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Superbase Mediated Indirect Friedländer Reaction: A Transition Metal-Free Oxidative Annulation toward Functionalized Quinolines

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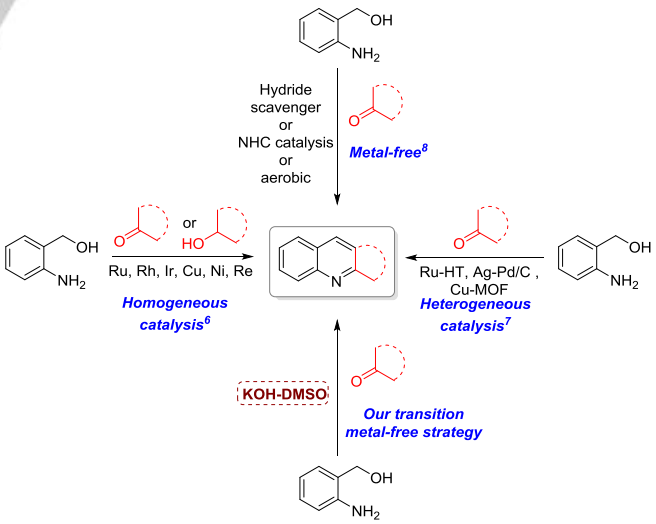
Abstract: A superbase mediated indirect Friedländer reaction towards functionalized quinolines has been realized. The reaction was performed with o-aminobenzyl alcohol and ketones having an active methylene moiety in the presence of KOH and in DMSO. The reaction proceeds predominantly via initial formation of an imine intermediate and subsequent oxidation of the benzyl alcohol functionality and condensation to afford substituted quinolines. We could also demonstrate that a minor fraction of the reaction proceeds via a chalcone intermediate. The transition metal-free oxidative annulation was found to be general affording 2-substituted, 2,3-disubstituted/fused or multi-substituted quinolines. The reaction was extended towards the functionalization of natural products and the applicability of the reaction for gram scale synthesis of quinolines was also demonstrated.

Introduction

The class of quinoline derivatives pose a continuous challenge to synthetic chemists in devising straightforward routes for accessing them.[1] The profound interest invested in this heterocyclic moiety is due to its wide applicability in pharmaceuticals,[2] materials[3] and industry.[4] Substituted quinolines exhibit promising biological activities such as antimalarial, antibacterial, antiviral, antitumor, analgesic, anticonvulsant, anti-inflammatory etc.[2] These findings have resulted in the development of blockbuster drugs (of natural and synthetic origin) such as quinine, chloroquine, camptothecin, pitavastatin, bedaquiline, lenvatinib, tipifarnib and saquinavir which are being heavily used worldwide for the treatment of different ailments.

Several classical organic reactions exist which utilizes arylamines as precursors for the synthesis of quinoline and its derivatives and out of which Friedländer quinoline synthesis can still be considered as one of the most direct routes for accessing this important heterocycle.[5] The traditional Friedländer reaction involves a base promoted condensation of 2-amino-substituted carbonyl compound (aromatic) and an α-methylene group containing carbonyl derivative followed by dehydration. Recently, modified or indirect Friedländer quinoline synthesis protocols with dehydrogenative cyclisation of 2-aminobenzyl alcohol with carbonyl compounds (or alcohols) were developed in the presence of metal catalysts (Scheme 1).[6] Different complexes of metals such as Ru,[6b] Rh,[6c] Ir,[6d-f] Cu,[6g] Ni[6h-i] and Re[6j] were utilized as catalysts in indirect Friedländer quinoline synthesis. In addition, several heterogeneous catalysts which includes Ru-HT (ruthenium on hydrotalcite support), Pd/C, $Pd(OAc)_2$/PEG-2000, Ag-Pd alloy on carbon and a Cu based MOF were also developed and used for synthesizing substituted quinolines (Scheme 1).[7]

Another advancement in the area of indirect Friedländer quinoline synthesis was the introduction of metal-free strategies.[8] The first among them was reported in 2008 by Ramón, Yus and co-workers which combined the Meerwein-Ponndorf-Verley reaction of 2-aminobenzyl alcohols with benzophenone and the Friedländer annulation to synthesize quinoline derivatives.[8a] Recently, an *N*-heterocyclic carbene-catalyzed indirect Friedländer quinoline synthesis was reported by Zhu and Cai.[8b] and an aerobic one-pot synthesis by Singh *et al* (Scheme 1).[8c] These reported metal-free methodologies required additional reagents (benzophenone for the MPV reaction of 2-aminobenzyl alcohol[8a] or the presence of a catalyst.[8b] We were interested in developing a transition metal-free and additional reagent-free methodology for quinoline synthesis based on the indirect Friedländer reaction.



Scheme 1. Indirect Friedländer synthesis of quinolines from 2-aminobenzyl alcohol.

Superbasic medium (mainly the combination of KOH and DMSO) have been utilized extensively by Trofimov and others

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for effecting different organic transformations such as chalcogenation, cross-coupling, intramolecular cyclization, heterocyclic synthesis, styrylation, inter- and intramolecular hydromaminations etc.[9] Verma and co-workers made use of the KOH-DMSO system for the synthesis of functionalized quinolines from *o*-aminobenzyl alcohol and alkynes.[10] The reaction proceeded via a [4 + 2] cycloadditions of alkyne with azadiene (in situ generated from *o*-aminobenzyl alcohol). An efficacious methodology for the oxidation of active methylenes and benzhydrols to corresponding carbonyl compounds mediated by a base-DMSO system was reported by Ravikumar et al.[11] Motivated by the above mentioned reports on the use of superbasic media and owing to our interest in heterocyclic synthesis,[12] we hypothesized that functionalized quinolines could be generated from *o*-aminobenzyl alcohol and α-methylene group containing carbonyl derivatives via an oxidation-condensation sequence in the presence of a base-DMSO system and most importantly in the absence of any additional reagent or catalyst.

Result and Discussions

We commenced our investigations by selecting *o*-aminobenzyl alcohol **1a** and 4'-methoxy acetophenone **2a** as model substrates. The initial reaction was performed with one equivalent each of **1a** and **2a** in the presence of KOH (1.0 equivalent) and DMSO (1.0 mL) at 80 °C for 7 h. As expected, 2-(4-methoxyphenyl)quinoline **3a** was isolated in 80% yield (Table 1, entry 1). Different bases other than KOH such as ^{t}BuONa, ^{t}BuOK, NaOH and K_2CO_3 were screened for the present indirect Friedländer quinoline synthesis (Table 1, entries 1-5). From the tested bases, KOH was found to be the best and the reaction failed to furnish any product in presence of K_2CO_3. Increasing the equivalents of *o*-aminobenzyl alcohol had a beneficial effect on the outcome of the reaction. Thus, with 1.2 equivalents of **1a**, the substituted quinoline was isolated in 88% yield (Table 1, entries 1, 6 and 7). Next, we checked the effect of change in temperature on the yield of the reaction. It was found that both increasing (to 120 °C) and decreasing the temperature (to RT) considerably decreased the yield of **3a** (Table 1, entries 7-9). A decrease in the equivalents of KOH (to 0.5 equivalents) was found to lower the yield of **3a** to 72% (Table 1, entry 10) and the reaction failed to afford any product in the absence of KOH (Table 1, entry 11). Finally, conducting the reaction under inert atmosphere didn't significantly influence the outcome of the reaction proving that oxygen is not required for the oxidation step (Table 1, entry 12).

The scope and limitation of the indirect Friedländer quinoline synthesis was then studied (Table 2) under the optimized conditions [**1** (1.2 equiv.), **2** (1.0 equiv.), KOH (1.0 equiv.), DMSO (1.0 mL), 80 °C, 7 h]. Both acetophenone **2b** and 4'-methylacetophenone **2c** participated in the oxidative annulation with *o*-aminobenzyl alcohol **1a** affording the corresponding products **3b** and **3c** in 75 and 80% respectively. 2-Phenyl quinoline **3b** was also synthesized in gram scale and in good yield (70%) by starting with 1.0 g of acetophenone **2b.** A substituent on the *ortho*-position of the aryl ring of acetophenone did not affect the reaction yield and in this line the reactions with 2'-methoxy (**2d**) and 2'-methylacetophenone (**2e**) afforded the products **3d** and **3e** in good yields, whereas the reaction with 2'-hydroxyacetophenone (**2f**) furnished the product **3f** only in 56% yield.

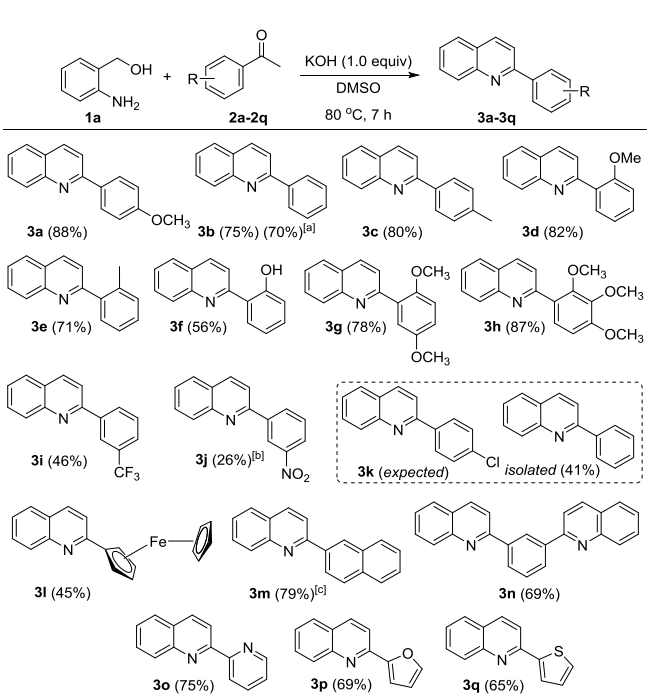
Table 1. Optimization studies

Entry	Base	Time	T (°C)	Yield of **3a**[a] (%)
1	KOH	7	80	80
2	^{t}BuONa	7	80	48
3	^{t}BuOK	7	80	51
4	NaOH	7	80	61
5	K_2CO_3	7	80	-
6[b]	KOH	7	80	83
7[c]	**KOH**	**7**	**80**	**88**
8[c]	KOH	7	120	59
9[c]	KOH	48	RT	23
10[d]	KOH	7	80	72
11[c]	-	7	80	-
12[e]	KOH	7	80	86

Reaction conditions: [a] **1a** (1.0 equiv.), **2a** (1.0 equiv., 0.6 mmol), base (1.0 equiv.), DMSO (1.0 mL), 80 °C, 7 h. [b] **1a** (1.1 equiv.). [c] **1a** (1.2 equiv.). [d] **1a** (1.2 equiv.), KOH (0.5 equiv.). [e] **1a** (1.2 equiv.), argon atmosphere.

The superbase mediated oxidative annulation proceeded well with di- (**2g**) and tri-methoxy acetophenones (**2h**) affording the products **3g** and **3h** in excellent yields. The presence of electron withdrawing groups were found to influence the reaction outcome as the reactions with both 3'-(trifluoromethyl)acetophenone (**2i**) and 3-nitroacetophenone (**2j**) could only furnish the corresponding 2-substituted quinolines **3i** and **3j** in poor yields. Another interesting observation that we came across was in the reaction with 4'-chloroacetophenone and *o*-aminobenzyl alcohol **1a**. In contrary with our expectation of 2-(4-chlorophenyl)quinoline **3k**, we obtained a dehalogenated quinoline derivative. The dehalogenation of aromatic compounds with a DMSO-base combination was reported earlier which might be the reason for the present observation.[13] The oxidative annulation also worked with acetylferrocene affording 2-ferrocenylquinoline **3l** in 45% yield. 2-Naphthylquinole **3m** was synthesized in excellent yield but after 14 h of reaction time. By starting with 1,3-dicetylbenzene we could synthesize 1,3-di-quinolylbenzene **3n** in 69% yield. Finally, the reactivity of different acetylheteroarenes toward the present indirect Friedländer reaction was examined and thus pyridyl (**3o**), furyl (**3q**) and thienyl (**3r**) substituted quinolines were synthesized in good yields.

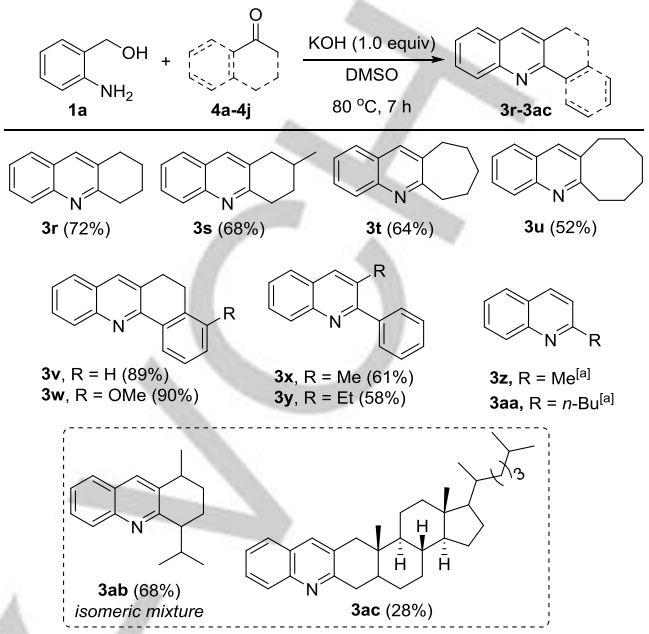
Table 2. Generality of indirect Friedländer reaction toward 2-substituted quinolines



Reaction conditions: **1a** (1.2 equiv.), **2** (1.0 equiv., 0.6 mmol), KOH (1.0 equiv., 0.6 mmol), DMSO (1.0 mL), 80 °C, 7 h. [a] started with 1.0 g of **2b**. [b] 120 °C, 12 h. [c] 14 h.

Next, we turned our attention in synthesizing 2,3-disubstituted/fused quinolines *via* the developed superbase mediated oxidative annulation (Table 3). We commenced our investigations with *o*-aminobenzyl alcohol **1a** and cyclohexanone under the optimized conditions and 1,2,3,4-tetrahydroacridine **3r** was isolated in 72% yield. The reaction with 4-methylcyclohexanone also afforded the corresponding substituted tetrahydroacridine derivative **3s** in 68% yield. Other cyclic ketones such as cycloheptanone and cyclooctanone afforded the 2,3-fused quinoline derivatives **3t** and **3u** in good yields. The indirect Friedländer reaction was also found to work well with tetralone **4e** and methoxytetralone **4f** from which the respective dihydrobenzo[c]acridine derivatives **3v** and **3w** were isolated in excellent yields. We then checked the reactivity of propiophenone **4g** and butyrophenone **4h** and these ketones reacted well under the optimized conditions affording the corresponding 2,3-disubstitued quinolines **3x** and **3y** in good yields. We have also checked the reactivity of acyclic ketones such as acetone and 2-hexanone but to our dismay, after the required time an intractable reaction mixture was observed. The importance of the present oxidative annulation was exemplified by performing 'quinolization' of natural products containing an enolizable ketone moiety. Thus both menthone (mixture of isomers) and 5α-cholestan-3-one were treated with *o*-aminobenzyl alcohol **1a** under our optimized conditions and the corresponding annulated natural products **3ab** and **3ac** were isolated.

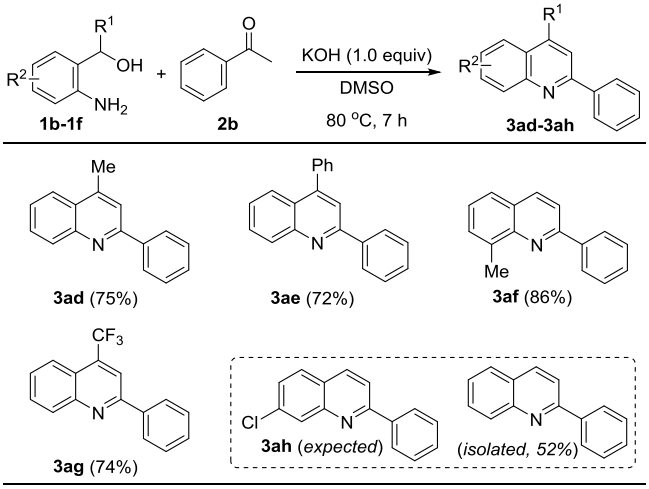
Table 3. Generality of indirect Friedländer reaction toward 2,3-disubstituted/fused quinolines



Reaction conditions: **1a** (1.2 equiv.), **4** (1.0 equiv., 0.6 mmol), KOH (1.0 equiv., 0.6 mmol), DMSO (1.0 mL), 80 °C, 7 h. [a] intractable reaction mixture.

Subsequently, we examined the effect of substituents on *o*-aminobenzyl alcohols on the outcome of the superbase mediated quinoline synthesis (Table 4). We commenced with the reaction of acetophenone **2b** with 1-(2-aminophenyl)ethan-1-ol **1b**. The reaction was complete in 7 h and from which the 2,4-disubstituted quinoline **3ad** was isolated in 75% yield. 2-aminobenzhydrol **1c** also reacted with ease affording the 2,4-diphenylquinoline **3ae** in good yield.

Table 4. Generality of indirect Friedländer with substituted *o*-aminobenzyl alcohol.

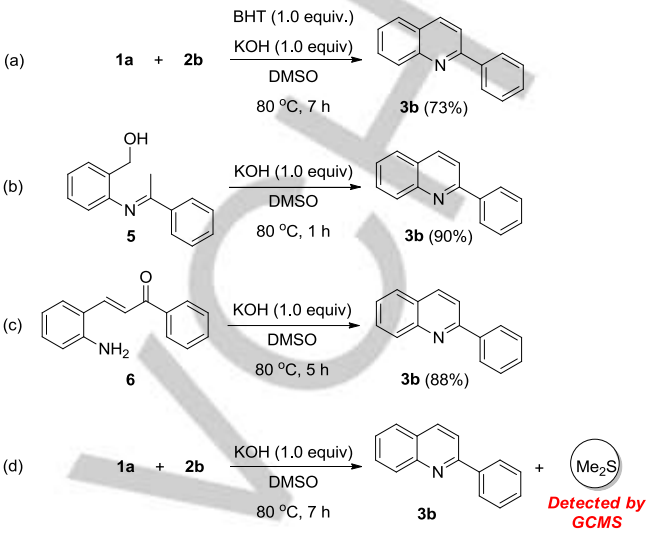


Reaction conditions: **1a** (1.2 equiv.), **2** (1.0 equiv., 0.6 mmol), KOH (1.0 equiv., 0.6 mmol), DMSO (1.0 mL), 80 °C, 7 h.

Next, we checked the reactivity of 2-amino-3-methylbenzyl alcohol **1d** under the optimized conditions and the respective quinoline derivative **3af** was obtained in 86% yield (Table 4). The reaction of 1-(2-aminophenyl)-2,2,2-trifluoroethan-1-ol **1e** also proceeded well affording 2-phenyl-4-(trifluoromethyl)quinoline **3ag** in 74% yield. Lastly we checked the reactivity of 2-amino-4-chlorobenzyl alcohol **1f** with acetophenone and as observed earlier (Table 2, compound **3k**) we obtained the dehalogenated product.

In order to prove the mechanism of the superbase mediated indirect Friedländer quinoline synthesis we carried out several experiments with substrates **1a** and **2b** (Scheme 2). The possibility for a radical mediated reaction was ruled out with the first reaction (Scheme 2a) where **1a** and **2b** were allowed to react under the optimized conditions but in the presence of 1.0 equivalent of BHT from which 2-phenylquinoline **3b** was isolated in 73% yield. It is reported that the classical Friedländer quinoline synthesis can proceed either *via* the imine **5** or *o*-amino chalcone **6** as intermediates.[5] When **5** was subjected to the optimized conditions, we were able to isolate the expected product **3b** in 90% yield after an hour (Scheme 2b). On the other hand, when *o*-amino chalcone **6** was allowed to react at the optimized conditions, the reaction took 5 h to furnish 88% of **3b** (Scheme 2c). These results show that the present superbase mediated quinoline synthesis might be proceeding predominantly *via* the imine intermediate **5** rather than the chalcone **6** and that imine formation must be happening preferentially over the oxidation of the benzyl alcohol moiety. Finally, we were able to detect the formation of Me_2S as a by-product by conducting a GCMS experiment (Scheme 2d).[14]

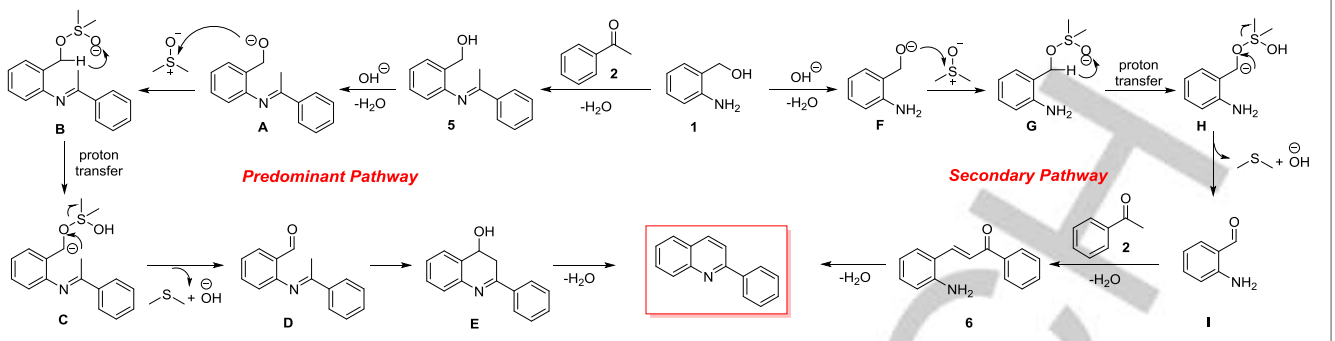
From the results obtained for the experiments depicted above, we believe that the first step of quinoline synthesis (predominant pathway) would be the condensation of amino group of 2-aminobenzylalcohol and acetophenone to yield the imine **5** (Scheme 3). This will be followed by the oxidation of the alcohol to the corresponding carbonyl group which proceeds *via* a mechanism analogous to the one proposed by Ravikumar *et al*.[11a] Initially the base will generate the alkoxide intermediate **A** from **5**. The adduct **B** is then formed by the attack of the alkoxide to the electrophilic sulfur of DMSO. Subsequently proton transfer occurs from the benzylic carbon to the alkoxide generating the carbanion **C** which further undergoes an $E1_{cb}$ elimination furnishing the corresponding carbonyl compound **D**. An intramolecular aldol addition occurs in intermediate **D** to furnish the dihydroquinoline **E** from which water is eliminated to finally afford the substituted quinoline derivative.[5] The secondary pathway will commence with the benzylic alcohol functionality to the *o*-amino benzaldehyde I by following a similar mechanism as shown before. The *o*-amino chalcone **6** is then formed by the condensation of **I** with acetophenone. The intermediate **6** subsequently undergoes intramolecular annulation to furnish 2-substituted quinoline by the elimination of H_2O.



Scheme 2. Reactions to support the mechanism of superbase mediated indirect Friedländer quinoline synthesis.

Conclusion

In conclusion, we have developed a mild, transition metal-free and general methodology for the synthesis of functionalized quinolines. In contrast to the reported methods that required either metal catalysts (homogeneous or heterogeneous) or additional reagents (hydride scavenger or NHC catalyst) our strategy required only the combination of KOH in DMSO. In this superbasic medium, the reaction proceeds predominantly *via* the formation of an imine and successive oxidation of 2-aminobenzyl alcohol to the corresponding aldehyde followed by condensation with the enamine moiety. We could propose a mechanistic postulate by isolating the imine intermediate and by subjecting it to oxidative annulation conditions. We could also show that a minor fraction of the reaction proceeds *via* a chalcone intermediate. This oxidative annulation worked well affording mono-, di- and poly-substituted quinolines in good yields. In the case of halogen substituted quinoline derivatives, dehalogenation was observed as reported earlier. It is noteworthy to mention that we could synthesize substituted quinoline by this methodology in gram scale thereby proving the applicability of the reaction. In addition, we also utilized this superbase mediated oxidative annulation to functionalize natural products. We are currently focusing on other superbase mediated reactions of 2-aminobenzyl alcohol and the results will be published.



Scheme 3. Mechanism of superbase mediated indirect Friedländer quinoline synthesis.

Experimental Section

General

All chemicals were of the best grade commercially available and were used without further purification. All solvents were purified according to the standard procedures; dry solvents were obtained according to the literature methods and stored over molecular sieves. Analytical thin-layer chromatography was performed on polyester sheets pre-coated with silica gel containing fluorescent indicator (POLYGRAMSIL G/UV254). Gravity column chromatography was performed using neutral alumina, and mixtures of ethyl acetate/ hexanes were used for elution. Melting points were determined using a calibrated digital melting point apparatus (Büchi 530 melting point apparatus). NMR spectra were recorded with Bruker Avance-300 (300 MHz for ^{1}H NMR, 75 MHz for ^{13}C{1H} NMR) and Bruker AMX-500 (500 MHz for ^{1}H NMR, 125 MHz for ^{13}C{1H} NMR) instruments. All spectra were measured at 300 K, unless otherwise specified. The chemical shifts δ are given in ppm and referenced to the external standard TMS or internal solvent standard. 1H NMR coupling constants (J) are reported in Hertz (Hz) and multiplicities are indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets). Mass spectra were performed with a ThermoFinnigan MAT95XL, a ThermoFisher Scientific LTQ Orbitrap Velos, and an Agilent 6890 gas chromatograph with JMS-T100GC spectrometer or with a ESI/ HRMS at 60,000 resolution using Thermo Scientific Exactive mass spectrometer with orbitrap analyzer. Gas chromatographic analysis was performed using GCMS-TQ8030 SHIMADZU.

Experimental procedure for the synthesis of substituted quinoline derivatives: To a reaction tube equipped with a magnetic stirring bar, acetophenone **2** (1.0 equiv.), *o*-aminobenzylalcohol **1** (1.2 equiv.) and KOH (1 equiv.) and 1 mL of DMSO were added. The resultant reaction mixture was kept for stirring at 80°C for 7 h. After completion of the reaction, water was added and the aqueous layer extracted thrice with ethylacetate. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was then purified by column chromatography (neutral alumina, eluent: mixtures of ethylacetate/hexanes) to afford the corresponding 2-substituted quinolines

2-(4-methoxyphenyl)quinoline (**3a**).[6i,14a] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 4-methoxyacetophenone **2a** (100 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3a** as white solid (138mg, 88%). Analytical data of **3a**: Mp: 125−126 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS): δ 8.18−8.13 (m, 4H), 7.84−7.79 (m, 2H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 3.89 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 160.8, 156.9, 148.3, 136.6, 132.3, 129.6, 129.5, 128.9, 127.4, 126.9, 125.9, 118.6, 114.2, 55.4 ppm. HRMS (ESI-Orbitrap) m/z: (M +H)$^{+}$ calcd for $C_{16}H_{14}NO$ 236.1070, found 236.1078.

2-phenylquinoline (**3b**).[6i,14a] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), acetophenone **2b** (81 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3b** as white solid (103 mg, 75%). For the gram-scale preparation of **3b**, the yield was 70% (1.19 g). Analytical data of **3b**: Mp: 84−87 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.20−8.15 (m, 4H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.73−7.70 (m, 1H), 7.53−7.49 (m, 3H), 7.47−7.44 (m, 1H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, TMS) δ 157.4, 148.3, 139.7, 136.8, 129.8, 129.7, 129.3, 128.9, 127.6, 127.5, 127.2, 126.3, 119.1 ppm. HRMS (ESI-Orbitrap) m/z: (M+H)$^{+}$ calcd for $C_{15}H_{12}N$ 206.0964, found 206.0975.

2-(p-tolyl)quinoline (**3c**).[6i,14a] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80mmol), 4-methylacetophenone **2c** (90mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3c** as white solid (117 mg, 80%). Analytical data of **3c**: Mp: 81−84 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.17 (t, *J* = 9 Hz, 2H), 8.07 (d, *J* = 8 Hz, 2H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 8 Hz, 1H), 7.71 (t, *J* = 8 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.32 (d, J = 7.5 Hz, 2H), 2.43 (s, 3H) ppm . ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.4, 148.3, 139.4, 136.9, 136.7, 129.7, 129.6, 127.4, 127.1, 126.1, 118.9, 21.4 ppm. HRMS (ESI-Orbitrap) m/z: (M+H)$^{+}$ calcd for $C_{16}H_{14}N$ 220.1121, found 220.1124.

2-(2-methoxyphenyl)quinoline (**3d**).[6i,14a] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 2-methoxyacetophenone **2d** (100 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3d** as colorless liquid (129 mg, 82%). Analytical data of **3d**: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.18−8.13 (m, 2H), 7.89−7.82 (m, 3H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 8 Hz, 1H), 7.13 (t, *J* = 7.5Hz, 1H), 7.03 (d, *J* = 8 Hz, 1H), 3.86 (s, 3H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 157.2, 157.2, 148.3, 135.1, 131.5, 130.4, 129.8, 129.6, 129.2, 127.4, 127.1, 126.2, 123.5, 121.3, 111.4, 55.7 ppm. HRMS (ESI-Orbitrap) m/z: (M+H)$^{+}$ calcd for $C_{16}H_{14}NO$ 236.1070, found 236.1072.

2-(o-tolyl)quinoline (**3e**).[6i,14a] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 2-methylacetophenone **2e** (90 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3e** as white solid, 104 mg (71%). Analytical data of **3e**: Mp: 69−71°C ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.21 (d, *J* = 8 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8 Hz, 1H), 7.74 (t, *J* = 8 Hz, 1H), 7.58−7.53 (m, 2H), 7.50 (d, *J* = 7 Hz, 1H), 7.36−7.33 (m, 3H), 2.41 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 160.3, 147.9, 140.8, 136.1, 136.0, 130.9, 129.7, 129.6, 128.5, 127.5, 126.8, 126.4, 126.0, 122.4, 20.4 ppm. HRMS (ESI-Orbitrap) *m/z*: $(M+H)^+$ calcd for $C_{16}H_{14}N$ 220.1121, found 220.1124.

2-(quinolin-2-yl)phenol (**3f**).[14c] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 2-hydroxyacetophenone **2f** (92 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3f** as white solid (83 mg, 56%). Analytical data of **3f**: Mp: 113−115 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 15.24 (s, 1H), 8.27 (d, *J* = 9 Hz, 1H), 8.06−8.03 (m, 2H), 7.95 (d, *J* = 8 Hz, 1H), 7.83 (d, *J* = 8 Hz, 1H), 7.74 (t, *J* = 8 Hz, 1H), 7.57−7.54 (m, 1H), 7.37 (t, *J* = 7. 5 Hz, 1H) 7.09 (d, *J* = 8.5 Hz, 1H), 6.96 (t, *J* = 7. 5 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, CDCl3) δ 161.0, 158.0, 144.8, 137.6, 130.5, 127.6, 127.5, 126.9, 126.7, 126.6, 119.0, 118.7, 118.7, 117.3 ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{15}H_{12}NO$ 222.0913, found 222.0924.

2-(2,5-dimethoxyphenyl)quinolone (**3g**). Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 2,5-dimethoxyacetophenone **2g** (121 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3g** as white solid (138 mg, 78%). Analytical data of **3g**: Mp: 141−143 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.16 (t, *J* = 9.5 Hz, 2H), 7.91 (d, *J* = 8 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.72−7.70 (m, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.45 (s, 1H), 6.98 (s, 2H), 3.86 (s, 3H), 3.81 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 156.9, 154.1, 151.6, 148.3, 135.2, 130.4, 129.7, 129.3, 127.4, 127.1, 126.3, 123.4, 116.2, 116.1, 113.3, 56.6, 55.9 ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{16}NO_2$ 266.1176, found 266.1181.

2-(2,3,4-trimethoxyphenyl)quinoline (**3h**). Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 2,3,4-trimethoxyacetophenone **2h** (141 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3h** as white solid (172 mg, 87%). Analytical data of **3h**: Mp: 104−106 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.16−8.15 (m, 2H), 7.90 (d, *J* = 9 Hz, 1H), 7.84 (d, *J* = 8 Hz, 1H), 7.71 (t, *J* = 7.5 Hz, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.5Hz, 1H), 3.95 (s, 3H), 3.93 (s, 3H), 3.77 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, CDCl3) δ 156.6, 154.6, 152.3, 148.3, 142.4, 135.5, 129.6, 129.3, 127.6, 127.4, 127.0, 126.1, 125.8, 122.9, 108.1, 61.5, 61.1, 56.2 ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{18}H_{18}NO_3$ 296.1281, found 296.1287.

2-(3-(trifluoromethyl)phenyl)quinoline (**3i**).[14b] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 3-trifluoromethylacetophenone **2i** (126 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexanes) to afford the desired product **3i** as white solid (84 mg, 46%). Analytical data of **3i**: Mp: 51−53 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.47 (s, 1H), 8.36 (d, *J* = 7.5 Hz, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.78−7.72 (m, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 155.6, 148.3, 140.4, 137.2, 131.3 (q, j = 32.5 Hz), 130.7, 130.0, 129.8, 129.3, 127.5, 127.4, 126.8, 125.9 (q, j = 3.8 Hz), 124.4 (q, j = 3.8 Hz), 118.6 ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{11}F_3N$ 274.0844, found 274.0851.

2-(3-nitrophenyl)quinoline (**3j**).[14a] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 1.2 0.80 mmol), 3-nitroacetophenone **2j** (110.6 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 120 °C and subsequent stirring for 12 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexanes) to afford the desired product **3j** as white solid (44 mg, 26%). Analytical data of **3j**: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 9.06 (s, 1H), 8.57 (d, *J* = 8 Hz, 1H), 8.33−8.31 (m, 2H), 8.20 (d, *J* = 8 Hz, 1H), 7.95 (d, *J* = 8.5Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.79 (t, *J* = 8 Hz, 1H), 7.72 (t, *J* = 8 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 148.3, 141.3, 137.4, 137.1, 133.3, 130.2, 129.9, 129.8, 127.6, 127.1, 123.9, 122.5, 118.4 ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{15}H_{11}N_2O_2$ 251.0815, found 251.0825.

2-Ferrocenylquinoline (**3l**).[14c] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), acetylferrocene **2l** (153 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3l** as red solid (94 mg, 45%). Analytical data of **3l**: Mp: 135−138 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.04 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 8 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.48– 7.45 (m, 1H), 5.07 (s, 2H), 4.47 (s, 2H), 4.06 (s, 5H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.5, 148.3, 135.4, 129.4, 129.0, 127.5, 126.7, 125.4, 119.5, 84.0, 70.4, 69.7, 68.0 ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{13}H_{10}NS$ 314.0627, found 314.0621.

2-(naphthalen-2-yl)quinoline (**3m**).[14c] Following the general experimental procedure with *o*-aminobenzyl alcohol **1a** (99 mg, 0.80 mmol), 2-acetonaphthone **2m** (114 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 14 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3m** as a pale yellow solid (135 mg, 79%). Analytical data of **3m**: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 8.63 (s, 1H), 8.39 (dd, J_1= 8.7 Hz, J2 = 1.8 Hz, 1H), 8.27–8.23 (m, 2H), 8.04–7.99 (m, 3H), 7.93–7.89 (m, 1H), 7.86–7.83 (m, 1H), 7.79−7.74 (m, 1H) 7.58−7.53 (m, 3H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 157.1, 148.3, 136.9, 136.8, 133.8, 133.5, 129.7, 129.7, 128.8, 128.6, 127.7, 127.5, 127.2, 127.1, 126.7, 126.3, 126.3, 125.0, 119.1 ppm.

1,3-di(quinolin-2-yl)benzene (**3n**).[14d] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (197 mg, 1.6 mmol), 1,3-diacetylbenzene **2n** (109 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3n** as white solid (153 mg, 69%). Analytical data of **3n**: Mp: 138-141 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.97 (s, 1H), 8.30–8.27 (m, 4H), 8.23 (d, *J* = 8.5 Hz, 2H), 8.04 (d, *J* = 9 Hz, 2H), 7.86 (d, *J* = 8 Hz, 2H), 7.75 (t, *J* = 7.5 Hz, 1H), 7.70 (t, *J* = 8 Hz, 1H), 7.55 (t, *J* = 8 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 157.2, 148.3, 140.3, 136.9, 129.8, 129.8, 129.5, 128.6, 127.5, 127.3, 126.8, 126.4, 119.2 ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{24}N_2$ 333.1386, found 333.1395.

2-(pyridin-2-yl)quinoline (**3o**).[14a] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 2-acetylpyridine **2o** (81 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3o** as white solid (103 mg, 75%). Analytical data of **3o**: Mp: 98−100°C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.74−8.73 (1H, m), 8.65 (d, *J* = 8 Hz, 1H), 8.56 (d, *J* = 8.5 Hz, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.88-7.84 (m, 2H), 7.73 (t, *J* = 8 Hz, 1H) 7.55 (t, *J* = 7.5Hz, 1H), 7.35 (t, *J* = 6 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 156.4, 156.2, 149.2, 148.0, 137.0, 136.8, 129.8, 129.6, 128.3, 127.6, 126.8, 124.1, 121.9, 119.0 ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{14}H_{11}N_2$ 207.0917, found 207.0922.

2-(furan-2-yl)quinoline (**3p**).[14a] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 2-acetylfuran **2p** (74 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexanes) to afford the desired product **3p** as white solid (90 mg, 69%). Analytical data of **3p**: Mp: 87−89 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.17 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8 Hz, 1H), 7.72−7.69 (m, 1H), 7.63 (s, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.22 (s, 1H), 6.60 (s, 1H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 149.0, 144.2, 136.7, 129.9, 129.4, 127.6, 127.2, 126.2, 117.5, 112.2, 110.2 ppm.

2-(thiophen-2-yl)quinoline (**3q**).[14a] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 2-acetylthiophene **2q** (85 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3q** as white solid (92 mg, 65%). Analytical data of **3q**: Mp: 131−134 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.15 (d, *J* = 8.5 Hz, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.82−7.76 (m, 3H), 7.70 (t, *J* = 7.5 Hz, 1H), 7.51−7.47 (m, 2H), 7.18−7.16 (m, 1H), ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 152.4, 148.1, 136.7, 129.8, 129.3, 128.6, 128.1, 127.5, 126.1, 125.9, 117.7 ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{13}H_{10}NS$ 212.0528, found 212.0539.

1,2,3,4-tetrahydroacridine (**3r**).[14c] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), cyclohexanone **4a** (66 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3r** as pale yellow solid (88 mg, 72%). Analytical data of **3r**: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 7.99 (d, *J* = 8.4 Hz, 1H), 7.77 (s, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.62−7.56 (m, 1H), 7.44−7.39 (m, 1H), 3.13 (t, *J* = 6.6 Hz, 2H), 2.94 (t, *J* = 6.6 Hz, 2H), 2.02−1.93 (m, 2H), 1.88−1.83 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 159.2, 146.3, 135.1, 130.9, 128.5, 128.0, 127.1, 126.8, 125.5, 33.4, 29.1, 23.1, 22.8 ppm.

2-methyl-1,2,3,4-tetrahydroacridine (**3s**).[14f] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 4-methylcyclohexanone **4b** (75mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3s** as white solid (90 mg, 68%). Analytical data of **3s**: Mp: 78−79°C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.97 (d, *J* = 8.5 Hz, 1H), 7.74 (s, 1H), 7.66 (d, *J* = 8 Hz, 1H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 3.23−3.20 (m, 1H), 3.12−3.05 (m, 1H), 3.00−2.96 (m, 1H), 2.59−2.53 (m, 1H), 2.06−1.95 (m, 2H), 1.62−1.54 (m, 1H), 1.11 (d, *J* = 7 Hz, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 159.1, 146.7, 135.0, 130.6, 128.5, 128.3, 127.2, 126.9, 125.5, 37.8, 33.1, 31.4, 29.1, 21.7 ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{14}H_{16}N$ 198.1277, found 198.1286.

7,8,9,10-tetrahydro-6H-cyclohepta[b]quinoline (**3t**).[14c] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), cycloheptanone **4c** (75 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3t** as white solid (84 mg, 64%). Analytical data of **3t**: Mp: 92−94°C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.00 (d, *J* = 8.5 Hz, 1H), 7.79 (s, 1H), 7.70 (d, *J* = 8 Hz, 1H), 7.61 (t, *J* = 8 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 3.21−3.20 (m, 2H), 2.93−2.92 (m, 2H), 1.89−1.74 (m, 6H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.7, 146.2, 136.5, 134.6, 128.5, 128.4, 127.4, 126.8, 125.8, 40.1, 35.5, 32.2, 28.9, 27.0 ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{14}H_{16}N$ 198.1277, found 198.1270.

6,7,8,9,10,11-hexahydrocycloocta[b]quinoline (**3u**).[14d] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), cyclooctanone **4d** (85mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3u** as colorless liquid (74 mg, 52%). Analytical data of **3u**: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.03 (d, *J* = 8.5 Hz, 1H), 7.84 (s, 1H), 7.73 (d, *J* = 8 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 3.17 (t, *J* = 6.5 Hz, 2H), 2.96 (t, *J* = 6 Hz, 2H), 1.90 (s, 2H), 1.78 (s, 2H), 1.41 (s, 4H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 163.2, 147.0, 135.2, 135.0, 128.5, 128.4, 127.6, 126.9, 125.6, 35.3, 32.7, 32.1, 31.0, 26.0, 25.9 ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{15}H_{18}N$ 212.1434, found 212.1438.

5,6-dihydrobenzo[c]acridine (**3v**).[14a] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80), 1-tetralone **4e** (98 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80°C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3v** as white solid (138 mg, 89%). Analytical data of **3v**: Mp: 59-62°C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.57 (d, *J* = 8 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 7.92 (s, 1H), 7.74 (d, *J* = 8 Hz, 1H), 7.66−7.63 (m, 1H), 7.48−7.41 (m, 2H), 7.37 (t, *J* = 7. 5 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 3.13 (t, *J* = 7 Hz, 2H), 3.01 (t, *J* = 7 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 153.4, 147.7, 139.4, 134.7, 133.7, 130.6, 129.7, 129.4, 129.1, 128.7, 128.0, 127.9, 127.4, 126.9, 126.1, 28.9, 28.4 ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{14}N$ 232.1121, found 232.1129.

4-methoxy-5,6-dihydrobenzo[c]acridine (**3w**). Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), 5-methoxy-1-tetralone **4f** (118 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3o** as white solid (157 mg, 90%). Analytical data of **3o**: Mp: 120-123°C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.22 (d, *J* = 7.5 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.92 (s, 1H), 7.74 (d, *J* = 8 Hz, 1H), 7.65−7.62 (m, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 8.5Hz, 1H), 6.96 (d, *J* = 8 Hz, 1H), 3.90 (s, 3H), 3.09 (t, *J* = 6.5 Hz, 2H), 3.02 (t, *J* = 6.5 Hz, 2H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 156.3, 153.4, 147.6, 135.9, 133.6, 130.6, 129.5, 128.5, 128.2, 127.9, 127.4, 126.9, 126.1, 118.4, 111.4, 55.7, 28.3, 20.4 ppm. HRMS (ESI-Orbitrap) m/z:$(M+H)^+$ calcd for $C_{18}H_{16}NO$ 262.1226, found 262.1236.

3-methyl-2-phenylquinoline (**3x**).[14a] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80

mmol), propiophenone **4g** (90 mg, 0.67 mmol), KOH (38 mg, 0.67 mg) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3x** as colourless liquid (89 mg, 61%). Analytical data of **3x**: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.13 (d, *J* = 8 Hz, 1H), 8.00 (s, 1H), 7.76 (d, *J* = 8 Hz, 1H), 7.67−7.64 (m, 1H), 7.58 (d, *J* = 7 Hz, 2H), 7.52−7.47 (m, 3H), 7.44-7.41 (m, 1H), 2.45 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 160.6, 146.6, 140.9, 136.8, 129.3, 129.2, 128.9, 128.8, 128.3, 128.2, 127.6, 126.8, 126.4, 20.7 ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{14}N$ 220.1121, found 220.1134.

3-ethyl-2-phenylquinoline (**3y**).[14a] Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg,0.80 mmol), butyrophenone **4h** (99 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexanes) to afford the desired product **3y** as colourless liquid (90 mg, 58%). Analytical data of 3y: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.13 (d, *J* = 8.5 Hz, 1H), 8.06 (s, 1H), 7.82 (d, *J* = 8 Hz, 1H), 7.68−7.65 (m, 1H), 7.56−7.53 (m, 3H), 7.50−7.42 (m, 3H), 2.90 (q, *J* = 7.5 Hz,2H), 1.20 (t, *J* = 7.5Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 160.7, 146.4, 140.9, 135.3, 134.9, 129.3, 128.8, 128.7, 128.3, 128.1, 127.8, 127.0, 126.4, 26.0, 14.7 ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{16}N$ 234.1277, found 234.1283.

4-isopropyl-1-methyl-1,2,3,4-tetrahydroacridine (**3ab**). Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), menthone (isomeric mixture) **4i** (104 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexanes) to afford the desired product **3ab** as a colourless liquid and as an isomeric mixture (ratio 2:1) (109 mg, 68%). Analytical data of **3ab**: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.99 (d, *J* = 8.5 Hz,1.5 H), 7.94 (s, 0.53H), 7.85 (s, 1H), 7.72 (t, *J* = 8.5 Hz, 1.5H), 7.60 (t, *J* = 7Hz, 1.54H), 7.43 (t, *J* = 7 Hz, 1.54H), 3.13−3.07 (m, 1.62H), 3.02 – 2.95 (m, 3.17H), 2.06−2.04 (m, 1.2H), 1.94−1.85 (m, 3.30H), 1.76−1.74 (m, 1.63H), 1.41 (d, *J* = 6.5 Hz, 1.6H), 1.37 (d, *J* = 7 Hz, 3.08H), 1.11 (d, *J* = 6.5 Hz, 3.04H), 1.07 (d, *J* = 7 Hz, 1.70H), 0.75 (d, *J* = 6.5 Hz, 3.00H), 0.67 (d, *J* = 6.5 Hz, 1.63H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 162.0, 161.7, 146.7, 146.4, 137.1, 136.8, 134.2, 132.4, 128.7, 128.5, 128.3, 128.2, 127.1, 126.9, 126.8, 125.4, 47.6, 47.0, 33.3, 32.9, 31.4, 31.3, 30.5, 28.6, 23.1, 21.8, 21.2, 21.0, 20.8, 18.7, 17.5, 17.0 ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{17}H_{22}N$ 240.1747, found 240.1752.

(3aS,3bR,13S,13bS,15aR)-13,15a-dimethyl-1-(6-methylheptan-2-yl)-2,3,3a,3b,4,5,5a,6,13,13a,13b,14,15,15a-tetradecahydro-1H-cyclopenta[5,6]naphtho[1,2-b]acridine (**3ac**). Following the general experimental procedure with *o*-aminobenzylalcohol **1a** (99 mg, 0.80 mmol), cholestan-3-one **4j** (260 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3ac** as white solid (88 mg, 28%). Analytical data of **3ac**: Mp: 183−186 °C. ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 7.97 (d, *J* = 8.5 Hz, 1H), 7.81 (s, 1H), 7.70 (d, *J* = 8 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 3.08 (dd, J_1 = 18 Hz, J_2 = 5.0 Hz, 1H), 2.99 (d, *J* = 16 Hz, 2H), 2.79 (dd, J_1 = 18 Hz, J_2 = 13 Hz, 1H), 2.61 (d, *J* = 16.0 Hz, 1H), 2.06 (d, *J* = 12 Hz, 1H), 1.88−1.75 (m, 3H), 1.67−1.62 (m, 5H), 1.54−1.47 (m, 2H), 1.40−1.34 (m, 4H), 1.28−1.21 (m, 2H), 1.15−1.04 (m, 6H), 1.02−0.98(m, 2H), 0.94 (d, *J* = 6 Hz, 3H), 0.87 (d, *J* = 6 Hz, 6H), 0.80 (s, 3H), 0.70 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 158.6, 146.7, 135.7, 130.3, 128.5, 128.3, 127.3, 126.8, 125.4, 56.5, 56.4, 53.6, 43.6, 42.5, 42.3, 40.0, 39.5, 37.5, 36.2, 35.8, 35.6, 35.3, 31.7, 28.8, 28.3, 28.2, 24.3, 23.9, 22.8, 22.6, 21.4, 18.7, 12.0, 11.7 ppm. HRMS (ESI-Orbitrap) m/z: $(M+ H)^+$ calcd for $C_{17}H_{22}N$ 472.3938, found 472.3962.

4-methyl-2-phenylquinoline (**3ad**).[14g] Following the general experimental procedure with 1-(2-aminophenyl)ethan-1-ol **1b** (110 mg, 80 mmol), acetophenone **2b** (81 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3ad** as a pale yellow solid (110 mg, 75%). Analytical data of **3ad**: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 8.31 – 8.24 (m, 3H), 7.99 (d, *J* = 8.7 Hz, 1H), 7.80– 7.75 (m, 1H), 7.72 (s, 1H), 7.62 – 7.53 (m, 4H), 2.74 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 156.8, 147.9, 144.6, 139.6, 130.1, 129.1, 129.0, 128.6, 127.4, 127.0, 125.8, 123.4, 119.5, 18.8 ppm.

2,4-diphenylquinoline (**3ae**).[14g] Following the general experimental procedure with (2-aminophenyl)(phenyl)methanol **1c** (159 mg, 0.80 mmol), acetophenone **2b** (81 mg, 0.67 mmol), KOH (38 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3ae** as a pale yellow solid (135 mg, 72%). Analytical data of **3ae**: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 8.27 (d, *J* = 8.4 Hz, 1H), 8.22 – 8.20 (m, 2H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.83 (s, 1H), 7.77 – 7.72 (m, 1H), 7.58 – 7.46 (m, 9H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 156.9, 149.2, 148.8, 139.6, 138.4, 130.1, 129.6, 129.4, 128.8, 128.6, 128.4, 127.6, 126.3, 125.8, 125.6, 119.4 ppm.

8-methyl-2-phenylquinoline (**3af**).[14a] Following the general experimental procedure with (2-amino-3-methylphenyl)methanol **1d** (110 mg, 0.80 mmol), acetophenone **2b** (81 mg, 0.67 mmol), KOH (37.5 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (10% ethyl acetate in hexane) to afford the desired product **3af** as a pale yellow solid (126 mg, 86%). Analytical data of **3af**: ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 8.29−8.26 (m, 2H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.59 – 7.56 (m, 1H), 7.54−7.51 (m, 2H), 7.49−7.45 (m, 1H) 7.44−7.39 (m, 1H), 2.92 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 155.5, 147.1, 139.8, 137.7, 137.0, 129.7, 129.2, 128.8, 127.5, 127.1, 126.0, 125.4, 118.2, 17.9 ppm.

2-phenyl-4-(trifluoromethyl)quinoline (**3ag**). Following the general experimental procedure with 1-(2-aminophenyl)-2,2,2-trifluoroethan-1-ol **1e** (151 mg, 0.80 mmol), acetophenone **2b** (81 mg, 0.67 mmol), KOH (37.5 mg, 0.67 mmol) in DMSO (1.0 mL) at 80 °C and subsequent stirring for 7 h. The crude product was purified by neutral alumina column chromatography (5% ethyl acetate in hexane) to afford the desired product **3ag** as a white solid, 135 mg (74%). Analytical data of **3ag**: ^{1}H NMR (500 MHz, $CDCl_3$, TMS) δ 8.30 (d, *J* = 8 Hz, 1H), 8.23−8.20 (m, 3H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.85 (t, *J* = 7.5 Hz, 1H), 7.69 (t, *J* = 8 Hz, 1H), 7.60-7.52 (m, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 156.7, 149.2, 138.5, 130.7, 130.4, 130.0 129.0, 127.9, 127.5, 123.9 (q, *J* = 2.5 Hz), 116.0(q, *J* = 1.3Hz) ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{16}H_{11}F_3N$ 274.0838, found 274.0842.

(2-((1-phenylethylidene)amino)phenyl)methanol (**5**). The imine intermediate was synthesized by treating o-aminobenzylalcohol **1a** (200 mg, 1.62 mmol), acetophenone **2b** (194 mg, 1.62 mmol) in benzene (5.0 mL) at 100 °C during which water was removed by azeotropic distillation. After 12 h, the reaction mixture was allowed to cool and the precipitate formed was filtered and purified by washing with benzene to afford the desired product **5** as a white solid (218 mg, 60%). Analytical data of **5**: ^{1}H NMR (500 MHz, Acetone-d_6, TMS) δ 8.22 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.80 (d, *J* = 8. Hz, 2H), 7.62 (t, *J* = 7.5. Hz, 1H), 7.41 (t, *J* = 7.5. Hz, H), 6.97(d, *J* = 8 Hz, 2H), 3.76 (s, 2H), 1.92 (s, 3H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 161.2, 156.3, 148.3,

136.7, 131.8 ,129.5, 129.3, 128.7, 127.6, 127.0, 125.9, 118.1, 114.1, 54.8, 29.4 ppm. HRMS (ESI-Orbitrap) m/z: $(M+Na)^+$ calcd for $C_{15}H_{15}NNaO$ 248.1046, found 248.1055.

(E)-3-(2-aminophenyl)-1-phenylprop-2-en-1-one (**6**).[15] To a mixture of 2-nitrobenzaldehyde (2g, 13.2 mmol) in ethanol (10 mL.) was added acetophenone **2b** (1.589 g, 13.24 mmol), NaOH (53 mg, 1.32mmol) and stirred at room temperature for 2h. After the complete consumption of 2-nitrobenzaldehyde, the reaction mixture was quenched with water. The crude product was filtered and recrystallized from ethanol. To a solution of the resulting (*E*)-2-nitrochalcone (1 mmol) in ethanol (15 mL) was added iron powder (183 mg, 3 mmol), followed by HCl (1.0 N, 1.3 mL.). The reaction mixture was vigorously stirred at 80 ^oC. After the complete consumption of (*E*)-2-nitrochalcone, the reaction mixture was allowed to cool at room temperature and then extracted with ethylacetate. The organic layer was washed with saturated Na_2CO_3 solution and brine, dried over Na_2SO_4, and concentrated to afford the desired product **6** as yellow solid, 116 mg (52%). Analytical data of **6**: ^1H NMR (500 MHz, $CDCl_3$, TMS, δ 8.04-8.02 (m, 2H), 8.00 (d, *J* = 15.5 Hz, 1H), 7.60−7.57 (m, 1H), 7.54-7.48(m, 4H), 7.23−7.20 (m, 1H), 6.81(t, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 8 Hz, 1H), 4.07 (s, 2H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 190.3, 146.2, 140.1, 138.4, 132.8, 131.7, 128.6, 128.5, 128.2, 121.8, 120.3, 119.0, 116.8, ppm. HRMS (ESI-Orbitrap) m/z: $(M+H)^+$ calcd for $C_{15}H_{14}NO$ 224.1070, found 224.1072.

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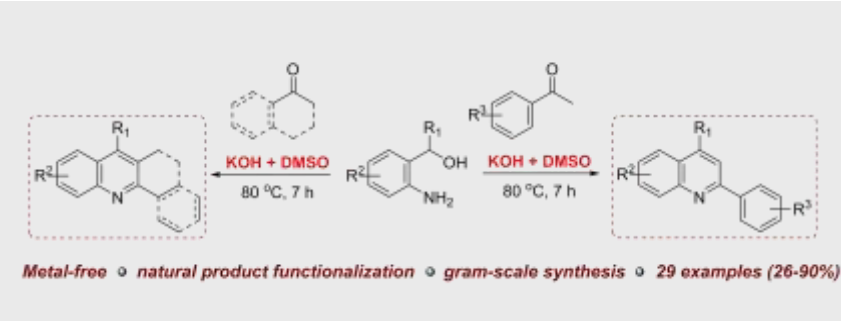

Indirect Friedländer Reaction*

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Superbase Mediated Indirect Friedländer Reaction: A Transition Metal-Free Oxidative Annulation toward Functionalized Quinolines

A transition metal-free superbase mediated indirect Friedländer reaction was developed for accessing functionalized quinolines.