 1H, *p*-cym $CH(CH_3)_2$), 2.14 (s, 3H, *p*-cym CCH_3), 1.30 (d, 3H, *p*-cym $CH(CH_3)_2$), 1.18 (d, 3H, *p*-cym $CH(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 172.98, 159.13, 129.71, 125.48, 122.48, 114.40, 101.37, 83.96, 45.46, 30.26, 21.51, 17.96, 8.23. ESI-MS: *m*/*z* 500.06 $(M + H)^+$ (calcd 499.06).

2.3 | Coupling Cyclization of 2-Aminobenzyl Alcohol with Aryl, Heteroaryl and Cyclic Ketones

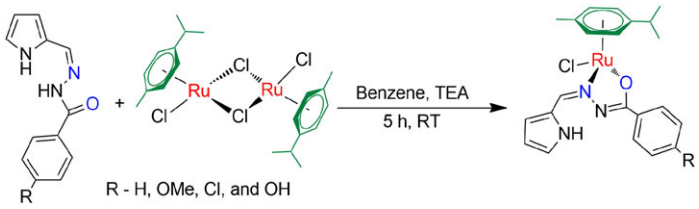
A mixture of 1 mmol of 2-aminobenzyl alcohol, 1.2 mmol of ketone and 0.003 mmol of Ru catalyst in toluene with KOH (1 mmol) under open air was stirred at 80°C for 5 h. Then, the reaction mixture was cooled to room temperature and the aqueous layer was separated using diethyl ether (3 × 3 ml). Further, the organic layer was concentrated and was purified by column chromatography (*n*-hexane–EtOAc).

2.4 | Coupling Cyclization of 2-Aminobenzyl Alcohol with Secondary Alcohols

In a Schlenk tube, 1 mmol of 2-aminobenzyl alcohol, 1.2 mmol of secondary alcohol and 0.003 mmol of Ru catalyst (1.2 equiv.) in toluene and KOH (1 equiv.) were stirred at 80°C for 35 h under nitrogen atmosphere. The reaction mixture cooled in room temperature and quenched by adding water. After extraction with diethyl ether–water mixture and the collection of organic layer, removal of solvent left the product and it was further purified by column chromatography using ethyl acetate–hexane as eluent to yield the product.

3 | RESULTS AND DISCUSSION

The benzhydrazone ligands were obtained in excellent yields by the reaction of pyrrole-2-aldehyde and substituted benzhydrazone in equimolar ratio in ethanol at room temperature. The formation of new ruthenium(II) benzhydrazone complexes was accomplished from the reaction of 2 mol of ligands and 1 mol of $[Ru_2(\eta^6\text{-}p\text{-cymene})_2Cl_2]$ in the presence of a few drops of TEA in dry benzene under reflux conditions for 5 h (Scheme 3). All the complexes were isolated as yellow crystals and are air stable in both solid and liquid states.



SCHEME 3 Synthesis of ruthenium(II) arene complexes of pyrrole-2-aldehyde benzhydrazones

The complexes are soluble in common solvents such as chloroform, dichloromethane, acetonitrile, DMF and DMSO producing intense brown-coloured solutions. The elemental analysis data for the Ru(II) arene benzhydrazone complexes match well with the general molecular formula proposed.

The IR stretching frequency of N—H functional group of the ligands shows a band in the region of 2968–3217 cm^{-1}. The absence of this band and the appearance of new band in the region of 1603–1647 cm^{-1} confirm coordination through the deprotonated oxygen to the Ru(II) ion via enolization of N—NH—C=O. A decrease in C=N band of the ligand at around 1508–1525 cm^{-1}indicates the coordination of the azomethine nitrogen to the Ru(II) ion. The electronic absorption spectra of all the complexes in acetonitrile showed highly intense ligand-centred π–π^* and n–π^* transitions at around 219–303 nm and ligand-to-metal charge transfer bands in the region 365–370 nm. The ^{1}H NMR spectra for all the complexes were recorded in $CDCl_3$ solution and the results were consistent with the molecular structures confirmed using the single-crystal X-ray diffraction method. Multiplets were observed at around 6.22–8.06 ppm due to aromatic protons of the ligands. In addition, the signal of downfield shift at 8.66–8.78 ppm is attributed to the coordinated azomethine proton. The free ligand undergoes tautomerization and coordinates to the Ru(II) ion via imidolate oxygen. This is further supported by the disappearance of signal due to —NH proton of the free ligand. The other characteristic arene ligand signals are presented in Section 2.2.

The molecular structure of complex **1** was determined using single-crystal X-ray analysis. Single crystals of complex **1** were grown by slow evaporation of dichloromethane–petroleum ether solutions and crystallized in the monoclinic system with P21/c space group. A summary of the data collection and refinement parameters are given in the supporting information (Tables S1 and S2). Based on these results, the azomethine nitrogen and imidolate oxygen of the ligand coordinate to ruthenium in a bidentate manner. A piano-stool geometry has been observed for the complexes similar to other reported half-sandwich arene Ru(II) complexes (Fig. 1). The benzhydrazone ligand bonded to the metal centre at N and O forming a five-member chelate ring with bite

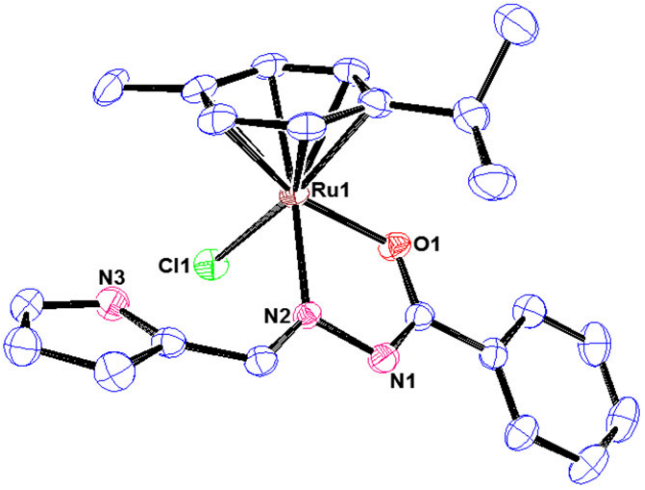
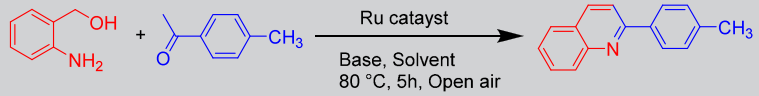


FIGURE 1 The ORTEP diagram of the complex **1** with 50% probability. All the hydrogens are omitted for clarity

angles of 133.2(4)° (C(16)–Ru(1)–N(2)), 112.8(4)° (O(1)–Ru(1)–C(7)) and 85.7(1)° (N(2)–Ru(1)–Cl(1)). The bond lengths of Ru(1)—N(2) and Ru(1)—O(1) were 2.070(5) and 2.066(4) Å, respectively. The Ru—Cl bond length was found to be 2.427(2) Å which is in agreement with other structurally established arene ruthenium complexes.[34] The average C—C bond length in the arene ring is 1.41(1) Å with alternating short and long bonds and an average Ru—C distance of 2.187(7) Å is observed for ruthenium arene bond.

Our effort is to initiate the oxidative cyclization of amino alcohol and a range of ketones towards synthesis of derivatives of quinoline using the Ru(II) benzhydrazone catalysts. Ketones are readily available inexpensive precursors for many organic syntheses and it is possible to alter the electronic properties of quinoline through a suitable substitution of the ketones. Hence, it is interesting to investigate the catalytic property of ruthenium benzhydrazone catalysts for quinoline synthesis using substituted ketones. Therefore, the reaction of 2-aminobenzyl alcohol with 4-methylacetophenone in open atmosphere with catalyst **1** (1 mol%) in 5 h is considered as a model reaction to establish the practicability of our study and to optimize the various reaction parameters together with catalyst loading, temperature, time, solvents and bases (Tables 1 and 2). When the reaction was conducted in dioxane with 1.0 equiv. of KOH at

TABLE 1 Optimization of reaction conditions[a]



Entry	Solvent	Base	Yield (%)[b]	TON[c]
1	Dioxane	KOH	90	90
2	THF	KOH	64	64
3	Toluene	KOH	97	97
4	Dioxane	KOH	34[d]	34
5	H_2O	KOH	37	37
6	Toluene	—	—	—
7	Toluene	NaOH	81	81
8	Toluene	^tBuOK	85	85
9	Toluene	^tBuONa	81	81
10	Toluene	Bu_4NOH	65	65
11	Toluene	K_3PO_4	66	66
12	Toluene	K_2CO_3	12	12
13	Toluene	Na_2CO_3	10	10
14	Toluene	Et_3N	—	—
15	Toluene	Pyridine	—	—

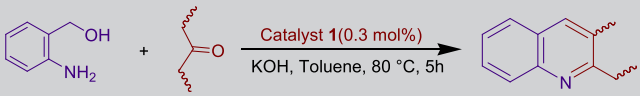
[a]Reaction conditions: 4-methylaceophenone (1.2 mmol), 2-aminobenzyl alcohol (1 mmol), base (1 mmol), catalyst **1** (1 mol%) and solvent (2 ml) at 80°C for 5 h under open air.

[b]Isolated yield after column chromatography based on 4-methylacetophenone (average of two runs).

[c]TON: mol product/mol catalyst.

[d]Reaction at room temperature for 22 h.

TABLE 2 Effect of catalyst loading[a]



Entry	Catalyst (mol%)	Yield (%)[b]	TON[c]
1	1.0	99	99
2	0.5	99	198
3	0.3	97	323
4	0.1	74	740
5	0.05	69	1 380
6	0.01	43	4 300
7	0.001	31	31 000
8	0.0001	Trace	—

[a]Reaction conditions: 4-methylacetophenone (1.2 mmol), 2-aminobenzyl alcohol (1 mmol), base (1 mmol) and solvent (2 ml) at 80 °C, under open air for 5 h.

[b]Isolated yield after column chromatography based on 4-methylacetophenone (average of two runs).

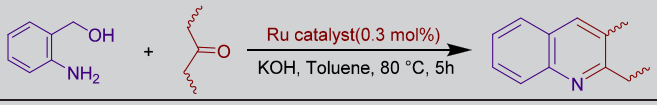
[c]TON: mol product/mol catalyst.

80°C, the yield of product was 90% (Table 1, entry 1). Hence, attempts were made to increase the rate of the reaction by optimizing the various solvents and co-solvent. Tetrahydrofuran (THF) solvent with KOH gave a decreased yield of 64% (entry 2). A maximum yield of 97% was obtained when toluene as the choice of solvent

(entry 3). A further drop in the yield to 37% was noticed when water was used. No reaction was observed in the absence of base, indicating that base is essential for the reaction (entry 6). Therefore, a series of bases, namely KOH, NaOH, ^{t}BuOK, ^{t}BuONa, K_3PO_4, Bu_4NOH, K_2CO_3, Na_2CO_3, NEt_3 and pyridine, were screened with KOH affording the highest yield. Among the bases used, inorganic bases (entries 7–13) furnished better results than organic bases because the latter may coordinate with metal and result in no product (entries 14 and 15). In addition, bases such as hydroxides or ^{t}BuOK facilitate the reaction. Based on the results, we chose KOH as base and toluene as solvent for further studies. With regard to the industrial use of catalytic systems for the synthesis of quinoline derivatives, different catalyst-to-substrate (C/S) ratios were used to optimize the reaction. The corresponding yields are listed in Table 2. The reaction of 4-methylacetophenone with 2-aminobenzyl alcohol gave the maximum yield of 99% when a catalyst loading of 1.0 or 0.5 mol% was used (entries 1 and 2). A marginal decrease of yield (97%) was obtained when 0.3 mol% of catalyst was used (entry 3). It is worth noting that the reaction with a catalyst loading of 0.01 mol% proceeds with a drop in isolated yields with high turnover number (entry 6). To our great surprise, a catalyst loading of 0.001 mol% gave the highest turnover number of 31 000 (entry 7). Hence, 0.3 mol% catalyst loading was chosen for further studies based on the results. For any synthetic protocol the stability and longevity of the catalyst are important. So, the performance of the catalyst was examined by changing R on the ligand coordinated to ruthenium (Table 3). In this regard, the catalytic activity of all complexes **1**–**4** in the quinoline synthesis was determined using 0.3 mol% catalyst loading. Based on the quantitative yield, complex **1** was chosen for further studies.

The coupling of γ- amino alcohols with various functionalized ketones/alcohols was carried out to evaluate the scope of the modified Friedlander reaction for the synthesis of quinolines under optimized conditions (Tables 4 and 5). Initially, electronically activated and deactivated acetophenones were readily coupled and cyclized with 2-aminobenzyl alcohol and offered the expected quinolines in moderate to good yields (92–60%) indicating good activity and high selectivity (Table 4, entries 1–7) of the catalyst. Among the substrates, 4-chloroacetophenone was easily coupled and cyclized with 2-aminobenzyl alcohol and provided excellent yield of 2-(4-chlorophenyl)quinoline (Table 4, entry 4). Interestingly, with an electron-withdrawing group in the *ortho* position of acetophenone, the yield was not significantly affected, indicating that the position of the substituent had no major effect on the yield of the product (Table 4, entry 6). When 4-hydroxyacetophenone was used, a considerable decrease in the yield (60%) was encountered (Table 4, entry 7). Based on these results, it is generalized that lower yields are generally observed for substrates with electron-donating substituents compared with those with electron-withdrawing substituents. Moreover, this methodology is more useful for the preparation of quinoline derivatives from alkyl heteroaryl ketones. Accordingly, 2-acetylfuran afforded 76% of 2-(furan-2-yl) quinoline without affecting any heterocyclic ring (Table 4, entry 8). Moreover, 2-acetylpyridine was coupled and cyclized with γ-amino alcohol and afforded the desired product in a high yield of 89% (Table 4, entry 9). Reaction of pyrrole-2-ketone with amino alcohol proceeded to give quinoline product in 76% isolated yield (Table 4, entry 10). In addition, 2-acetylthiophene under the same experimental conditions afforded 82% yield (Table 4, entry 11). In the case of aryl(methyl) ketones, the corresponding quinolines were obtained as a regio-isomeric mixture, favouring cyclization at less hindered position of α-methylene. It was observed that the reactivity and product yield for heteroaryl ketones were found to be lower than those for aryl(methyl) ketones. Moreover, the

TABLE 3 Substituent effect on quinoline synthesis[a]

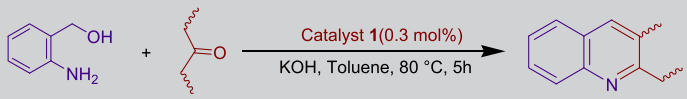


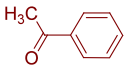
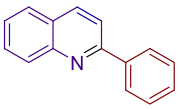
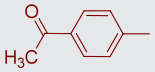
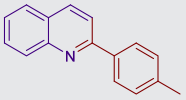
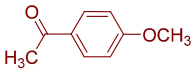
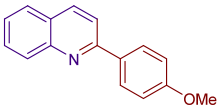
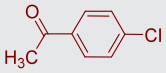
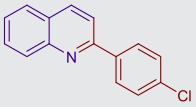
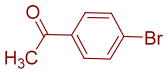
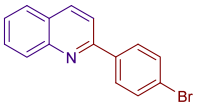
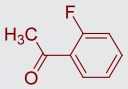
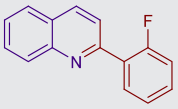
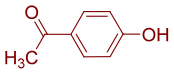
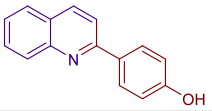
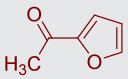
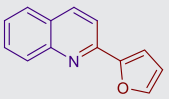
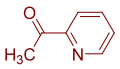
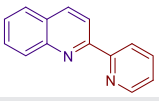
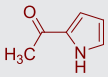
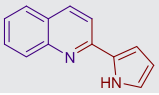
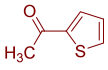
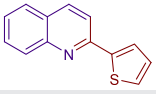
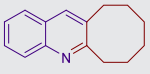
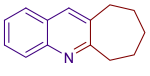
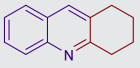
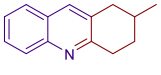
Entry	Catalyst	Yield (%)[b]
1	**1**	97
2	**2**	93
3	**3**	96
4	**4**	92

[a]Conditions: 4-methylacetophene (1.2 mmol), 2-aminobenzyl alcohol (1 mmol), catalyst (0.3 mol%), KOH (1.0 mmol), toluene (3 ml), 80°C, under open air for 5 h.

[b]Isolated yields.

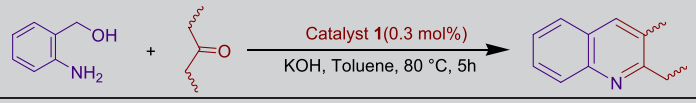
TABLE 4 Effect of catalyst on quinoline synthesis from ketones[a]

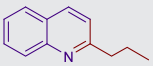


Entry	Ketone	Product	Yield (%)[b]	TON[c]
1			96	320
2			94	313
3			91	303
4			96	320
5			95	316
6			96	320
7			60	200
8			92	306
9			89	296
10			76	253
11			82	273
12			96	320
13			95	316
14			91	303
15			90	300

(Continues)

TABLE 4 (Continued)



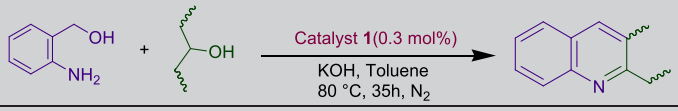
Entry	Ketone	Product	Yield (%)[b]	TON[c]
16			63	210

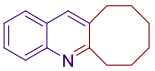
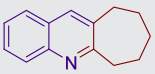
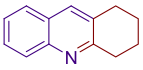
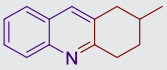
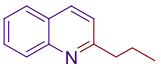
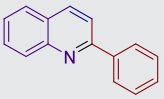
[a]Reaction conditions: substituted acetophenone or cyclic ketone (1.2 mmol), 2-aminobenzyl alcohol (1 mmol), KOH (1 mmol), catalyst **1** (0.3 mol%) and solent (2 ml) at 80°C for 5 h under open air.

[b]Isolated yield after column chromatography based on corresponding alcohols (average of two runs).

[c]TON: mol product/mol catalyst.

TABLE 5 Effect of catalyst on quinoline synthesis from secondary alcohols[a]



Entry	Alcohol	Product	Yield (%)[b]	TON[c]
1			96	300
2			85	283
3			81	270
4			76	253
5			61	203
6			75	250

[a]Reaction conditions: secondary alcohols (1.2 mmol), 2-aminobenzyl alcohol (1 mmol), KOH (1 mmol), catalyst **1** (0.3 mol%) and solvent (2 ml) at 80°C for 35 h under nitrogen atmosphere.

[b]Isolated yield after column chromatography based on alcohols (average of two runs).

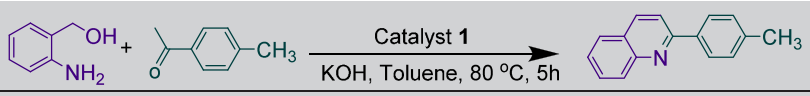
[c]TON: mol product/mol catalyst.

protocol operated well with aliphatic ketones and afforded excellent results (Table 4, entries 12–16). Cyclooctanone underwent coupling followed by cyclization to the corresponding quinoline product in 96% isolated yield (Table 4, entry 12). When cycloheptanone was used, a significantly lower yield was obtained which might be due to ring constraints (Table 4, entry 13). From the results it has been presumed that the smaller the ring of the cyclic ketone used, the lower the yield of the corresponding product. It is noteworthy that electron-donating substitution on the cyclic ketone further decreased the product yield (Table 4, entry 15). Long-chain 2-pentanone gave the corresponding quinoline product in lower yield (63%) without any side product (Table 4, entry 16).

An adventitious activity of our catalyst, we were motivated to synthesize quinoline derivatives from the catalytic coupling cyclization of secondary alcohols as an alternative to ketones (Table 5, entries 1–6). Syntheses of quinoline derivatives from readily available alcohols are a judicious methodology in modern organic synthesis. Recently, Milstein and co-workers reported coupling cyclization reactions of alcohols using Ru(II) bipyridine

pincer complexes in toluene–THF solvent system under argon atmosphere in 24 h.[31] Moreover, an efficient iridium complex-catalysed coupling cyclization reaction of alcohols in THF with high reaction temperature (130°C) has been described by Kempe and co-workers.[24] Liu *et al*. have reported PNN-type R(II) pincer complexes as

TABLE 6 Recycling of catalyst[a]

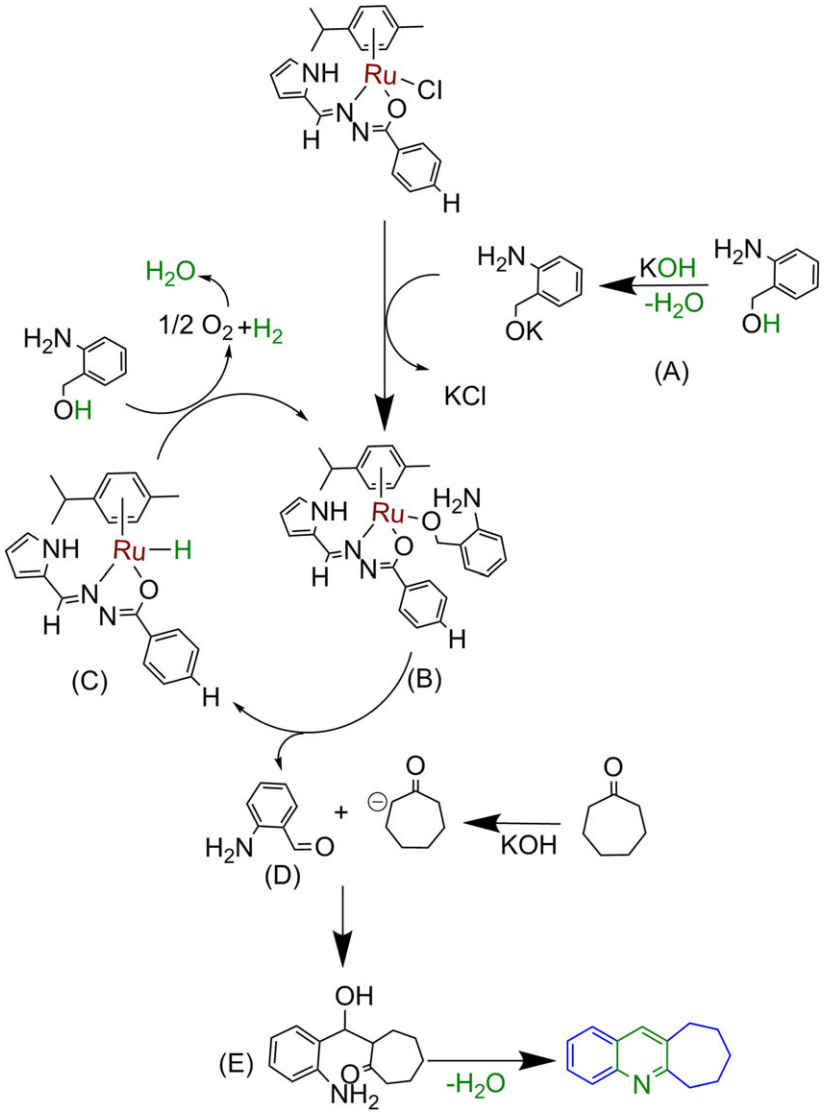


Catalyst recycle	Yield (%)[b]	TON[c]
1	97	323
2	90	300
3	83	276
4	66	220
5	Trace	—

[a]Conditions: 4-methyloacetophene (1.2 mmol), 2-aminobenzyl alcohol (1 mmol), catalyst **1** (0.3 mol%), KOH (1.0 mmol), toluene (3 ml), 80°C, under open air for 5 h.

[b]Isolated yields.

[c]TON: mol product/mol of catalyst.



SCHEME 4 Plausible mechanism for quinoline synthesis

catalysts for coupling cyclization reaction of γ-amino alcohols and secondary alcohols under argon atmosphere for 72 h.[32] Still, the development of coupling cyclization of γ-amino alcohols and secondary alcohols remains challenging. Herein, we developed a methodology for quinoline synthesis by one-step reaction using readily available starting materials like γ-amino alcohol and secondary alcohols using the aforementioned optimal conditions under nitrogen atmosphere. The coupling cyclization of γ-amino alcohol with various cyclic alcohols, including cyclooctanol, cycloheptanol, cyclohexanol, 3-methylcyclohexanol, cyclohexanol and 2-pentanol, was carried out. It was observed that secondary alcohols having larger rings reacted smoothly with excellent yield of corresponding quinolines compared to secondary alcohols with smaller rings. Methyl substituent on cyclohexanol decreased the yield of quinoline product from 81 to 76% (Table 5, entry 4). When 2-pentanone was employed under the same experimental conditions, it afforded 61% yield of the corresponding quinoline derivative (Table 5, entry 5). Interestingly, 1-phenylethanol readily reacted with amino alcohol and furnished 2-phenylquinoline in 75% isolated yield (Table 5, entry 6). Based on these results, complexes under investigation have proven to be efficient catalysts for quinoline synthesis.

The reaction of 2-aminobenzyl alcohol with 4-methylacetophenone was carried under optimal reaction conditions in order to verify the recyclability of catalyst **1** (Table 6). It was observed that the recovered catalyst could be successfully reused for three cycles leading to 97, 90 and 83% isolated yields, respectively (Table 6, entries 1–3). The formation of product was considerably reduced in the fourth cycle (Table 6, entry 4) and a marked decrease in yield was observed after the fifth run (Table 6, entry 5).

The excellent activity of the ruthenium arene catalyst in quinoline synthesis encouraged us to propose a plausible mechanism (Scheme 4).[28] The reaction involves initial oxidation of 2-aminobenzyl alcohol (A) by the ruthenium catalyst leading to the formation of a ruthenium–alkoxide species (B). Then β-hydride abstraction leads to the formation of a ruthenium–hydride complex (C) by releasing aldehyde intermediate D. Then aldehyde D and ketone C undergo a cross aldol condensation to form E. Further, form C enters into the next catalytic cycle with the release of water as the only by-product. Ultimately, form E is converted to quinoline through self-condensation reaction. In the case of secondary alcohols (Table 5), ruthenium-mediated oxidation leads to corresponding ketone and then follows the same mechanism as described in Scheme 4 with evolution of molecular H_2.[35]

4 | CONCLUSIONS

In summary, the present study describes an environmentally benign, sustainable and practical synthesis of substituted quinolines catalysed by well-characterized arene Ru(II) benzhydrazone complexes. Quinolines can be accessed in good to excellent yields from cyclization of γ-amino alcohol with various functionalized ketones and secondary alcohols under mild reaction conditions. The experimental results seem to reveal that the mechanism involves oxidation of alcohol followed by intramolecular aldol-type condensation. The optimized reaction conditions allow the presence of a wide range of organic functional groups. The synthetic procedure is very simple and works well with 0.3 mol% catalyst loading in 5 h. The excellent activity of these catalysts makes this methodology very useful for the synthesis of biologically important heterocyclic compounds. A detailed mechanistic study of this reaction is under way.

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