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ARTICLE

Brønsted Acid-Catalyzed Metal- and Solvent-Free Quinoline Synthesis from *N*-alkyl Anilines and Alkynes or Alkenes

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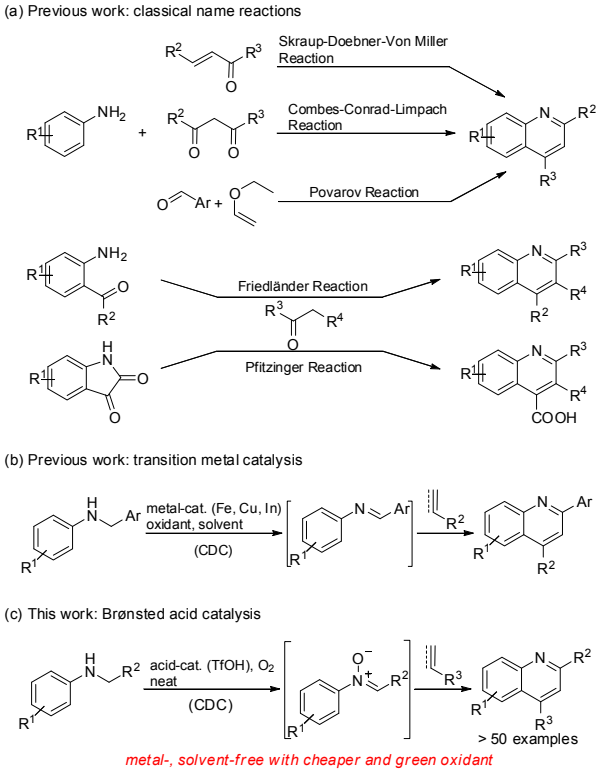
Waqar Ahmed,[a†] Sheng Zhang,[a†] Xiaoqiang Yu,[a] Yoshinori Yamamoto,[a,c] and Ming Bao[a,b,*]

Brønsted acid-catalyzed cyclization reactions of *N*-alkyl anilines with alkynes or alkenes in the presence of oxygen gas as an oxidant under metal- and solvent-free conditions are described. Various quinolinne derivatives are obtained in satisfactory to excellent yields. Different groups, such as methyl, fluoro, chloro, bromo, methoxy, and ester linked on benzene rings, are tolerated under optimized reaction conditions.

Introduction

Quinoline motif has attracted considerable interest due to its potent applications[1] in photoelectric materials[2] and pharmaceuticals[3], including antimalarial, antibacterial, antileishmanial, anti-inflammatory, and insecticidal agent.[4] Many methods have been established for the conversion of anilines to various substituted quinolines in the presence of different reaction partners since the late 1800s. Various classical name reactions are identified for quinoline synthesis; these reactions include Skraup, Doebner–von Miller, Combes, Conrad–Limpach, Povarov, Friedländer, and Pfitzinger reactions (Scheme 1a).[5] These methods either use adverse conditions, such as high temperature of approximately 200 °C, or hazardous reagents in stoichiometric amount, which adversely affect the environment-friendly chemistry and atom economy. Moreover, some methods rely on reagents for quinoline synthesis that needs additional steps.

Recently, transition metal-catalyzed coupling reactions have been used as potent tools for the synthesis of heterocyclic compounds, especially quinolines[6]. Fe, Cu, In, Bi, Pd, and Ag salts have been used as catalysts for quinoline synthesis. Furthermore, a transition-metal-catalyzed quinoline synthesis uses *N*-alkyl anilines and arylacetylenes or arylethylenes through direct cross-dehydrogenative coupling (CDC) of C–H bond to construct new C–C bond (Scheme 1b).[7] Given its high atom economy and environment-friendly nature, CDC reaction has frequently been used to construct quinoline motif. Liu[8] and Mancheño[9] groups independently reported iron-catalyzed synthesis of quinolines using either *N*-benzylanilines or *N*-aryl glycine esters and arylacetylenes or



Scheme 1. Various approaches for the synthesis of quinolines.

arylethylenes as reaction partners in the presence of di-tertiary-butyl peroxide or TEMPO oxoammonium salt as an oxidant in stoichiometric amount through direct CDC method. Liu and coworkers recently reported about copper-catalyzed synthesis of quinolines via CDC reaction of *N*-aryl glycine esters with olefins in the presence of either $K_2S_2O_8$ (in stoichiometric amount) or *N*-hydroxyphthalimide combined with O_2 as oxidants.[10] Jia and Wang revealed that the CDC reaction of *N*-aryl glycine esters with olefins or arylacetylene for synthesis of quinolines can be promoted in the presence of catalytic $InCl_3$

[a] *State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian 116023, China. Fax: +86-0411-84986181; Tel: +86-0411-84986180; E-mail: mingbao@dlut.edu.cn.*
[b] *School of Petroleum and Chemical Engineering, Dalian University of Technology, Panjin 124221, China.*
[c] *WPI-AIMR (WPI-Advanced Institute for Materials Research), Tohoku University, Sendai 980-8577, Japan and Research Organization of Science and Technology, Ritsumeikan University, Kusatsu, Shiga 525-8577, Japan.*
[†] *These authors contributed equally to this work.*
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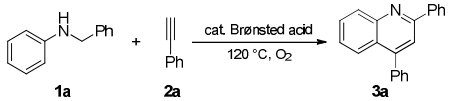
and tris(4-bromophenyl)ammonium hexachloroantimonate ($TBPA^{+\bullet}$) using O_2 as the terminal oxidant.[11] Quinoline synthesis via transition-metal-catalyzed CDC reaction commonly requires the use of costly inorganic or organic oxidants. Notably, Jia and coworkers recently succeeded on the metal-free CDC reaction of *N*-benzylanilines with arylethylenes for quinoline synthesis in the presence of catalytic radical cation salt, namely, $TBPA^{+\bullet}$ using O_2 as the oxidant.[12]

Although these existing methods can provide easy access to quinoline derivatives, the development of remarkably efficient, environment-friendly, and economic organic synthetic process is still desirable. In the course of our research on the development of efficient methods for heterocyclic synthesis[13], we found that quinolines can readily be obtained from the Brønsted acid-catalyzed metal- and solvent-free CDC reaction of *N*-alkyl anilines with arylacetylenes or arylethylenes using O_2 as the oxidant (Scheme 1c). Results are reported in this paper.

Results and discussion

Table 1. Optimization of Reaction Conditions[a]



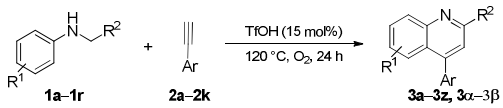
1a **2a** **3a**

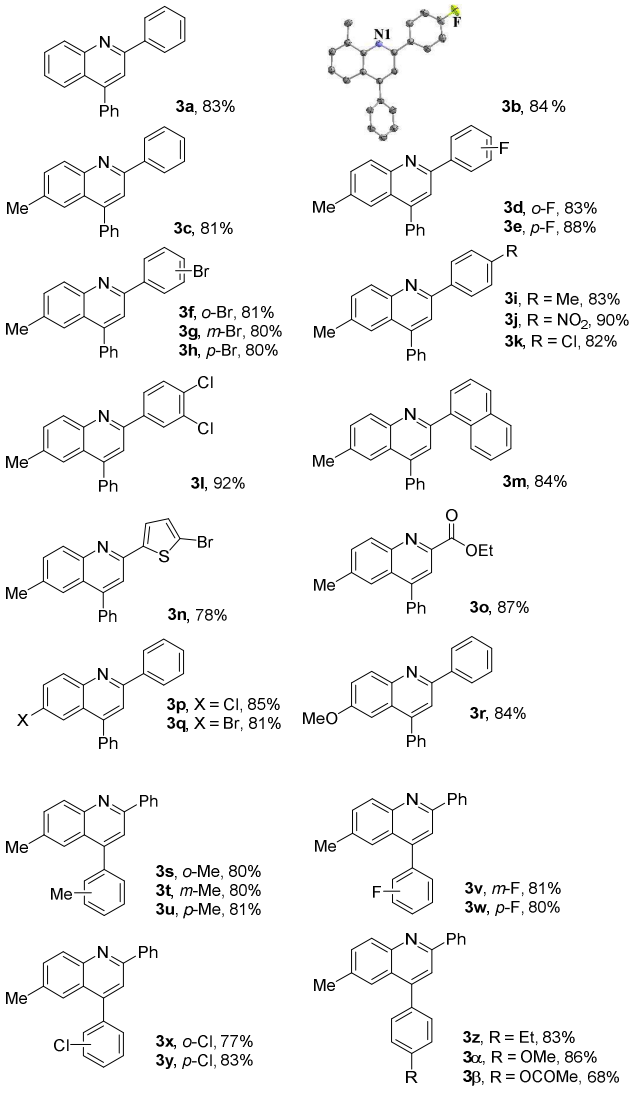
entry	acid cat.	solvent	O_2	time (h)	yield (%)[b]
1	TFA	DCE	O_2 in air	15	48
2	PTSA	DCE	O_2 in air	15	45
3	CH_3SO_3H	DCE	O_2 in air	15	40
4	BzOH	DCE	O_2 in air	15	NR[c]
5	H_2SO_4	DCE	O_2 in air	15	trace
6	TfOH	DCE	O_2 in air	15	57
7	TfOH	toluene	O_2 in air	15	43
8	TfOH	1,4-dioxane	O_2 in air	15	54
9	TfOH	DMF	O_2 in air	15	43
10	TfOH	CH_3CN	O_2 in air	15	NR[c]
11	TfOH	DCE	O_2 balloon	15	62
12	TfOH	none	O_2 balloon	15	77
13	TfOH	none	O_2 balloon	24	83
14	TfOH	none	O_2 balloon	24	76[d]
15	TfOH	none	O_2 balloon	24	71[e]
16	TfOH	none	N_2	24	NR[c]
17	none	none	O_2 balloon	24	NR[c]

[a] Reaction conditions: *N*-benzyl aniline (**1a**, 0.2 mmol, 36.7 mg), phenylacetylene (**2a**, 1.0 mmol, 102.1 mg), Brønsted acid (15 mol%), and solvent (2.0 mL), 120 °C. [b] Isolated yield. [c] No reaction; the starting materials were recovered. [d] The reaction occurred at 110 °C. [e] The reaction was performed in the presence of 10 mol% TfOH.

N-Benzyl aniline (**1a**) cyclization with phenylacetylene (**2a**) was selected as a model to optimize the reaction conditions. Results are shown in Table 1. Brønsted acid catalysts, including trifluoroacetic acid (TFA), *p*-toluene sulfonic acid (PTSA), methanesulfonic acid, benzoic acid (BzOH) acid, sulphuric acid (H_2SO_4) and trifluoromethanesulfonic acid (TfOH), were initially screened in 1,2-dichloroethane (DCE) under air at 120 °C for 15 h. A relatively high yield (57%) of quinoline **3a** was obtained when TfOH was used as the catalyst (entry 6 vs. entries 1–5). The solvent was subsequently screened, but the **3a** yield could not be improved (entry 6 vs. entries 7–10).

Scheme 2. Synthesis of Quinolines from *N*-alkyl anilines and Alkynes[a]





Reaction conditions: *N*-alkyl aniline (**1**, 0.2 mmol), alkyne (**2**, 1.0 mmol), and TfOH (2.7 μL, 0.03 mmol, 15 mol%) at 120 °C for 24 h under O_2 atmosphere. [a]All yields are of isolated materials.

Additionally, an increased **3a** yield (62%) was observed when the model reaction was performed under pure oxygen atmosphere (O_2 balloon) in DCE for 15 h (entry 11 vs. entry 6). The further increased yield was observed under solvent-free conditions (entry 12, 77%). The highest **3a** yield was finally obtained when the model reaction was treated for prolonged time (entry 13, 24 h, 83%). The **3a** yield decreased with the reduced reaction temperature and acid catalyst loading (entries 14 and 15). No reaction was observed in the absence

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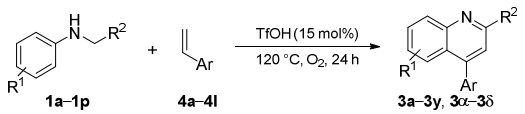
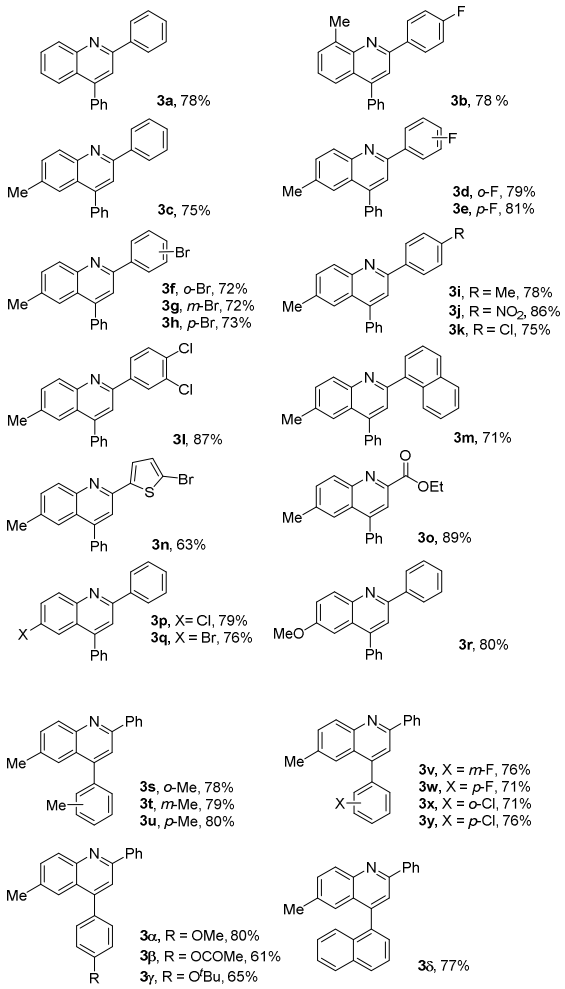
of oxygen gas or acid catalyst (entries 16 and 17). Therefore, we performed the subsequent reactions of the *N*-alkyl anilines with arylacetylenes or arylethylenes in the presence of TfOH as a catalyst at 120 °C under solvent-free conditions for 24 h. During optimization, starting materials were recovered along with product in case of low yield (table 1).

On the basis of the optimized reaction conditions, we explored the scope and limitation of this type of cyclization reaction. Results are summarized in Scheme 2. Initially, alkyne **2a** was used as a reaction partner to investigate the scope of *N*-alkyl anilines. As described in Table 1, the desired product **3a** was obtained in 83% yield. The reactions of *N*-(4-fluorobenzyl)-2- methylaniline (**1b**) and *N*-benzyl-4-methylaniline (**1c**) proceeded well to produce the corresponding quinoline products **3b** and **3c** in good yields (84% and 81%, respectively). Good to excellent yields were obtained in the reactions of *N*-benzyl-4-methylanilines **1d–1k** bearing a substituent (F, Br, Me, NO_2, or Cl) on *ortho*-, *meta*-, or *para*-position of benzyl group (**1d–1k**, 80%–90%). The reactions of *N*-(3,4-dichlorobenzyl)-4-methylaniline (**1l**), 4-methyl-*N*-(naphthalen-1-ylmethyl)aniline (**1m**), *N*-((5-bromothiophen-2-yl)methyl)-4-methylaniline (**1n**), and ethyl 2-(*p*-tolylamino)acetate (**1o**) also proceeded well and produced quinoline products **3l–3o** in 78%–92% yields. Moreover, the reaction of *N*-benzylanilines **1p–1r** having substituent (Cl, Br, and MeO) at *para*-position of aniline ring also produced corresponding quinoline products **3p–3r** in 81%–85% yields. Afterward, the reactions of *N*-benzyl-4-methylaniline (**1c**) with various arylacetylenes **2b–2k** were examined to explore the scope of alkyne substrates. Quinolines **3s–3β** were obtained in 68%–86% yields. These results indicated that different groups, such as methyl, fluoro, chloro, bromo, methoxy, nitro, and ester linked on benzene rings, were tolerated under the optimized reaction conditions. The notably maintained Br and Cl atoms in the structures of products should make the products considerably useful in organic transformation.

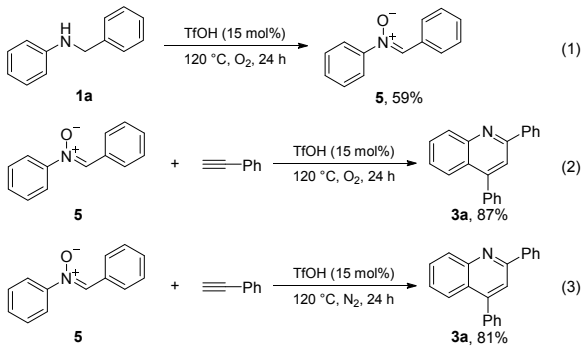
We found that arylethylenes, instead of arylacetylenes, can be used for quinoline synthesis under the optimized reaction conditions. Results are summarized in Scheme 3. The similar good results were obtained, as shown in Scheme 2. Quinoline products **3a–3y** and **3α–3δ** were obtained in satisfactory to good yields (61%–89%).

Scheme 3. Synthesis of Quinolines from *N*-substituted Arylamines and Alkenes[a]





Reaction conditions: *N*-substituted arylamine (**1**, 0.2 mmol), alkene (**4**, 1.0 mmol), and TfOH (2.7 μL, 0.03 mmol, 15 mol%) at 120 °C for 24 h under O_2 atmosphere. [a]All yields are of isolated materials.



Scheme 4. Control experiments.

Control experiments were conducted to gain insights into the mechanism of this type of cyclization reaction (Scheme 4). An imine-*N*-oxide **5** (59%) was obtained when the *N*-benzyl aniline substrate **1a** was treated solely under the optimized reaction conditions (Eq. 1). Subsequently, imine-*N*-oxide **5** was used as a starting material to react with phenylacetylene under the standard conditions; 87% of quinoline **3a** was obtained (Eq. 2). The quinoline **3a** was also obtained in good yield (81%) when the imine-*N*-oxide **5** was treated with phenylacetylene under N_2 atmosphere (Eq. 3). These results suggested that the current cyclization reaction might involve imine-*N*-oxide intermediate.

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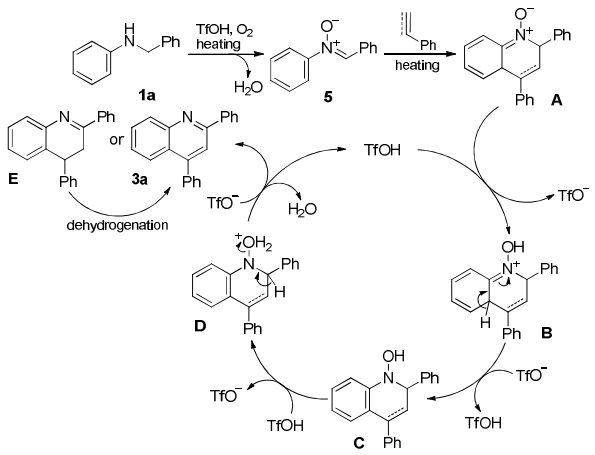

Scheme 5. Proposed mechanism.

On the basis of our experimental outcomes and previous reports,[8,14] a plausible catalytic cycle is proposed to account for the present Brønsted acid-catalyzed cyclization reaction (Scheme 5). *N*-Benzylaniline substrate **1a** was oxidized in the presence of O_2 and acid to produce imine-*N*-oxide **5**. The imine-*N*-oxide **5** subsequently underwent Diels–Alder-type cyclization reaction in the presence of phenylacetylene or styrene as a dienophile at heating conditions to generate an imine-*N*-oxide intermediate **A**. The intermediate **A** abstracted a proton from TfOH to form intermediate **B**, which underwent rearomatization reaction to produce intermediate **C**. Protonation of *N*-OH in intermediate **C** occurred to generate intermediate **D**. Dehydration and aromatization of intermediate **D** finally occurred to yield quinoline product **3a** (generated from phenylacetylene) or an intermediate **E** (generated from styrene) and regenerated acid catalyst TfOH. The intermediate **E** subsequently underwent dehydrogenation reaction in the presence of O_2 gas at heating conditions to generate the target product **3a**.

Conclusions

A convenient and efficient method for quinoline synthesis was developed using simple and readily available *N*-alkyl anilines and arylacetylenes or arylethylenes as the starting materials. The Brønsted acid-catalyzed metal- and solvent-free cyclization proceeded well under O_2 atmosphere to furnish quinolines in satisfactory to excellent yields. The widespread availability of the starting materials, cheap and environment-friendly oxidant, and experimental simplicity make the present methodology considerably useful in organic synthesis.

Experimental

General Information

The reactions were performed in clean, oven-dried reactors fitted with air-tight stoppers. All the chemicals were used without further purification. The solvents were used after drying according to the given procedure. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker Avance II-400 spectrometer (400 MHz for 1H, 100 MHz for ^{13}C) or a Varian Inova-500 spectrometer (500 MHz for 1H, 125 MHz for 13C); $CDCl_3$ and TMS were used as solvent and internal standard, respectively. The chemical shifts are reported in ppm downfield (δ) from TMS, the coupling constants *J* are given in Hz. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High-resolution mass spectra were recorded on either a Q-TOF mass spectrometry or a GC-TOF mass spectrometry. TLC was used with SiO_2 (silica gel 60 F254, Merck) as stationary phase. Spots were viewed under UV light. Flash column chromatography was performed with SiO_2 (80 mesh) as stationary phase.

General Procedure for the Synthesis of Quinolines 3

N-substituted arylamines **1a–1r** (0.20 mmol), **2a** phenylacetylenes (110 µL, 1 mmol, 5 equiv.), or styrenes (115 µL, 1 mmol, 5 equiv.) were added to a clean, oven-dried reactor and stirred for 1 min. Triflouromethanesulfonic acid (2.7 µL, 0.03 mmol, 15 mol%) was then added. Oxygen was purged directly from the cylinder such that the environment was completely saturated with it for 24 h at 120 °C. Afterward, the reaction mixture was purified by flash column chromatography on silica gel (eluent: petroleum ether/DCM = 8:2) to yield quinoline **3**.

Procedure for synthesis of Imine-oxide 5

1a was added into an oven-dried 100 mL round bottom flask, (366.4 mg, 2.0 mmol). Triflouromethanesulfonic acid (27.0 µL, 0.3 mmol) was also added to the above flask after heating, until **1a** was melted. Oxygen was purged directly from the cylinder at 120 °C for 24 h. The acid catalyst and water generated were evaporated on rotary. The crude mixture was dissolved in diethyl ether:DCM mixture (9.5:0.5), washed two times with K_2CO_3 solution and subsequently with distilled water, and dried over anhydrous Na_2SO_4. The solvent was evaporated, which resulted in yellow feathery solid. This solid was washed with ice-cold diethyl ether, which yielded white crystals of titled compound.

Acknowledgements

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Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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Graphical Abstract

Brønsted Acid-Catalyzed Metal- and Solvent-Free Quinoline Synthesis from *N*-alkyl Anilines and Alkynes or Alkenes

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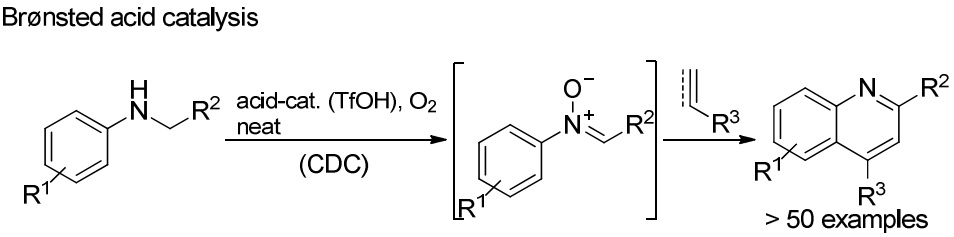

A convenient and efficient method for quinoline synthesis was developed using simple and readily available starting materials under green conditions.