A green, solvent-free one-pot synthesis of disubstituted quinolines via A^3-coupling using 1 mol% $FeCl_3$

By

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School of Chemistry and Physics

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UNIVERSITY OF
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Thesis Declaration

The experimental work described in this thesis was carried out in the School of Chemistry and Physics, University of KwaZulu-Natal in Pietermaritzburg, South Africa under the supervision of Dr. Vineet Jeena. The studies represent original work by the author and have not been submitted in candidature for any other degree.

Signed ……. S. Naidoo (Candidate)

I hereby certify that the above statement is correct.

Signed……. Dr. Vineet Jeena (Supervisor)

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Publication Declaration

The experimental work discussed in the publication as well as the writing of the publications was performed by myself and was carried out within the School of Chemistry and Physics, University of KwaZulu-Natal, Pietermaritzburg, under the supervision of Dr. Vineet Jeena.

A green, solvent-free one-pot synthesis of disubstituted quinolines via A^3-coupling using 1 mol% $FeCl_3$, Shivani Naidoo, Vineet Jeena, article in preparation.

Signed…….. S. Naidoo (Candidate)

I hereby certify that the above statement is correct.

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Contents

CHAPTER 3: EXPERIMENTAL

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Abbreviations

AChE	Acetylcholinesterase
AD	Alzheimer's disease
Ag(OTf)	Silver(I) triflate
Ag^{I}-K10	Silver(I)-K10
$AuBr_3$	Gold(III) bromide
AuCl	Gold(I) chloride
$AuCl_3$	Gold(III) chloride
Aβ	β-amyloid
BMI	Body mass index
CH_3NO_2	Nitromethane
CNS	Central nervous system
$Cu(OTf)_2$	Copper(II) triflate
CuBr	Copper(I) bromide
CuCl	Copper(I) chloride
DALYs	Disability-adjusted life-years
DCE	Dichloroethane
DCM	Dichloromethane
DMF	Dimethyl formamide
DPP	Diphenyl phosphate
DS	Down syndrome
DSCR	Down syndrome critical region
DYRK1A	Dual-specificity tyrosine phosphorylation-regulated kinase 1A
$Fe(OTf)_3$	Iron(III) triflate
Fe_3O_4	Iron(II, III) oxide
$FeCl_3$	Iron(III) chloride
GC-MS	Gas chromatography- mass spectroscopy
H_2SO_4	Sulfuric acid
HCl	Hydrochloric acid

$HClO_4$	Perchloric acid
IR	Infrared
$K_5CoW_{12}O_{40}.3H_2O$	Potassium dodecatungstocobaltate trihydrate
*K*a	Acid dissociation constant
KOH	Potassium hydroxide
m/z	Mass to charge ratio
M+	Molecular ion
MAOS	Microwave assisted organic synthesis
MCH	Melanin concentrating hormone
MDR-TB	Multi-drug resistant TB
MeOH	Methanol
Mont.K-10	Montmorillonite K-10
NaOH	Sodium hydroxide
NMR	Nuclear magnetic resonance
PBI	Perylene bisimide
$Pd(dba)_2$	Tris(dibenzylideneacetone) dipalladium
$Pd(OAc)_2$	Palladium(II) acetate
PEG-2000	Polyethylene glycol 2000
PPh_4	Tetraphenylphosphonium
$RuCl_3$	Ruthenium(III) chloride
SiO_2	Silicon dioxide
TB	Tuberculosis
THAB	Tetrahexylammonium bromide
THF	Tetrahydrofuran
TLC	Thin layer chromatography
XDR-TB	Extremely-drug resistant TB
$Yb(Pfb)_3$	Ytterbium pentafluorobenzoate

Abstract

Quinoline derivatives are important compounds due to their broad range of applications in medicinal, synthetic and industrial chemistry. However, current synthetic techniques such as the classical Skraup, Döebner-Miller, Friedländer and Pfitzinger reactions have numerous drawbacks such as the use of expensive reagents/catalysts, strong acidic conditions, long reaction times, high temperatures and the use of environmentally unfriendly solvents. As a result, the development of new synthetic routes to access quinoline derivatives is vital. One such approach is the coupling between an aldehyde, amine and alkyne, known as A^3-coupling, which results in the formation of propargylamine, which has been well documented in the literature. The synthesized propargylamines have multiple reaction sites and in the presence of a Lewis acid catalyst results in the formation of quinoline derivatives.

In this research project, a multitude of catalysts were tested under various conditions for the formation of 2,4-disubstituted quinolines. As part of a test reaction an optimized system was developed by using just 1 mol% $FeCl_3$ to obtain 2,4-diphenylquinoline, in an excellent yield (91%), via microwave irradiation under solvent-free conditions. The aldehyde, amine and alkyne were varied to synthesize a series of 2,4-disubstituted quinolines, in good to excellent yields of 55-95%. To compliment the studies above, a preliminary investigation was conducted, where the catalyst loading was further decreased to 0.5 mol% producing the desired product in a satisfactory yield (73%). The use of low catalyst loading, solvent-free conditions, short reaction times, good to excellent yields, no ligands or additives and the inexpensive nature of $FeCl_3$, makes this an attractive route towards the synthesis of quinoline derivatives.

CHAPTER 1

Introduction

1.1 What is quinoline?

Quinoline, also known as 1-*aza*naphthaline, 1-benzazine or benzo-[*p*]-pyridine, is an important *N*-based heterocyclic structure, that is characterized by a benzene ring fused to a pyridine ring (Fig. 1),[1] that has gained the interest of researchers, due to its' wide range of biological applications such as antimalarial, antibacterial and immune depressing activities to name a few.[2],[3]

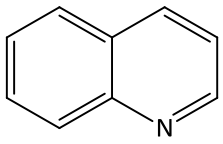


Figure 1: Structure of quinoline

Quinoline was first extracted from coal tar in 1834 by German analytical chemist, Friedlaub Ferdinand Runge,[4] when he distilled coal tar, which was a by-product of gas liquor, and treated it with hydrochloric acid.[5] He discovered phenol, aniline and pyrrole and a mixture of compounds which he later found to be quinoline, isoquinoline and quinaldine.[5] Coal processing, petroleum and shale oil, still remain the primary sources of quinoline.[2],[3]

It has been estimated that roughly 4 tons of quinoline are produced annually, as it serves as a major component for numerous dyes, pesticides and herbicides.[3]

1.2 Biological applications of quinoline derivatives

A large number of studies are carried out on quinolines and their derivatives, as they are used as the 'parent' moiety, to synthesize compounds of medicinal value. These derivatives are endowed with various activity such as; antimalarial, antibacterial, antifungal and immune depressing activity to name a few.[2] Some of the applications of quinoline derivatives are mentioned below.

Obesity is described as a disease in which excess body fat has accumulated such that the health of the individual may be adversely affected.[6] In 2010, it was estimated that obesity caused 3.4 million deaths, 3.9% of years of life lost and 3.8% of disability-adjusted life-years (DALYs).[7] In 2002, the first reported MCH antagonist, was an aminotetralin, T-226296 (Takeda) (Fig. 2).[8]

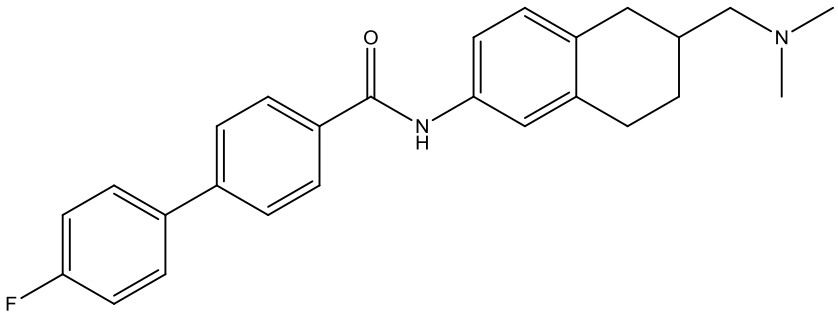


Figure 2: Structure of T-226296 (Takeda)

Based on this structure, Warshakoon *et al.* synthesized compounds bearing a quinoline moiety (Fig. 3) that displayed potent binding abilities to the melanin concentrating hormone (MCH) receptor, these receptors are responsible for the regulation of food intake, energy homeostasis and weight gain.[8],[9]

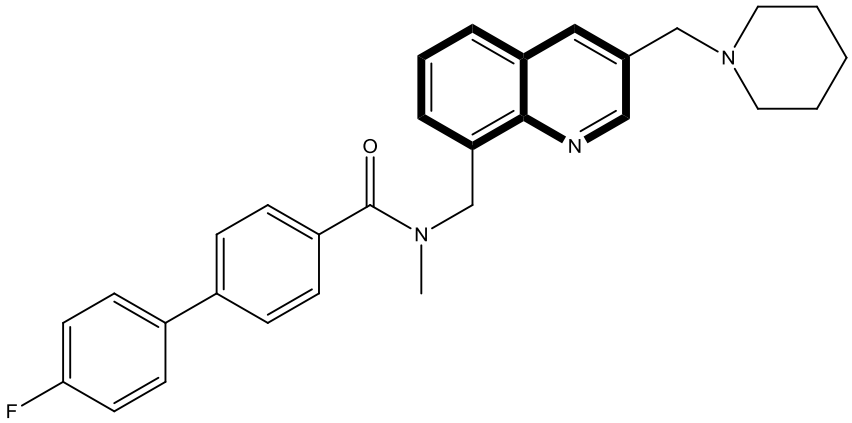


Figure 3: Current antiobesity compound displaying quinoline core.

Tuberculosis (TB) is a contagious disease caused largely by *Mycobacterium tuberculosis,*[10],[11] and is largely responsible for the deaths of 1.7 million people annually, as reported in 2010.[12] Recently, the strains of multi-drug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB) has emerged.[12],[13] MDR-TB, are strains that are resistant to the first-line anti-TB drugs such as isoniazid, rifampicin and pyrazinamide to name a few.[10],[11],[13] XDR-TB are resistant to first and second-line anti-TB drugs.[10] An innovative approach to target TB was to use antimalarial drugs, such as mefloquine (Fig. 4), which contains a quinoline core, however, this drug shows limited activity against TB.[11],[14],[15] Franzblau and co-workers showed that manipulation of mefloquine increased activity of the compound, thereby having a greater impact on TB with IC_{50} values of 25.3 nM, 77.9 nM and 128 nM being observed (Fig. 5a, b and c).[16]

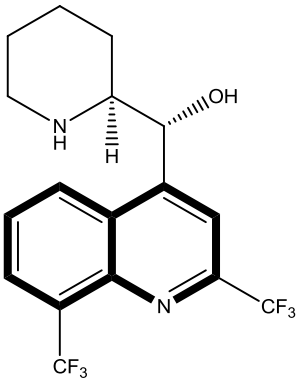
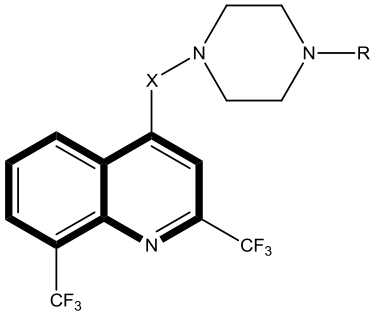


Figure 4: Structure of mefloquine.



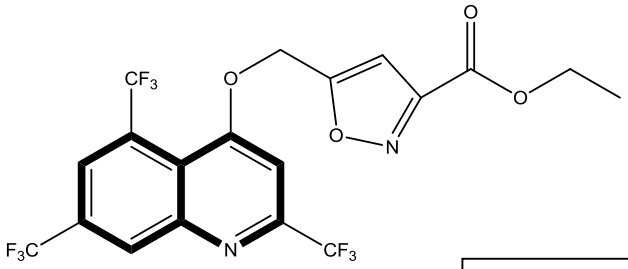
a X = -CH = N, R = $-CH_2-CH=CH_2$

b X = $-CH_2$, R = $-CH_2-CH_2-N(CH_3)_2$

c X = $-CH(OH)-CH_2$, R = $-(CH_2)_3-N(CH_3)_2$

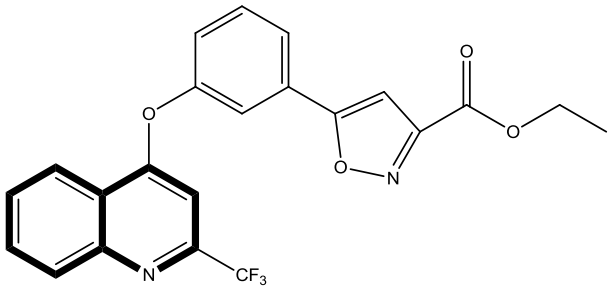
Figure 5: Modifications of the lead compound.

Thereafter, in 2009, Kozikowski and co-workers identified a set of compounds, that were modified from mefloquine although, changes were made to both the quinoline core (Fig. 6) and the side chain linker (Fig. 7).[11] These compounds proved to be more potent than mefloquine, by altering or removing the position of the CF_3 group, and showed promising results as lead TB drugs.[11] IC_{50} values of > 128 nM were observed.



IC_{50} = > 128 nM

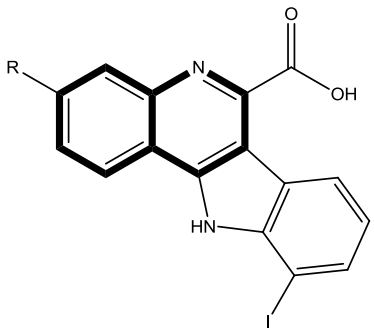
Figure 6: Modification to quinoline core.



IC_{50} = > 128 nM

Figure 7: Modification to side chain linker.

Down syndrome (DS) which occurs in 1 out of 700 live births,[17] is caused by trisomy of chromosome 21 during meiotic cell division.[18] Symptoms of DS include; dysmorphia of the face and skeleton, congenital heart disease and mental disorders.[17] It was found that alterations in the Down syndrome critical region (DSCR) are linked to the above-mentioned symptoms.[18] In this region, overexpression of the protein kinase, DYRK1A (dual-specificity tyrosine phosphorylation-regulated kinase 1A), has been linked to the early inception of Alzheimer's disease (AD) in individuals with DS.[18] Falke and co-workers have recently developed, DYRK1A inhibitors that contain a quinoline core (Fig. 8a and b).[18] These compounds displayed strong activity against DYRK1A, with IC_{50} values of 6 nM and 22 nM (Fig. 8).[18]



a = R = -H

b = R = $-OCH_3$

Figure 8: DYRK1A inhibitors with quinoline core.

One of the five leading causes of death in the world, for persons over the age of 65, is Alzheimer's disease (AD).[19],[20] The disease is a complex neurodegenerative process that occurs in the central nervous system (CNS).[21] A build-up of β-amyloid (Aβ) fragments and twisted fragments of the protein, *tau*, form in dead or dying neurons within the CNS, are some of the many causes that promote AD.[19],[20],[21] Individuals with AD begin to suffer from; disorientation, memory loss, as well as trouble eating, speaking and walking.[19] Research shows that decreasing the amount of Aβ concentrations, could be the lead for possible AD treatment.[21] An approach for AD treatment is to decrease acetylcholinesterase (AChE) inhibitors, thus decreasing the amount of Aβ fragment build up.[20],[21] AChE is responsible for neuronal development and allows for the formation of Aβ fibrils *in vitro*.[21] A common AChE inhibitor containing a quinoline core is, Tacrine (Fig. 9), which was first introduced in 1993.[22] However this drug has displayed liver toxicity, therefore, there are continuous efforts made towards increasing antioxidant properties within Tacrine derivatives.[21]

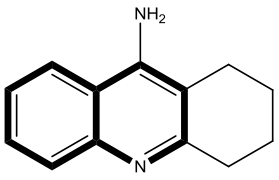
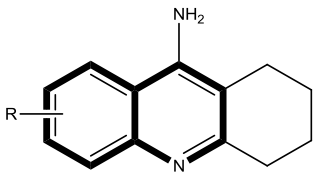


Figure 9: Structure of Tacrine, leading drug in AD treatment.

In 2000, Recanatini and co-workers developed several compounds, based on the structure of tacrine, by adding substituents to the quinoline ring core (Fig. 10a and b).[22] These compounds showed great inhibitory potency towards AChE, with IC_{50} values of 28 nM and 3800 nM.[22]

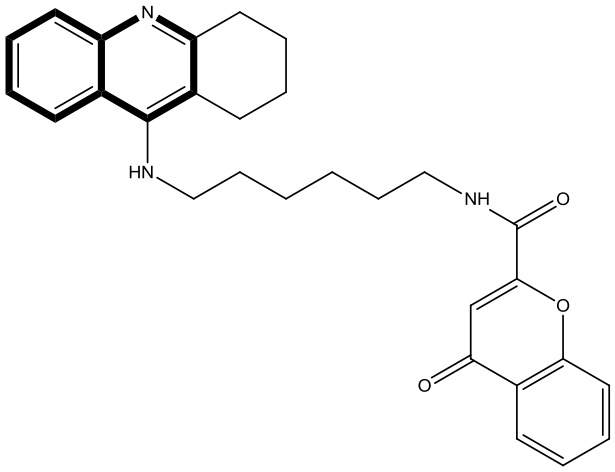


a = R = 7 – NO_2

b = R = 6 – NH_2

Figure 10: Modifications to Tacrine ring.

In 2012, hybrid compounds of Tacrine and flavanoids (Fig. 11) were synthesized by Fernández-Bachiller and co-workers.[21] These compounds proved to be much more potent compared to Tacrine and showed greater inhibition towards AChE.[21] The addition of the flavanoid compound showed great antioxidant properties, as well as easier drug penetration into the CNS.[21] While synthesis of Tacrine derivatives showed great activity against AD, the authors did not report on liver toxicity.



IC_{50} = 150 nM

Figure 11: Hybrid Tacrine and flavanoid compounds.

Estrogens are naturally occurring steroid hormones that apply their biological functions via estrogen receptors (ER).[23] Previously, the biological activity of estrogens were associated with a single receptor, ERα, however the discovery of a second estrogen receptor ERβ, which has a vital role in the development of the mammalian reproductive system, has allowed for further research in determining the differences of the two ERα and ERβ receptor sites.[23] The ligand binding domains (LBD) of ERα and ERβ have a modest variation in the binding cavities thus presenting a great challenge in the development of ER ligands.[24] Vu *et al.* synthesized 2-phenylquinoline compounds that closely resemble genistein (Fig. 12), which is commonly known to be fundamental in its binding to the ER.[24] The 2-phenylquinoline derivatives (Fig. 13a and b)showed high affinity towards the ERβ binding site with IC_{50} values between 3 – 5 nM.[24]

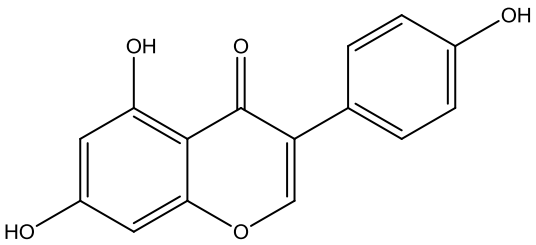
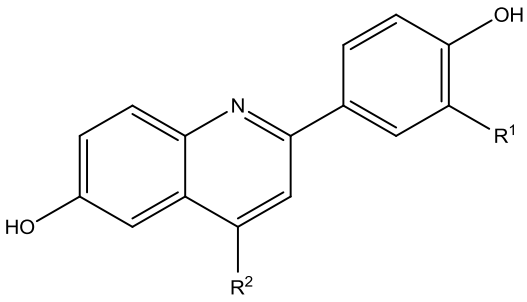


Figure 12: Structure of Genistein which is commonly used for binding to ERβ.



a R^1= H; R^2 = CH=CH_2

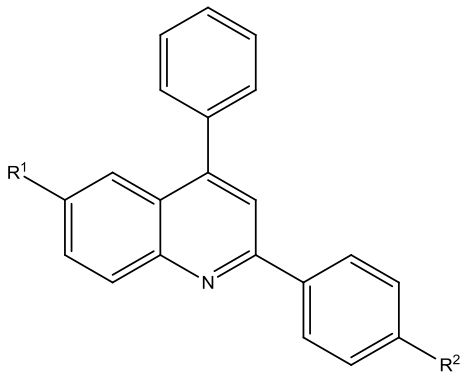
b R^1 = F; R^2 = Br

Figure 13: Current 2-phenylquinoline derivatives which show high affinity towards ERβ binding sites.

It can be seen from the above examples that the quinoline moiety forms the backbone of many complex compounds that display biological activity. There are however simple 2,4-diphenylquinoline compounds which display photophysical properties as explained below.

1.3 Photophysical properties of 2,4-diphenylquinoline

It has been found that organic materials (organic phosphors) possess applications in organic electronics, chemical and biological detection and organic light emitting diodes (OLEDs).[25] However compared to their inorganic counterparts, organic phosphors are still deemed inefficient this is due to the highly bonded nature of the electrons in the metal-free organic materials.[26] 2,4-Diphenylquinoline derivatives were synthesized via a three component domino sequence using $BF_3.Et_2O$ (10 mol %) as a catalyst.[26] It was found that the diphenylquinoline and the chloro diphenylquinoline compounds (Fig. 14a – c) were strong candidates for the use as blue emitting organic phosphors.[26]



a $R^1 = R^2 = H$

b $R^1 = Cl$, $R^2 = H$

c $R^1 = R^2 = Cl$

Figure 14: Structure of diphenylquinoline used as blue light emitting diodes.

In 2015, Dahule *et. al.* synthesized 6-chloro-2-(4-amino-phenyl)-4-phenylquinoline (Fig. 15) via an acid catalyzed Friedländer condensation reaction using 2-amino-5-chlorobenzophenon and 4-aminoacetophenon.[27] The synthesized polymer showed emission in the blue region which showed promising results for the synthesis of organic devices.[27]

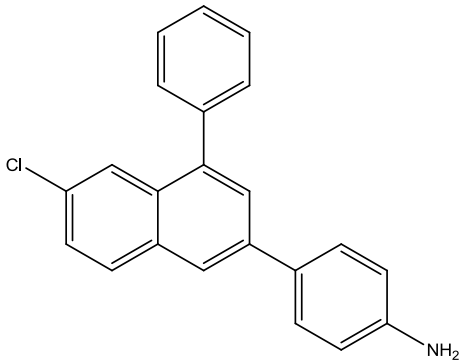


Figure 15: Structure of 6-chloro-2-(4-amino-phenyl)-4-phenylquinoline.

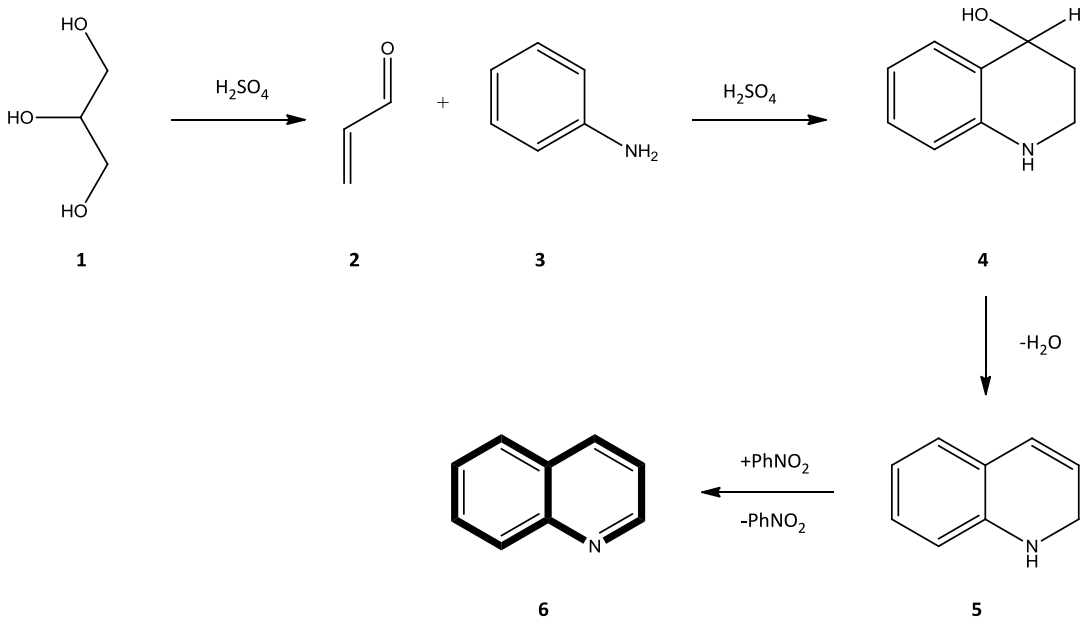
As can be seen from the above mentioned applications, the quinoline moiety forms the backbone of many pharmacologically active and photophysical compounds, therefore, synthetic routes, both traditional and new, to develop quinoline derivatives are of crucial importance. The discussion of the most classical synthetic routes for quinoline derivatives will be explained below.

1.4 Classical synthetic techniques for the synthesis of quinoline derivatives

There are a variety of synthetic techniques described in literature that can be used for the synthesis of quinoline derivatives. Classic synthetic methods that date back to the 1880's include; Skraup, Doebner-Miller, Friedländer and Pfitzinger reactions and these methods are briefly discussed below.

1.3.1 The Skraup quinoline synthesis

The Skraup quinoline synthesis was first reported in 1880 by Czech chemist, Zdenko Hans Skraup.[28] This classic method involves the dehydration of glycerine **1** to acrolein **2**, via the influence of sulfuric acid which is then reacted with aniline **3** via conjugate addition forming an intermediate **4**.[29],[30],[31] Ring closure by dehydration forms 1,2-dihydroquinoline **5**, followed by oxidation to quinoline **6** (Scheme 1).[29],[30],[31] A limitation of this technique results if aniline contains a *meta* substituent, an isomeric mixture of quinoline is thus formed making it difficult to separate.[32]

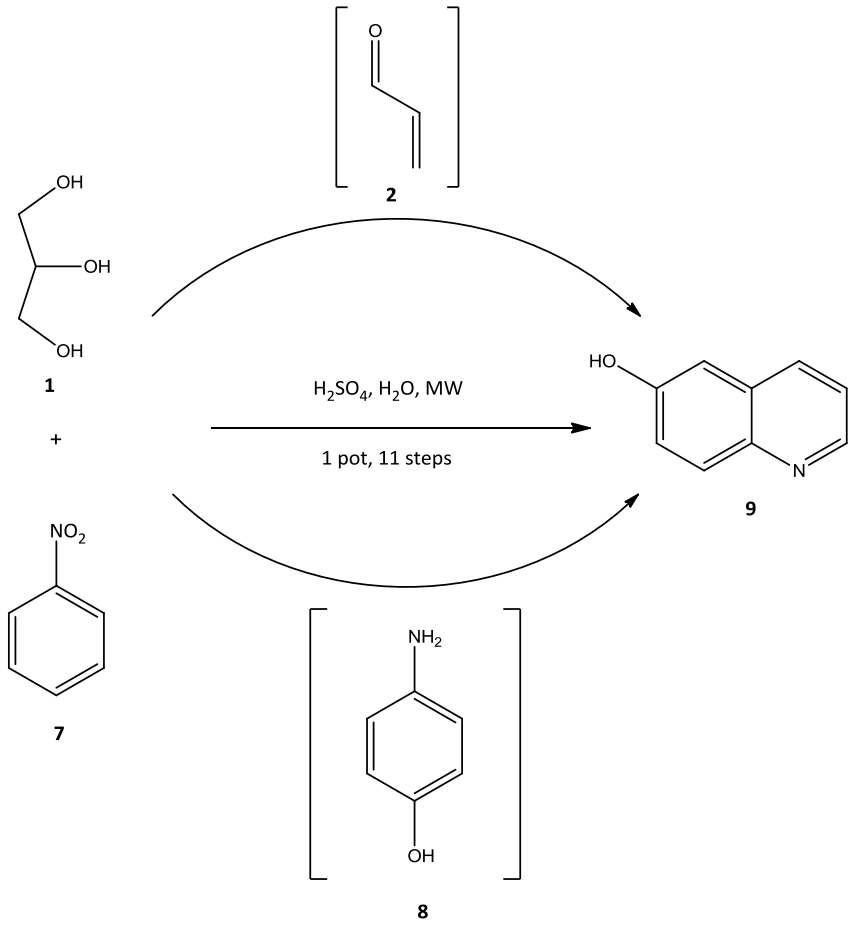


Scheme 1: The Skraup quinoline synthesis.

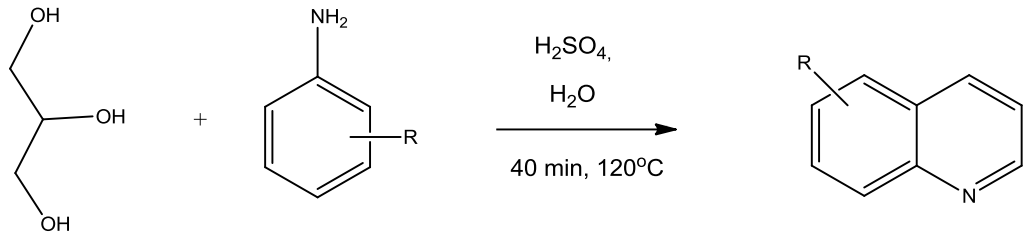
The Skraup synthesis displays several drawbacks such as; high-temperature (> 200°C) and highly acidic conditions which results in low yields being observed.[33]

The Skraup synthesis continues to garner interest into the 21st century, as demonstrated by a report in 2014 (134 years later) by Len and co-workers, who used the methodology as a basis for their current research with modifications such as microwave conditions and the use of

nitrobenzene **7** which is reduced to 4-aminophenol **8** and glycerol **1** which is reduced to acrolein **2** thereafter this is followed by a series of reactions, that the authors explain as a one-pot eleven step reaction, to synthesize 6-hydroxyquinolines **9** with a yield of 77%, using the Skraup synthesis (Scheme 2).[33] The authors were then able to synthesize 5-, 6-, 7-and 8-substituted quinolines **11** from aniline derivatives **10**, using the Skraup synthesis in conjunction with green techniques, such as the addition of water and microwave irradiation. Yields of 5-66% (Table 1) were observed using various aniline derivatives **10** (Scheme 3).[34] Advantages of this technique include the use of microwave irradiation and water as a solvent.



Scheme 2: Len modified Skraup quinoline synthesis.



1 **10** **11**

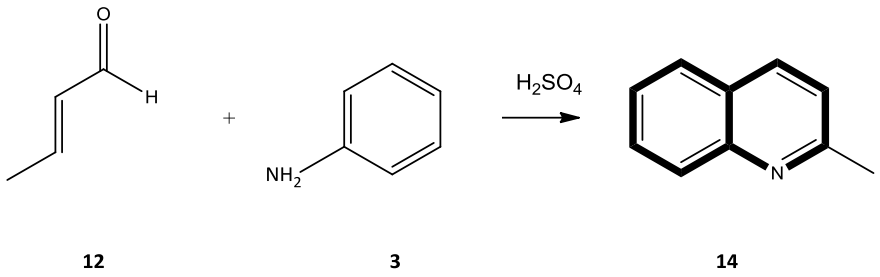
Scheme 3: Len modified Skraup quinoline synthesis.

Table 1: Yields obtained from modified Skraup synthesis.

Compound No.	R	Yield (%)
11a	6 – *i* - prop	66
11b	8 – OCH_3	44
11c	6 – Cl	21
11d	5 – $C(O)CH_3$	5

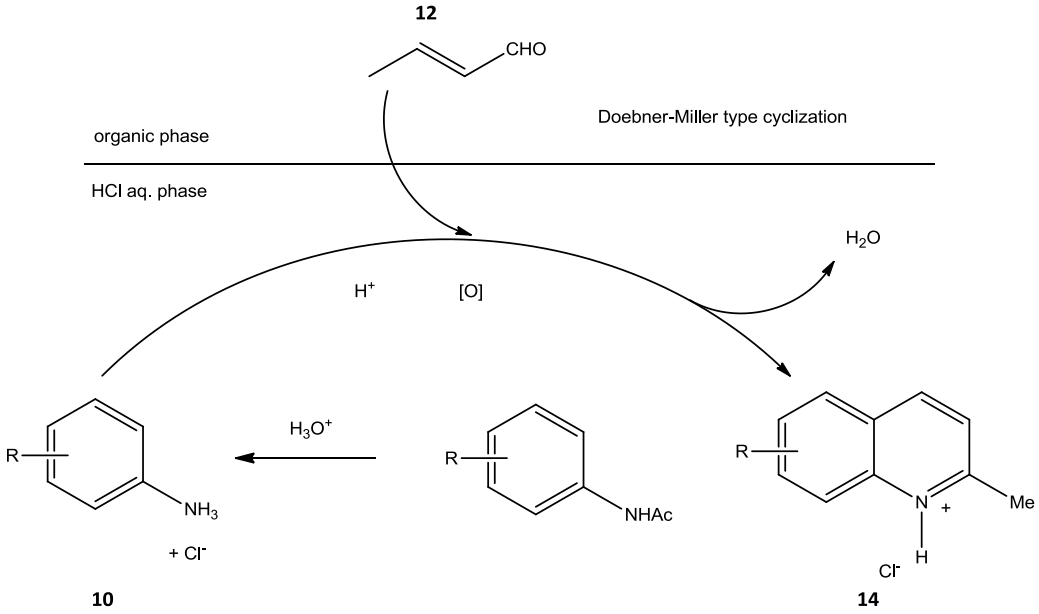
1.3.2 The Döebner-Miller quinoline synthesis

In 1881, based on the Skraup quinoline synthesis, Oscar Döebner and Wilhelm von Miller synthesized quinolines[35] by replacing the previously used glycerol, with α,β-unsaturated aldehydes and ketones **12** and heated with an aromatic amine **3** in the presence of an acid catalyst.[36] The first stage of the Döebner-Miller reaction is a crotonic condensation of two molecules of either an aldehyde or ketone, which results in the formation of an α,β-unsaturated compound (Scheme 4).[31]



Scheme 4: Döebner-Miller quinoline synthesis.

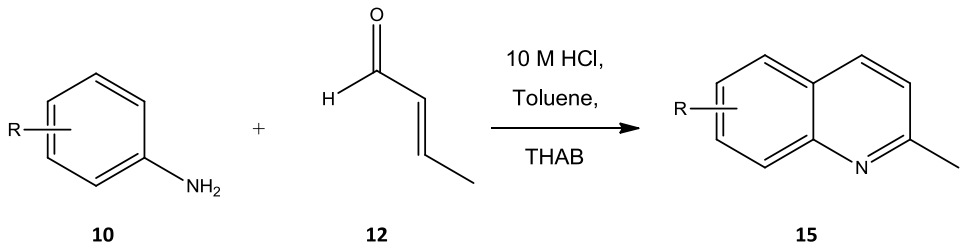
The Döebner-Miller reaction has several drawbacks such as harsh reaction conditions (concentrated hydrochloric acid and sulfuric acid)[31] and isolation of products from complex reaction mixtures which result in poor yields,[37] to name but a few. In 2000, Matsugi and co-workers used a two-phase system, an organic phase and an aqueous acid phase, to synthesize substituted quinolines **14**.[37] The best solvent system was toluene and 6M(!) HCl which afforded yields of 61-80%, after two hours of refluxing (Scheme 5).[37]



Scheme 5: Matsugi modified Döebner-Miller quinoline synthesis.

In 2010, Reynolds and co-workers, developed a biphasic system (10 M HCl and toluene) using crotonaldehyde **12** and various anilines **10**, to synthesize 2-methylquinoline derivatives **15**,

however, poor yields were obtained (7-57%) (Table 2), which highlighted the limitations of the two-phase system (Scheme 6).[38] The development of the two-phase system resulted in yields of 7-57 %, however one of the limitations of this system is that it is substrate specific.



10 **12** **15**

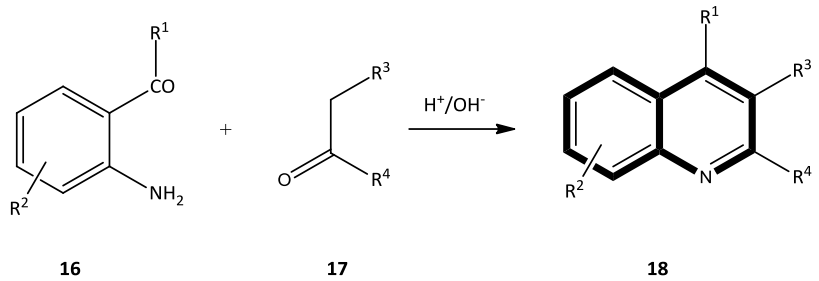
Scheme 6: Reynolds modified Döebner-Miller quinoline synthesis.

Table 2: Yields obtained from modified Döebner-Miller quinoline synthesis.

Compound No.	R	Yield (%)
15a	8 – CH_3	7
15b	6 – Br	16
15c	8 – CO_2H	57

1.3.3. The Friedländer condensation reaction for quinoline synthesis

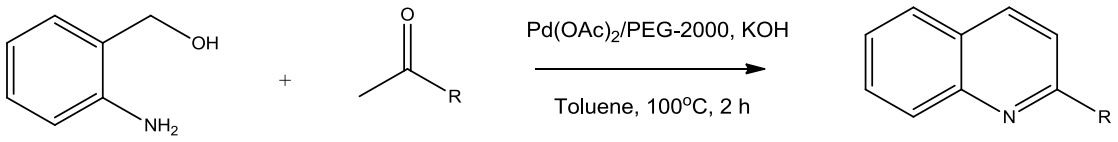
The Friedländer condensation reaction which was first reported by Paul Friedländer in 1882, is a common and convenient route for the synthesis of quinolines **18**.[39] It is a simple condensation of an aromatic *o*-aminoaldehyde or *o*-aminoketone **16** with an aldehyde or ketone **17** containing a methylene group that is alpha to a carbonyl moiety, under basic or acidic conditions (Scheme 7).[40] This synthesis although versatile and simple has one limitation, the preparation and stability of 2-aminobenzaldehyde which is known to undergo self condensation.[41]



16 17 18

Scheme 7: The Friedländer for quinoline synthesis.

In 2007, Cho and Ren modified the Friedländer condensation by using secondary alcohols **19** and a palladium catalyst.[42] The catalytic system using $Pd(OAc)_2$ combined with PEG-2000 (polyethyleneglycol) showed superior results of the quinoline derivatives **20** (31-94%).[42] Due to the expensive nature of palladium a tedious, time consuming catalyst recover and reuse studies were undertaken (Scheme 8).[42]

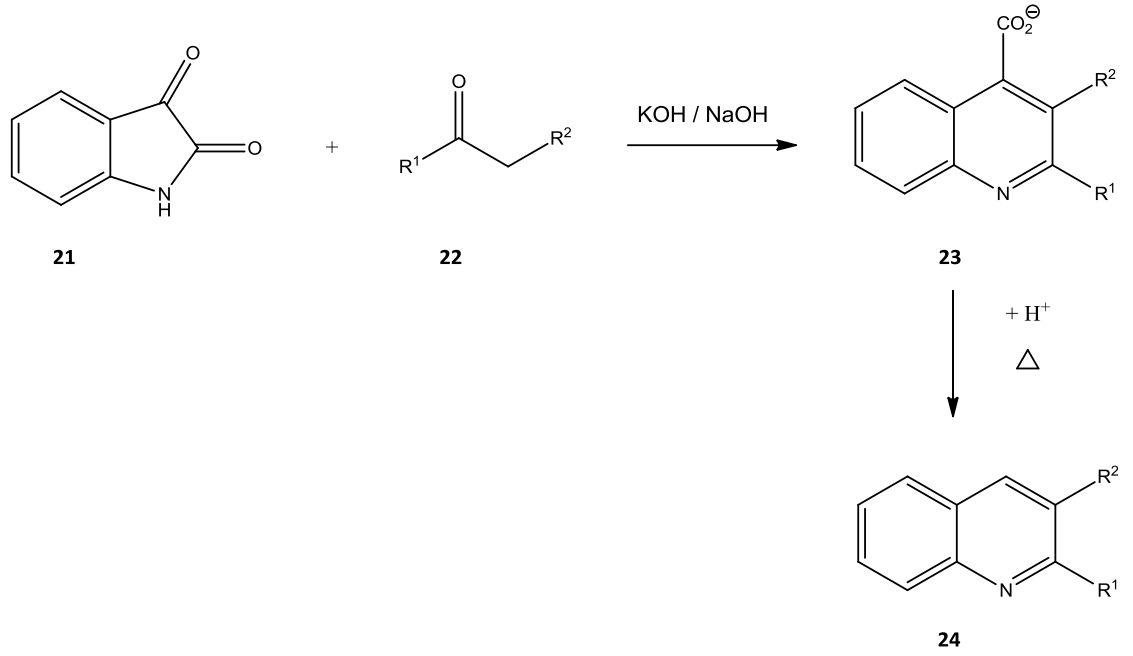


19 17 20

Scheme 8: Modified Friedländer condensation reaction for quinoline synthesis.

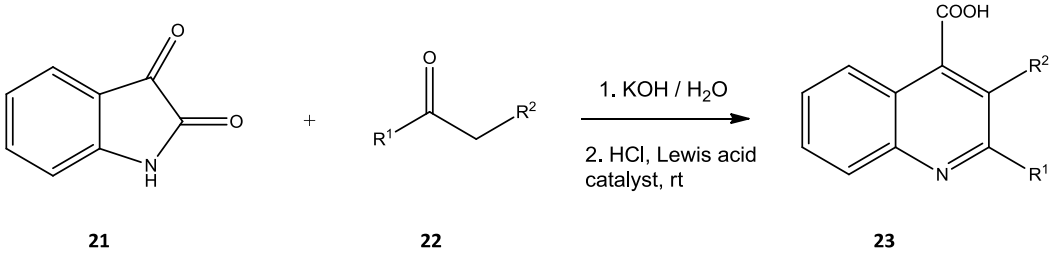
1.3.4. The Pfitzinger quinoline synthesis

This method which was first reported in 1886,[43] is widely used for the synthesis of physiologically active derivatives of substituted quinoline-4-carboxylic acids **23** using isatins **21** and α-methylene carbonyl compounds **22** as substrates.[44],[45] This condensation reaction is usually carried out under basic reaction conditions, followed by addition of an acid, to obtain the desired quinoline compounds **24** (Scheme 9).[44]



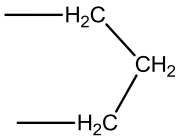
Scheme 9: Pfitzinger quinoline synthesis.

In 2013, Lv *et al.* modified the general Pfitzinger reaction by using water and various Lewis acid catalysts to afford quinolines in low to high yields, (12-95%) (Table 3) .[44] Isatin **21** was hydrolyzed in aqueous potassium hydroxide together with α-methylene carbonyl substrates **22**, which prevented the formation of a resin-like reaction by-product usually observed in typical Pfitzinger reactions, to obtain the substituted quinoline-4-carboxylic acids **23** in mediorce yields (Table 3) (Scheme 10).[44]



Scheme 10: Lv modified Pfitzinger quinoline synthesis.

Table 3: Yields obtained from modified Pfitzinger quinoline synthesis.

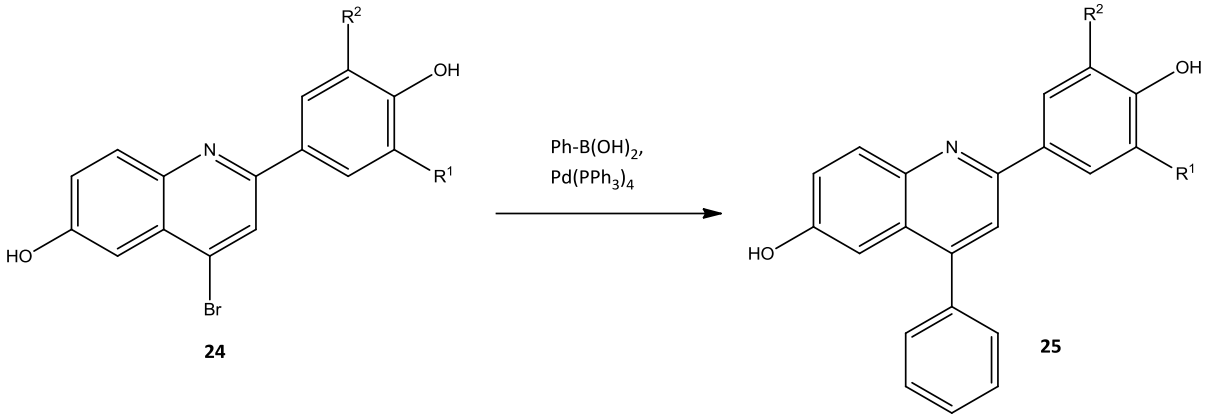
Compound No.	R^1, R^2	Yield (%)
23a	CH_3, CH_3	12
23b	CH_3, $C(O)CH_3$	55
23c		40

From the above examples it can be seen that some of these classical methods are still used in the 21st century for the synthesis of novel quinoline derivatives. However, these methods have numerous drawbacks that include; the use of expensive reagents/catalysts which result in tedious, time consuming recover and reuse methods, strong acidic conditions, long reaction times and high temperatures. As a result, it is imperative to develop alternate methodologies for the synthesis of quinoline derivatives.

1.5 Non-conventional methods for the synthesis of quinoline derivatives

1.5.1 Suzuki cross-coupling reaction

The Suzuki cross-coupling reaction is an extremely powerful tool in the organic synthesis of boranes, boronic esters or boronic acids using aryl halides or triflates in the presence of a palladium catalyst and a base.[46] In 2005, Vu *et. al.* used the Suzuki cross-coupling reaction and coupled 4-bromo-6-hydroxy-2-(substituted phenyl) quinoline **24** with phenylboronic acid and Ph(PP3)4 as a catalyst as well as sodium carbonate in dimethoxyethane to produce 6-hydroxy-2-(substituted phenyl)4-phenylquinoline **25** (Scheme 11).[24],[46]



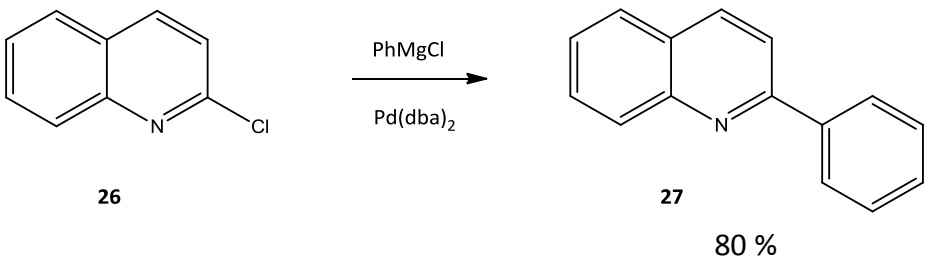
Scheme 11: Suzuki cross-coupling reaction for the synthesis of polysubstituted quinolines.

Table 4: Yields obtained from Suzuki cross-coupling reaction.

Compound No.	R^1, R^2	Yield (%)
25a	H, H	80
25b	F, H	91
25c	F, F	87

1.5.2 Kumada cross-coupling reaction

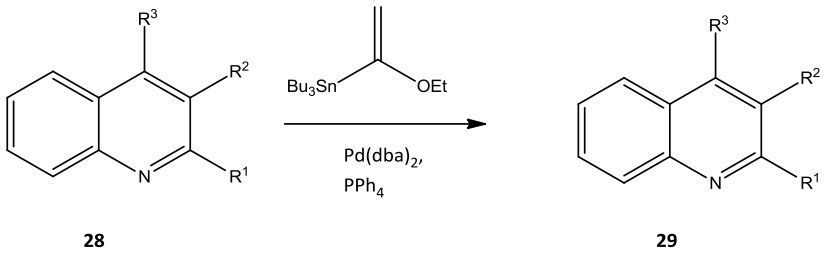
The cross-coupling reaction involves the use of a nickel or palladium-catalyzed coupling of Grignard reagents with aryl/vinyl halides and triflates.[46] Kumada cross-coupling reactions are noted to proceed better at room temperature with quinoline derivatives, due to the soft nature of the palladium metal.[46] Bonnet *et. al.* synthesized a substituted quinoline **27** using lithium tri(quinolyl) magnasate with a halopyridine **26** (Scheme 12).[47]



Scheme 12: Kumada cross-coupling reaction for the synthesis of quinolines.

1.5.3 Stille cross-coupling reaction

The Stille cross-coupling is a reaction of organotin reagents with organic electrophiles catalyzed by palladium and is one of the most commonly used methods for the formation of C-C bonds.[46],[48] In 2001, Legros *et. al.* reacted 2-chloroquinoline **28** with 1-ethoxy-2-tributylstannylester in the presence of $Pd(dba)_2/PPh_4$ to produce 2-(1-acetyl)quinoline **29** (Scheme 13).[49]



28 **29**

Scheme 13: Stille cross-coupling reaction for the synthesis of quinolines.

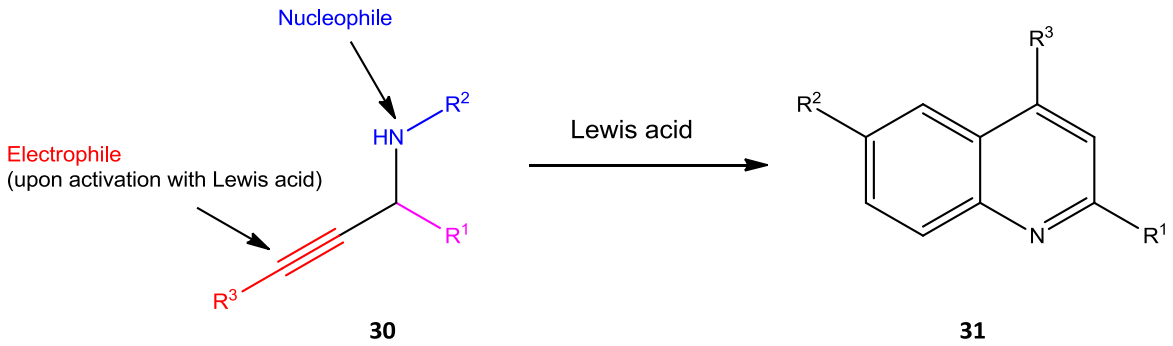
Table 5: Yields obtained from Stille cross-coupling reaction.

Compound No.	**Substrate** R^1, R^2, R^3	**Product** R^1, R^2, R^3	**Yield (%)**
29a	Cl, H, H	$C(O)CH_3$, H, H	68
29b	H, Br, H	H, $C(O)CH_3$, H	88
29c	H, H, Cl	H, H, $C(O)CH_3$	60

1.6 Synthesis based on A^3-coupling

The coupling of an **a**ldehyde, **a**mine and **a**lkyne is referred to as A^3-coupling which is a well known method for the synthesis of quinolines.[50],[51] Due to its' broad and important applications, A^3-coupling has drawn the attention of many researchers worldwide, as it is a key step in the synthesis of various biologically active compounds and natural products.[50]

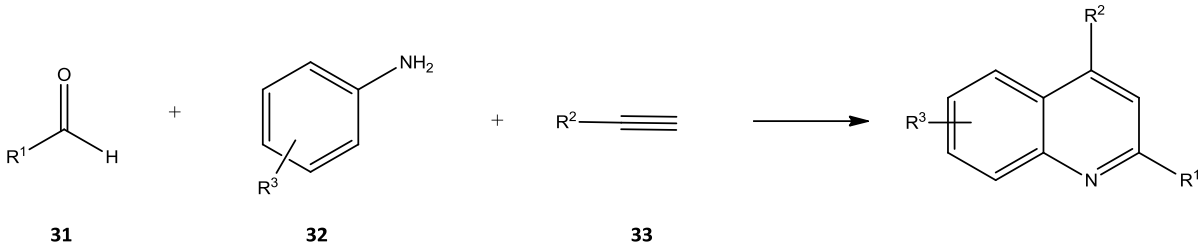
A^3-coupled propargylamines **30** have multiple reaction sites and in the presence of a Lewis acid catalyst, allow for further one-pot reactions to occur (Scheme 14).[50] These tandem, one-pot reactions, permit the formation of at least three new chemical bonds (two C–C and one C–N bonds) and have shown the widespread application in the synthesis of quinoline derivatives **31**.[51]



Scheme 14: A^3-coupled derived propargylamine showing reactive centers.

Recently, the use of metal catalysts have been used for the formation of C—C bonds and the activation of C—H bonds in quinoline synthesis. Discussed below (Scheme 15 and Figure 15) are the metal catalyst systems currently used to synthesize substituted quinolines via A^3-coupling.

Application of metal catalyts in the synthesis of substituted quinolines.



31 **32** **33**

Scheme 15: General scheme for synthesis of substituted quinolines.

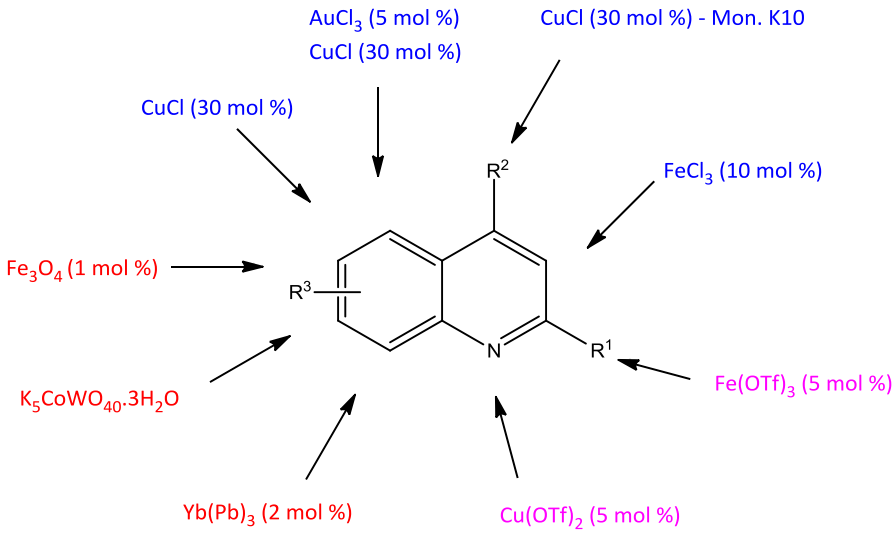


Figure 15: Metal catalysts used in synthesis of substituted quinolines.

1.6.1. Copper salt-catalyzed systems

The first A^3-coupled transition-metal catalyzed quinoline synthesis was reported by Iqbal and co-workers in 2002.[52] The reaction was performed with aromatic aldehydes **31**, arylamines **32** and terminal alkynes **33**, in the presence of 30 mol% CuCl as a catalyst, in dry THF under reflux for 10 hours to produce the desired quinolines (Scheme 15).[52] However, low yields of

quinoline were observed, (34-48%) due to the formation of side products such as the reduced imine and uncyclized propargylamine.[52] Drawbacks of this catalyst system are displayed in Table 6.

In 2008, based on the work above, Wang *et al.* used $AuCl_3$ and CuBr as a bimetallic catalyst system.[53] Various aldehydes **31**, amines **32** and alkynes **33** were reacted in the presence of 5 mol% $AuCl_3$ and 30 mol% CuBr in MeOH.[53] The reaction was left to stir overnight at room temperature under a nitrogen atmosphere to afford the disubstituted quinoline derivatives (Scheme 15) in moderate to good yields, (55-87%).[53] It was observed that the addition of the $AuCl_3$ allowed for greater cyclization of the propargylamines into quinolines.[53] Drawbacks of this catalyst system are displayed in Table 6.

In 2012, Zhang *et al.* synthesized fluorinated quinolines via A^3-coupling of fluorobenzaldehydes **31**, aniline **32** and phenylacetylene **33** in the presence of 30 mol% CuCl-doped montmorillonite, under microwave irradiation for 3 minutes.[54] This one-pot three-component reaction occurred under atmospheric conditions without the use of a solvent, to produce fluorinated quinolines in moderate to good yields, (61-86%) (Scheme 15).[54] Drawbacks of this catalyst system are displayed in Table 6.

1.6.2. Iron-catalyzed systems

Tu *et al.* then introduced $FeCl_3$ as a Lewis acid catalyst due to its high abundance, low cost and environmentally friendly properties.[55] Substituted aldehydes **31**, amines **32** and alkynes **33** were refluxed in toluene for 24 hours at 110 °C using 10 mol% $FeCl_3$ as a catalyst which resulted in the formation of disubstituted quinolines in moderate to good yields, (56-92%) (Scheme 15).[55] In an attempt to improve the yield and reduce reaction time, Wang and co-workers carried out the above reaction and changed the solvent used from toluene to dichloroethane.[56] A slight improvement of the reaction time, 12 hours, was observed

although the desired quinolines were synthesized in good to excellent yields (81-93%) (Scheme 15).[56] Drawbacks of this catalyst system are mentioned in Table 6.

1.6.3 Metal triflate-catalyzed systems

Recently the scientific community have begun to move away from the use of metal chlorides in A^3-coupled quinoline synthesis as they result in low yields, involve long reaction times and side product formation, and have directed their research towards metal triflates as catalysts in A^3-coupled quinoline synthesis. Compared to metal chlorides, the use of metal triflates has led to:

- Reduced reaction times
- Lower catalyst loading
- Solvent-free conditions
- Increased product yields
- Fewer side product formation

Yao *et al.* continued the trend of using iron sources and reacted various aromatic aldehydes **31**, amines **32** and alkynes **33** in the presence of 5 mol% $Fe(OTf)_3$, under solvent-free conditions at 100 °C.[57] The reaction time was shortened to 3 hours, to produce quinolines in good to excellent yields (69-88%) (Scheme 15).[57] However due to the use of an expensive catalyst, a recover and reuse study had to be undertaken.[57] Drawbacks of this catalyst system are displayed in Table 6.

In 2014, Larsen and Meyet synthesized disubstituted quinolines via A^3-coupling using 5 mol% copper(II) triflate ($Cu(OTf)_2$) under solvent-free conditions (Scheme 15).[58] Both aromatic and aliphatic aldehydes **31** and alkynes **33** were reacted with amines **32** at 80°C or 100°C for 4 hours to produce the desired substituted quinolines in good to excellent yields.[58] Drawbacks of this catalyst system are displayed in Table 6.

The use of metal triflates produced the desired quinolines in good to excellent yields, however, the drawback of using metal triflates as catalysts is that they are extremely expensive and, therefore, a catalyst recover and reuse study had to be employed. Drawbacks of this system are displayed in Table 6.

1.6.4 Miscellaneous-catalyzed systems for A^3-coupling

Wang and co-workers developed a recyclable, rare-earth metal catalyst, ytterbium pentafluorobenzoate ($Yb(Pfb)_3$) for the synthesis of quinoline derivatives.[59] The synthesis of the catalyst was an arduous technique that required the reaction of rare earth metals with pentafluorobenzoic acid and water. The Ytterbium catalyst (2 mol%) was used to promote the reaction of various aldehydes **31**, amines **32** and alkynes **33** under solvent-free conditions for 12 hours to produce the desired substituted quinolines in good to excellent yields (69-96%) (Scheme 15).[59] In addition, a catalyst recover and reuse study had to be applied, due to the cost of the expensive catalyst.[59] Drawbacks of this catalyst system are displayed in Table 6.

Mohammadpoor-Baltork *et al.* synthesized a series of disubstituted quinolines via A^3-coupling using potassium dodecatungstocobaltate trihydrate ($K_5CoW_{12}O_{40}.3H_2O$) as a catalyst.[60] Aromatic aldehydes **31**, amines **32** and alkynes **33** were reacted with 11 mol% $K_5CoW_{12}O_{40}.3H_2O$ under solvent-free microwave irradiation for 10 mins.[60] Disubstituted quinolines were produced in good to excellent yields, (80-98%) (Scheme 15).[60] A catalyst

recover and reuse study was carried out.[60] Drawbacks of this catalyst system are displayed in Table 6.

In 2015, Bhalla *et al.* prepared superparamagnetic Fe_3O_4 nanoparticles that allowed A^3-coupling for the synthesis of propargylamines and tandem intermolecular cyclization reaction for the synthesis of quinolines.[61] The preparation of the Fe_3O_4 nanoparticles is a complex process, as acknowledged by the authors, and required 1 M $FeCl_2$ to be added to a perylene bisimide (PBI) scaffold (previously synthesized) stirred in a mixture of H_2O/THF (3:7, v/v) at room temperature for 4.5 hours.[61] Quinoline derivatives were formed in good to excellent yields (79-92%) after reacting various aldehydes **31**, amines **32** and alkynes **33** with 1 mol% Fe_3O_4 in toluene at 110 °C (Scheme 15).[61] Drawbacks of this catalytic system are displayed in Table 6.

Although the above-mentioned protocols afforded the substituted quinolines in good to excellent yields several drawbacks (summarized in Table 6 below) are still observed such as; a large amount of metal catalyst was used, metal triflates are more expensive compared to metal chlorides, some catalysts were synthesized under long, complicated reaction conditions, catalyst recover and reuse methods would have to be employed and most of the above-mentioned protocols also required long reaction times and the use of chlorinated solvents.

It is, therefore, imperative that new synthetic techniques are employed to alleviate the drawbacks mentioned above.

Table 6: Drawbacks of catalyst systems currently used in A^3-coupling

Entry	Catalyst	Catalyst Loading	Reaction Time	Cost	Recover and Reuse
1	CuCl	×	×	✓	✓
2	$AuCl_3$/CuBr	×	×	×	×
3	CuCl-Mont.	×	✓	✓	✓
4	$FeCl_3$	×	×	✓	✓
5	$Fe(OTf)_3$	✓	✓	×	×
6	$Cu(OTf)_2$	✓	✓	×	×
7	$Yb(Pfb)_3$	✓	×	×	×
8	$K_5CoW_{12}O_{40}.3H_2O$	×	✓	×	×
9	Fe_3O_4	✓	✓	×	×

Key:

- Catalyst loading: ✓- low catalyst loading < 10 mol%

  ×- high catalyst loading > 10 mol%

- Reaction time: ✓- reaction time < 5 hours

  ×- reaction time > 5 hours

- Cost: ✓- inexpensive

  ×- expensive

- Recover and reuse study: ✓- No recover and reuse study conducted

  ×- Recover and reuse study conducted

1.7 The principles of Green Chemistry

Green Chemistry can be defined as " the design of chemical products and processes that reduce or eliminate the use or generation of hazardous substances."[62] In recent years the concern of the chemical industry on human development has become a major issue and has unsurprisingly put an increased amount of pressure on chemists and chemical engineers, to produce greener or more sustainable chemical processes.[62],[63] Many conventional methods of synthesis are very effective, however; they require numerous acids or reagents that are not environmentally friendly, produce a large amount of waste and require long reaction times (*vide supra*).[2] It has therefore become very important to follow methods that are more eco-friendly, use greener solvents such as; water and more "viable green synthetic methods".[64]

The Twelve Principles of Green Chemistry were introduced by Paul Anastas and John Warner in 1998, and they are used as guidelines to achieve green chemistry goals.[65],[66],[67],[68]

1. Prevention: It is better to prevent waste than to treat or clean up waste after it has been created.

2. **Atom economy:** Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. Less hazardous chemical syntheses: Synthetic methods should be designed to use and generate substances that possess little or no toxicity to the human health and the environment.

4. Designing safer chemicals: Chemical products should be designed to effect their desired function while minimizing toxicity.

5. Safer solvents and auxiliaries: The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible.

6. Design for energy efficiency: Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. Use of renewable feedstocks: A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. Reduce derivatives: Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/ chemical processes) should be minimized or avoided if possible because such steps require additional reagents and can generate waste.

9. Catalysis: Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. Design for degradation: Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. Real-time analysis for pollution prevention: Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. Inherently safer chemistry for accident prevention: Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

In the words of Professor Ryoji Noyori, " Green Chemistry is not a mere catch phrase; it is the key to the survival of mankind together with these principles and fundamental innovations in chemical sciences, will lead us to a new generation of chemical synthesis."[69]

A perfect system would incorporate all of the above mentioned goals, however, practically only a few of these goals can be incorporated.

1.7.1 Microwave chemistry - Alternative heating in Green Chemistry

One way of achieving clean chemical synthesis is the use of alternative energy sources like the use of microwave irradiation (fast and homogenous heating), ultrasound and sunlight/UV.[2] Microwave-assisted organic synthesis (MAOS) was first reported in 1986 by Richard Gedye,[70] however, this technology has not only been used for organic synthesis but in fields such as polymer synthesis, material sciences, nanotechnology and biochemical processes.[71] Microwave chemistry is based on the heating of materials by "microwave dielectric heating", which is based on the materials ability to absorb microwave energy and convert it to heat.[72],[73]

Microwave chemistry is able to reduce side reactions, increase yields and improve reproducibility, which has now led to microwave synthesis being viewed as a "first choice" for chemical synthesis on a laboratory scale.[72],[73] Recently, microwave chemistry has been performed under solvent-free (dry-media) conditions, where reagents are reacted neat or are adsorbed onto solid support such as clays, silica, alumina, etc.[71] Solvent-free microwave assisted reactions can occur at higher temperatures with open-vessel conditions thus avoiding the risk of higher pressure development.[74] This is a simple technique of mixing the reactants neat with a catalyst or having the reactants 'doped' onto supports or adsorbed onto minerals.[74] Solvent-free microwave synthesis is used for the synthesis of numerous reactions such as protection/deprotection, oxidation, condensation, reduction, rearrangement and heterocyclic synthesis reactions to name a few.[74] One of the main benefits of this chemistry is that it eradicates solvent pollution in organic synthesis 'at the source'.[74] Microwave chemistry has allowed for new routes in organic synthetic chemistry, as reactions that were previously not possible or produced the desired product in low yields, can now be performed

with ease, safely and smoothly in minutes.[73] In summary, microwave-assisted organic synthesis has revolutionized the domain of organic chemistry and drug discovery.

1.8 Aims and objectives of this research project

Quinolines and their derivatives occur in numerous biologically active natural products and due to their wide pharmacological activity, the synthesis quinolines has been greatly researched. However, many of these protocols are environmentally unfriendly, require harsh solvents, long reaction times and large amounts of expensive catalysts. Thus, the development of new methods to overcome the challenges mentioned above is vitally important and remains an active research area for the synthesis of substituted quinolines. The aim of this project is a broad one, to obtain a catalytic system for the synthesis of 2,4-disubstituted quinoline derivatives via A^3-coupling with particular emphasis on:

- Low catalyst loading
- Use of environmentally friendly solvents or solvent-free conditions
- Improved yields
- Short reaction times

CHAPTER 2

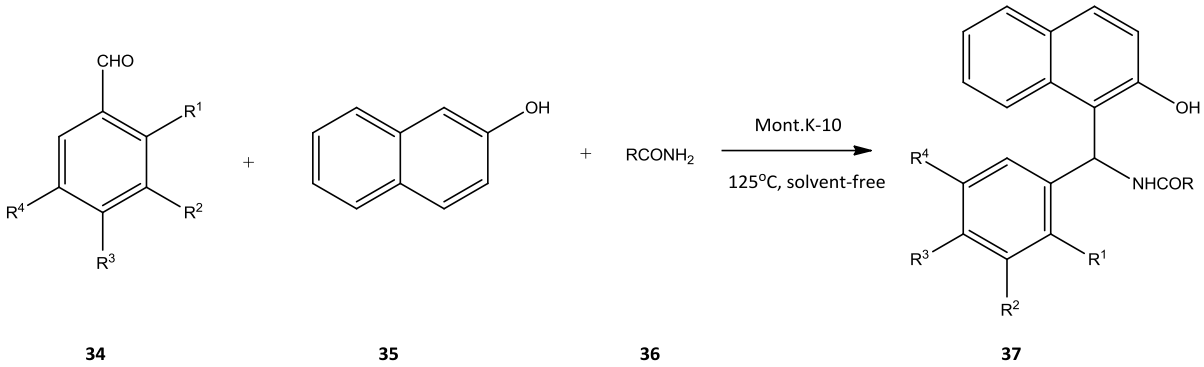
Results and Discussion

The synthesis of 2,4-diphenylquinoline derivatives via A^3-coupling has been vastly explored, however, many of these methodologies employ environmentally unfriendly techniques, as they use large amounts of expensive catalyst or environmentally unfriendly solvents. We decided to look at these mentioned procedures and try and improve their green properties without affecting isolated yields, as a starting point for our research efforts.

2.1 Montmorillonite-K10/ Silica gel systems

Our initial attempt at a green technique for 2,4-diphenylquinoline synthesis was to use montmorillonite K-10 (mont.K-10) as a catalyst for A^3-coupling.[75] Montmorillonite clays are layered silicate clays with the chemical formula, $Al_2Si_4O_{10}(OH)_2.nH_2O$, with the two most common clays being K-10 and KSF.[76] Both K-10 and KSF are produced from natural montmorillonite and while their physiochemical properties are similar, their BET surface areas differ, K-10 has a greater surface area (about 250 m^2g^{-1}) compared to KSF (about 10 m^2g^{-1}).[76],[77] Synthetic organic chemists have recently found interest in clay catalysts due to their eco-friendly nature, low-toxicity, non-corrosive properties, economical nature and these catalysts can be recycled.[76],[78]

In 2007, Kantevari *et al.* effectively synthesized amidoalkyl naphthols **37** using mont.K-10 together with benzaldehyde **34**, β-naphthols **35** and acetamide **36** under solvent-free conditions (Scheme 16),[79] with good to excellent yields being obtained (65-96%), under short reaction times, 0.5-1.5 hours.[79]

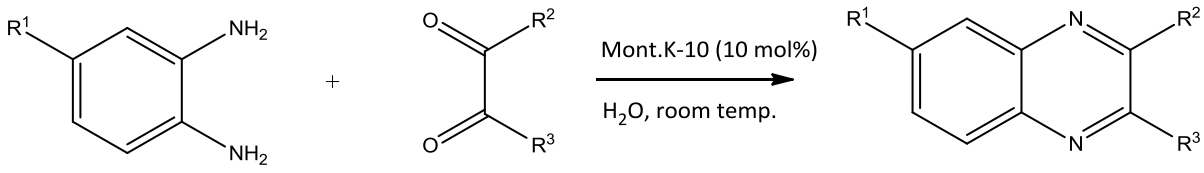


34 **35** **36** **37**

(65-96%)

Scheme 16: Synthesis of amidoalkyl naphthols using Mont.K-10.

Thereafter, in 2008 Lu *et al.* used montmorillonite K-10 as a catalyst for the synthesis of quinoxaline derivatives in water.[77] The montmorillonite K-10 catalyst was used, at room temperature to promote the reaction of 1,2-diketones **38** and 1,2-diamines **39** in water to afford quinoxaline derivatives **40** in good to excellent yields, 70-100% (Scheme 17).[77]

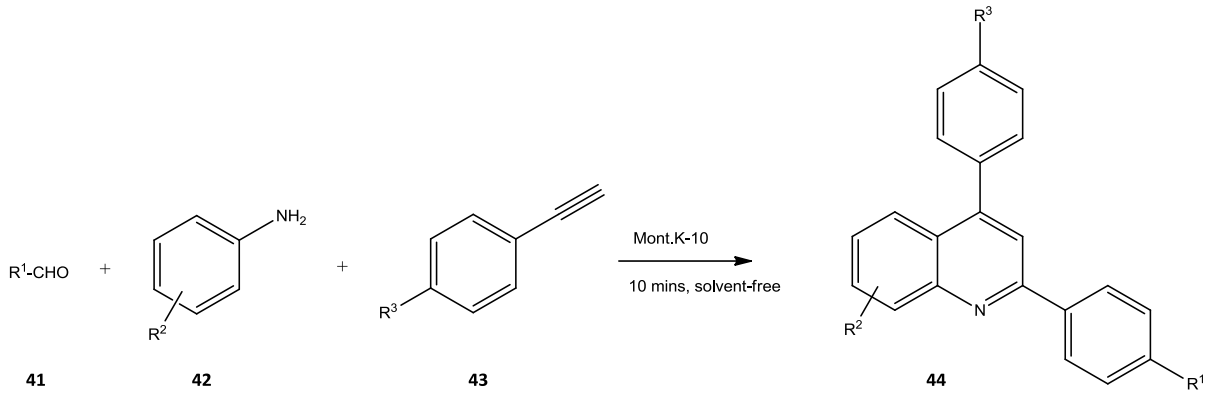


38 **39** **40**

(70-100%)

Scheme 17: Synthesis of quinoxaline derivatives using Mont.K-10.

In 2010, Kulkarni and Torök used montmorillonite K-10 to catalyze the A^3-coupling of aldehydes **41**, anilines **42** and terminal aryl alkynes **43** under solvent-free conditions to obtain substituted quinolines **44** (Scheme 18) in good to excellent yields, 56-94%, under short reaction times, 10 minutes, as all reactions were carried out under microwave conditions.[75]



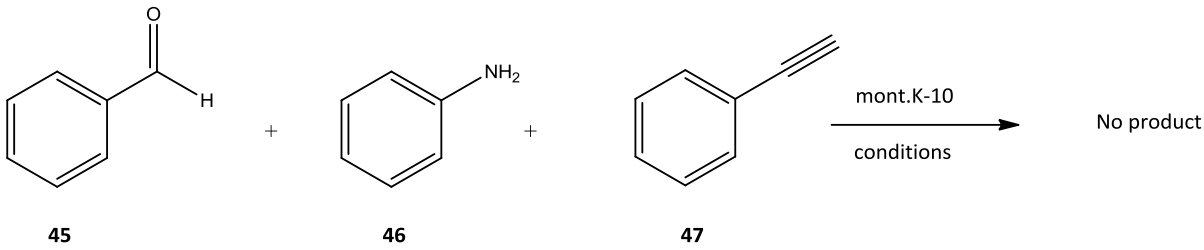
(56-94%)

Scheme 18: Disubstituted quinoline synthesis using Mont.K-10.

The technique proposed by Kulkarni and Torök attracted our interest as it adhered to our target goals. As a test reaction benzaldehyde **45**, aniline **46** and phenylacetylene **47** were added together with 0.500 g of mont.K-10 and left to react for 24 hours under solvent-free conditions (Scheme 19). To our disappointment the ^{1}H NMR crude spectrum showed the presence of large amounts of unreacted aldehyde (10 ppm) and imine (8.5 ppm) (Fig. 16).

This method was then carried out under various reaction conditions (Scheme 19, Table 7) in an attempt to synthesize the desired product in good yields. Solvents such as dichloromethane, toluene, ethyl acetate and water, were used keeping the reaction conditions, time and amount of catalyst constant (Table 7, entries 2-5). However, to our dismay no reaction took place. We then turned our attention towards microwave irradiation under solvent-free conditions. The reagents were reacted with mont.K-10 for 10 minutes (Table 7, entry 6), the ^{1}H NMR spectrum of the crude mixture showed only starting material present. The catalyst loading was then decreased to 0.200 g mont.K-10 and reacted with the reagents for 10 minutes under solvent-free conditions (Table 7, entry 7), however, no reaction was observed. The reaction time was then increased to 20 minutes and solvents, DCM (Table 7, entry 8) and toluene (Table 7, entry 9) together with the reagents were reacted with 0.500 g mont.K-10, once again, under both conditions, no reaction was observed. The amount of mont.K-10 was then increased to 1.0 g and reacted for 20 minutes under solvent-free conditions (Table 7, entry 10) and TLC analysis showed only starting material present. Toluene

was then reacted with the reagents and 1.0 g mont.K-10 and the reaction time increased to 30 minutes (Table 7, entry 11), TLC analysis showed starting material, with no traces of the product detected. Despite the fact that a literature procedure was followed and numerous attempts were made, in our hands the synthesis of disubstituted quinolines using mont.K-10 was unsuccessful.



Scheme 19: Results of A^3-coupling using Mont.K-10 as a catalyst.

Table 7: Reactions catalyzed by Montmorillonite-K10

Entry	Amount of K-10 (g)	Solvent	Conditions	Time	% Yield
1	0.5	-	Con. heating	24 hr	N.R
2	0.5	Toluene	Con. heating	24 hr	N.R
3	0.5	DCM	Con. heating	24 hr	N.R
4	0.5	Ethyl acetate	Con. heating	24 hr	N.R
5	0.5	Water	Con. heating	24 hr	N.R
6	0.5	-	Microwave	10 min	N.R
7	0.2	-	Microwave	10 min	N.R
8	0.5	DCM	Microwave	20 min	N.R
9	0.5	Toluene	Microwave	20 min	N.R
10	1.0	-	Microwave	20 min	N.R
11	1.0	Toluene	Microwave	30 min	N.R

* Con. heating – conventional heating

* N.R – No reaction

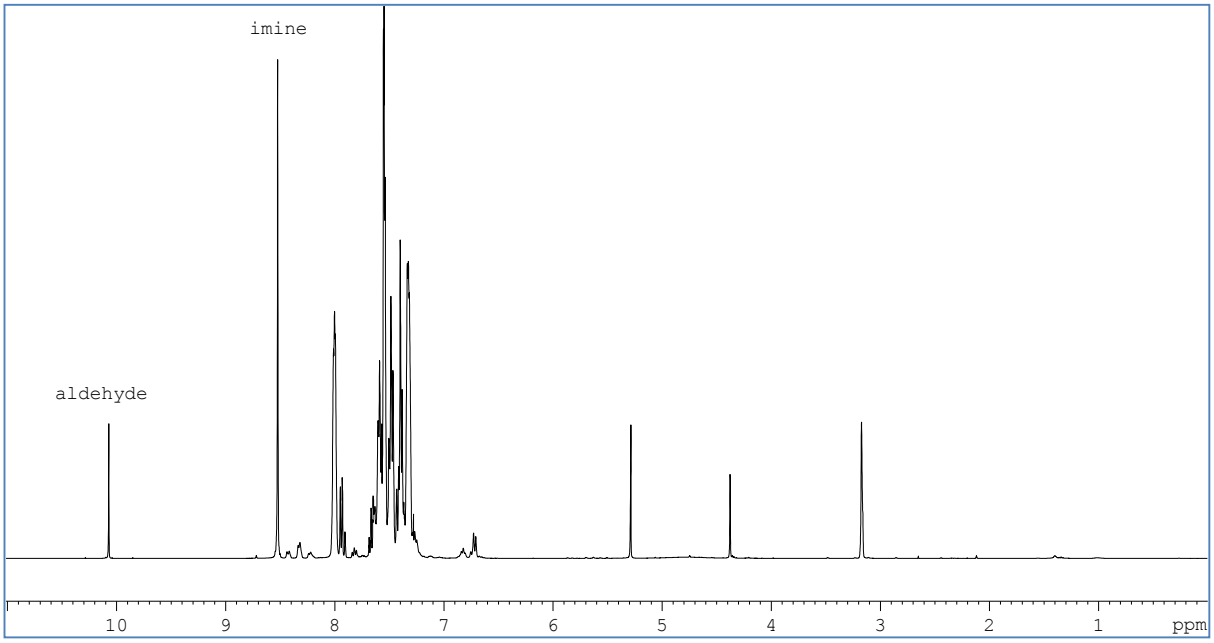


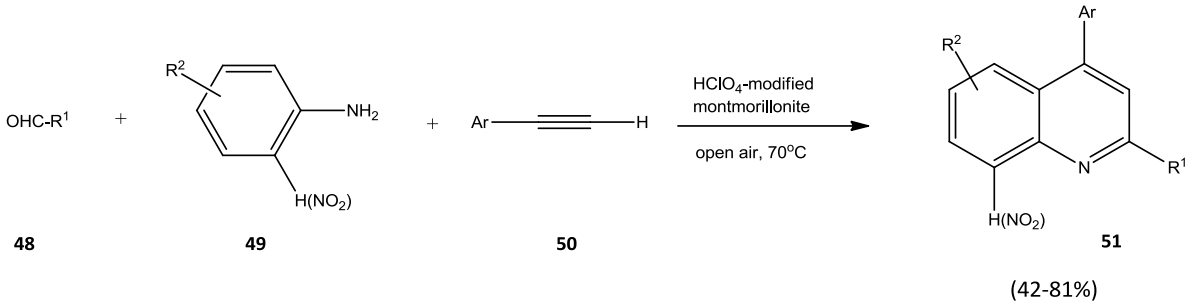
Figure 16: ^{1}H NMR spectrum showing imine and unreacted aldehyde.

2.2 Modified montmorillonite-K10/ silica gel systems

2.2.1 $HClO_4$-modified K-10/ silica gel systems

From our previous study, it was proposed that mont.K-10 was not acidic enough to allow for the three-component quinoline formation. We then decided to follow the method proposed by Guchhait *et al.* by modifying mont.K-10 with a stronger acid.[80] Perchloric acid ($HClO_4$) (K_a = 10^{10}) was chosen as it is most common as it provides strong acidity but with minimal interference as perchloric is a weak nucleophile.[81] A range of acids viz, $HClO_4$, HBF_4 and HCl were used to activate mont.K-10 and it was shown that $HClO_4$-mont.K-10 had the greatest activity to promote quinoline formation.[80] This method of adsorbed mont.K-10 was adapted from Chakraborti and Gulhane, in which perchloric acid was adsorbed onto silica gel.[82] Our view is that if this proposed method produced the desired disubstituted quinoline in good yields, we could modify it by using greener and environmentally friendly techniques such as; a less harsh acid, decreasing the amount of the acid adsorbed onto mont.K-10 and finally decreasing the amount of the modified acid-mont.K-10 used during the disubstituted quinoline synthesis. Guchhait and *et al.* reacted aldehydes **48**, amines **49** and alkynes **50**

together with 2.0 g of $HClO_4$-mont.K-10 to afford 2,4-disubstituted-8-nitroquinolines **51** (Scheme 20) in moderate to good yields, (42-81 %) (Table 8).[80]



Scheme 20: Synthesis of 2,4-disubstituted-8-quinolines using acid modified Mont.K-10.

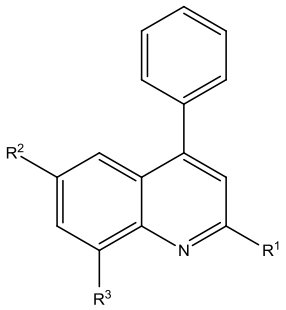
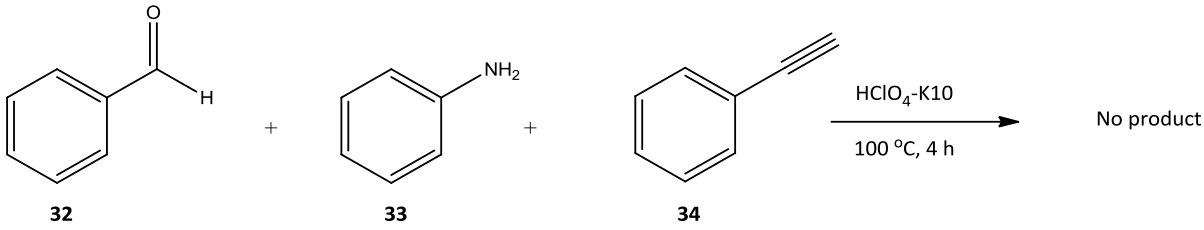


Table 8: Synthesis of polysubstituted quinolines using $HClO_4$-mont.K-10.

Compound	R^1	R^2	R^3	Yield (%)
1	$CH_3OC_6H_5$	NO_2	H	81
2	C_4H_4S	NO_2	H	48
3	C_6H_4Cl	OCH_3	NO_2	66
4	$C(CH_3)_3$	OCH_3	NO_2	41

Following this method, we reacted benzaldehyde **45**, aniline **46** and phenylacetylene **47** together with 2.0 g $HClO_4$-mont.K-10 for 4 hours under solvent-free conditions (Scheme 21). However, to our disappointment, TLC analysis and the ^1H NMR spectrum of the crude mixture showed no product formation, except the presence of aldehyde and imine peaks as well as peaks of a complex mixture of products that could not be characterized. In a further attempt to obtain better results, the method was then carried out under various reaction conditions such as; changing the acid (35% glacial acetic acid, 65% acetic acid, 35% hydrochloric acid and

vinegar) adsorbed onto mont.K-10 (Table 9), increasing reaction time and varying the amount of catalyst used. After numerous studies and modifications to this method, no product was obtained.



Scheme 21: Results of A^3-coupling using acid modified Mont.K-10 as a catalyst.

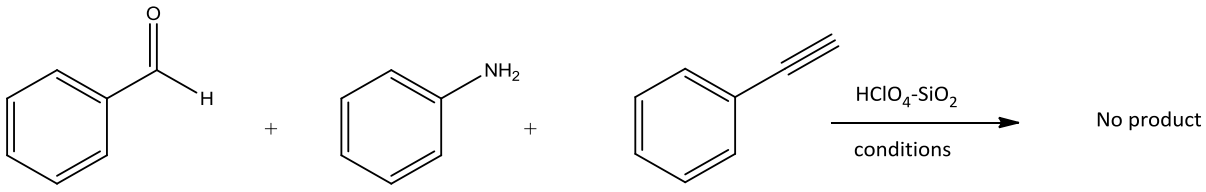
Table 9: Results of various acids adsorbed onto mont.K-10.

Entry	Acid adsorbed K-10	Yield (%)
1	35% Glacial acetic acid	N.R
2	65% Acetic acid	N.R
3	35% HCl	N.R
4	Vinegar (5% acetic acid)	N.R

*N.R – No reaction

Following the method of Chakraborti and Gulhane, a similar reaction was carried out using $HClO_4$-SiO_2 as a catalyst (Scheme 22). Perchloric acid is not environmentally friendly and if this method was a success, it would have been modified to a greener technique by using more environmentally friendly acids. Benzaldehyde **45**, aniline **46** and phenylacetylene **47** were adsorbed onto 0.500 g of the catalyst and thereafter reacted in solvents such as toluene, dichloromethane and water for 24 hours (Table 10, entries 1-3). However, no reaction took place as TLC analysis showed starting material present. The reaction was then carried out under microwave irradiation, the reagents were reacted in the presence of 0.500 g of catalyst in solvents such as, toluene and ethyl acetate, and irradiated for 20 minutes (Table 10, entries

4-5). ^{1}H NMR spectrum of the crude mixture showed peaks for only starting material. A solvent-free reaction was then attempted, in the presence of 0.500 g of catalyst and irradiated for 20 minutes (Table 10, entry 6). Once again TLC analysis showed that no reaction took place. We decided to reduce the amount of catalyst used to 0.200 g and increase the reaction time to 30 minutes (Table 10, entry 7), the ^{1}H NMR spectrum of the crude mixture showed no product peaks.



45 46 47

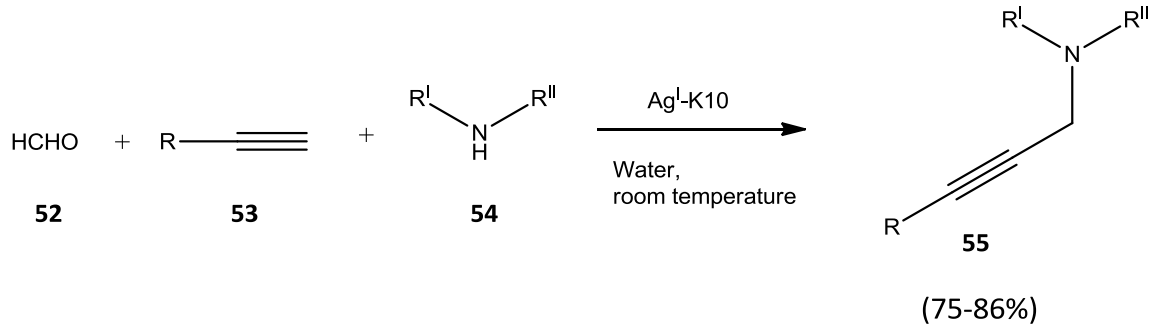
Scheme 22: Results of A^3-coupling using acid modified silica gel as a catalyst

Table 10: Varying reaction conditions with $HClO_4$-SiO_2 as a catalyst.

Entry	Amt. of $HClO_4$-SiO_2 (g)	Solvent	Conditions	Time	Yield (%)
1	0.5	Toluene	Con. heating	24 hr	N.R
2	0.5	DCM	Con. heating	24 hr	N.R
3	0.5	Water	Con. heating	24 hr	N.R
4	0.5	Toluene	Microwave	20 min	N.R
5	0.5	Ethyl acetate	Microwave	20 min	N.R
6	0.5	-	Microwave	20 min	N.R
7	0.2	DCM	Microwave	30 min	N.R

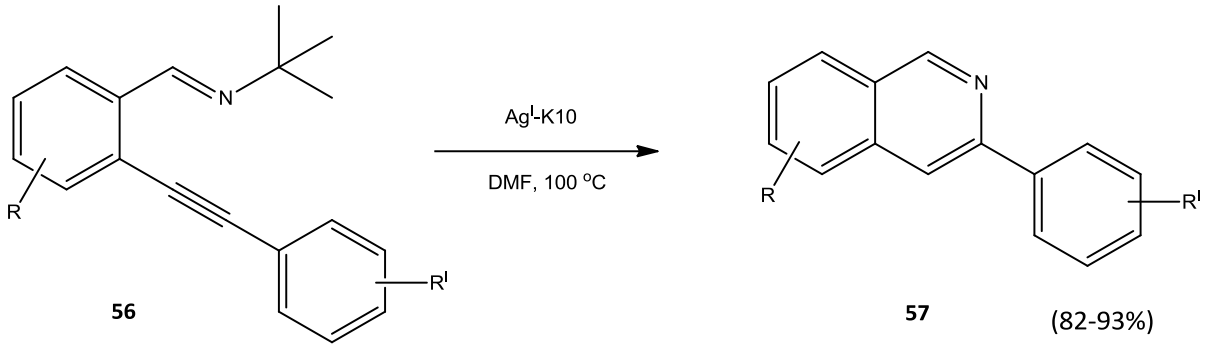
2.2.2 Ag^{I}- exchanged montmorillonite K-10

Recent studies have shown that silver species display interesting catalytic activity as a transition metal catalyst, although they are usually considered to have a decreased efficiency compared to other late transition metals in the synthesis of heterocyclic compounds.[83] Other transition metal catalysts used for heterocyclic compound synthesis include: Au, Cu, Ir, Re and bimetallic systems, however one of the major disadvantages of these catalysts are the large amounts required for synthesis, as well as the catalyst not being able to be recovered and reused.[84],[85] In 2014, Jeganathan *et al.* developed a Ag(I)-exchanged K10-montmorillonite clay that allowed for the formation of propargylamines and cyclization of iminoalkynes to form substituted isoquinolines.[84],[83] Silver ions were adsorbed onto mont.K-10, by stirring silver nitrate and mont.K-10 in water for 3 days at room temperature.[84] For the synthesis of propargylamines, the authors reacted formaldehyde **52**, alkynes **53**, amines **54** and Ag^{I}-K10 in water for 8-12 hours to obtain yields of 75-86% of the desired product **55** (Scheme 23).



Scheme 23: Proparyglamine synthesis using Ag(I) doped Mont.K-10.

Thereafter using the same catalytic system, Jeganathan *et al.* used the same catalyst complex to synthesize substituted isoquinolines **57** *via* cyclization of iminoalkynes **56** by using Ag^{I}-K10 clay (Scheme 24).[83] Iminoalkynes were adsorbed onto Ag^{I}-K10 clay and reacted for 6 hours in dimethyl formamide to produce substituted isoquinolines in good to excellent yields, 82-93%.[83]

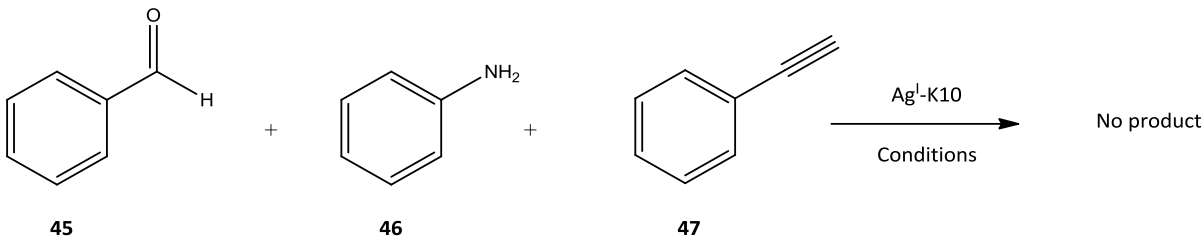


56 **57** (82-93%)

Scheme 24: Isoquinoline synthesis using Ag(I) doped Mont.K-10.

We were encouraged by the success of this method of using Ag^{I}-K10 as a catalyst and decided to couple it with microwave irradiation with the hope for complete cyclization of the A^{3}-coupled propargylamine into the desired disubstituted quinolines. Benzaldehyde **45**, aniline **46** and phenylacetylene **47** were reacted, in the presence of Ag^{I}-K10 catalyst and dichloromethane, toluene and water as solvents, for 24 hours as depicted in Scheme 25 (Table 11, entries 1-3). The ^{1}H NMR spectrum of the crude mixture showed large amounts of the unreacted aldehyde and imine together with traces of propargylamine.

A solvent-free reaction was then tested with 0.500 g of catalyst and reagents which were left to react for 24 hours (Table 11, entry 4). From TLC analysis only the spots of the starting material were present. Moving onto microwave reactions we used toluene and water as solvents and reacted with 0.500 g of catalyst and reagents and irradiated for 10 minutes (Table 11, entries 5-6). However, no formation of the product was observed. A solvent-free reaction was then attempted with 0.500 g catalyst reacted with reactants and the irradiation time increased to 20 minutes (Table 11, entry 7). Even in this case, no product was observed. Lastly under solvent-free conditions, 1.0 g of catalyst was reacted with reagents and irradiated for 40 minutes (Table 11, entry 8), unfortunately only starting material was observed.



Scheme 25: Synthesis of quinolines using Ag(I) doped Mont.K-10.

Table 11: Varying reaction conditions with Ag^{I}-K10 as a catalyst.

Entry	Amt. of Ag^{I}-K10 (g)	Solvent	Conditions	Time	Yield (%)
1	0.5	DCM	Con. heating	24 hr	N.R
2	0.5	Toluene	Con. heating	24 hr	N.R
3	0.5	Water	Con. heating	24 hr	N.R
4	0.5	-	Con. heating	24 hr	N.R
5	0.5	Toluene	Microwave	10 min	N.R
6	0.5	Water	Microwave	10 min	N.R
7	0.5	-	Microwave	20 min	N.R
8	1.0	-	Microwave	40 min	N.R

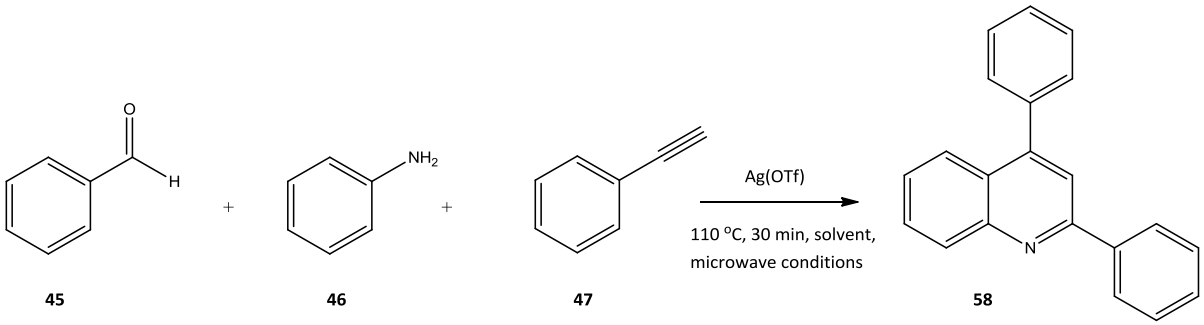
*N.R – No reaction

After numerous attempts of using montmorillonite-K10, adsorbed montmorillonite-K10 and silica-gel as catalysts with no successful results, we decided to abandon our montmorillonite-K10 and silica-gel studies and return to literature to find a catalyst system more suitable for our research.

2.3 Silver triflate (Ag(OTf)) system

Since metal triflates have already proved to be efficient catalysts for three component coupling (Chapter 1), we investigated this reaction by using silver triflate (Ag(OTf)) as a catalyst, hoping to replicate the results obtained by using other triflates. Ag(OTf) was used as a catalyst for a mixture with benzaldehyde **45**, aniline **46** and phenylacetylene **47**, in toluene, under microwave irradiation for 30 minutes (Scheme 26). The ^{1}H NMR spectrum of the crude mixture revealed only trace amounts of 2,4-diphenylquinoline **58**.

Different solvents were then tested in an attempt to increase the desired quinoline yield, however, to our disappointment product yield did not improve. Trace amounts of the desired product were however detected by ^{1}H NMR spectroscopy (Table 12):



Scheme 26: Synthesis of 2,4-diphenylquinoline using Ag(OTf) as a catalyst.

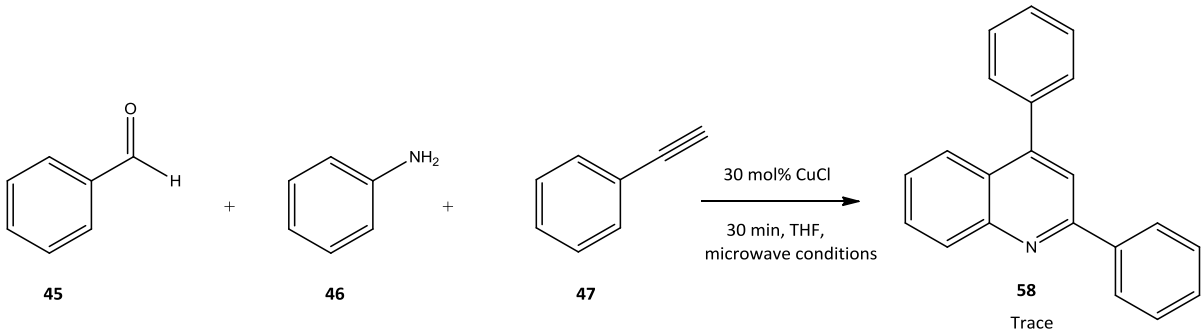
Table 12: Various solvents tested in Ag(OTf) catalyst system.

Entry	Solvent	Yield (%)
1	Absolute ethanol	Trace
2	Ethyl acetate	Trace
3	Diethyl ether	No product
4	THF	No product
5	Solvent-free	Trace

The use of Ag(OTf) as a catalyst was not favorable as after numerous attempts only trace amounts of the desired product was obtained. Recourse to the literature led to the establishment of an appropriate catalyst suitable for our research.

2.4 Copper-based systems

With the failure of the Ag(OTf) system, we then turned our attention towards metal salts as the use of metal triflates are expensive and often catalyst recover and reuse studies would have to be undertaken. We based our initial transition metal reaction on the work of Iqbal *et al.*, by using copper salts for the synthesis of substituted quinolines.[52] We hoped that with the use of microwave irradiation, complete cyclization of the side products would occur, to lead to improved yield of the isolated product. As per literature, 30 mol% of copper chloride (CuCl)[52] was reacted with reagents; benzaldehyde **45**, aniline **46** and phenylacetylene **47** in THF which was irradiated for 30 minutes (Scheme 27). Again, it was noted from crude ^{1}H NMR, that the 2,4-diphenylquinoline **58** was formed in a low yield with the propargylamine as the major product, along with a small amount of imine.



Scheme 27: Synthesis of 2,4-diphenylquinoline using CuCl as a catalyst.

Other copper-based catalysts such as copper iodide, copper acetate, copper(II) chloride and copper bromide were screened under the conditions mentioned above, however, disappointing results were still observed (Table 13).

Table 13: Copper catalysts tested for substituted quinoline synthesis.

Entry	Catalyst (30 mol%)	Time (min)	Yield (%)
1	Copper iodide (CuI)	30	No product
2	Copper acetate ($Cu(CH_3COO)_2$)	30	No product
3	Copper(II) chloride ($CuCl_2$)	30	No product
4	Copper bromide (CuBr)	30	Trace

Failure of the copper-based catalysts to promote the reaction led us to explore other catalytic systems.

2.5 Iron-based system

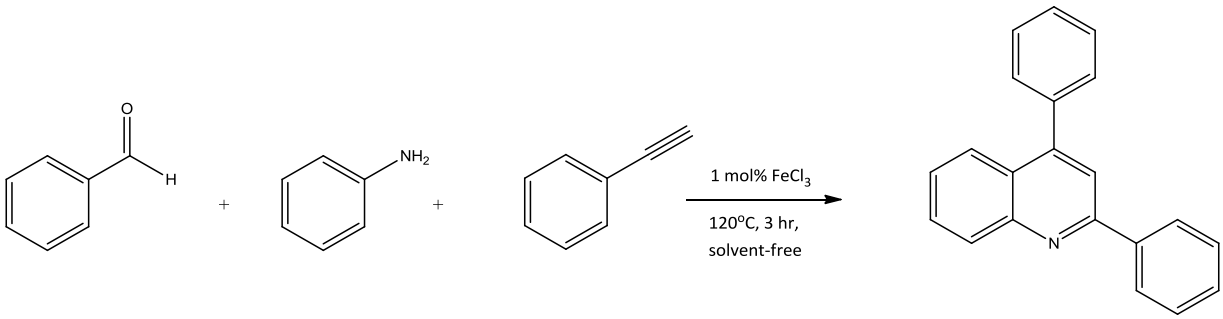
Iron-based catalytic systems proved to be proficient in the synthesis 2,4-disubstituted quinoline. $FeCl_3$ was chosen as the iron catalyst due to its; high abundance, low cost and environmentally friendly properties [86], however, it has been argued that the catalyst loading of $FeCl_3$ used was not satisfactory.[59]

From literature, $FeCl_3$ systems had large catalyst loading and required long reaction times and the use of a solvent,[55],[56] we decided to modify this methodology and in order for this system to be viable we had to decrease the amount of $FeCl_3$ to 1 mol% to determine if 2,4-disubstituted quinoline derivatives could still be synthesized in good to excellent yields. We envisaged that a low catalyst loading coupled with the inexpensive nature of $FeCl_3$ will generate a powerful catalytic system as it is one of the core principles of Green Chemistry.

2.5.1 Synthesis of 2,4-diphenylquinoline

Our studies commenced with a reaction of benzaldehyde, aniline and phenylacetylene under various conditions such as sonication and conventional heating. Under sonication reaction conditions, the reagents were reacted in the presence of 1 mol% $FeCl_3$ and left to react for 3 hours at room temperature (Fig. 21, experiment 1). However, TLC analysis showed the presence of spots corresponding to the starting materials. For conventional heating, the reaction mixture was heated for 3 hours at 120 °C under solvent-free conditions (Scheme 28) (Fig. 21, experiment 2) and encouragingly a yield of 26% of the target product was obtained.

The ^{1}H NMR spectrum (Fig. 17), showed the desired product, with the distinct singlet peak at 7.83 ppm, which indicated complete cyclization of the propargylamine into 2,4-diphenylquinoline. The ^{13}C NMR spectrum (Fig. 18), clearly showed peaks in the aromatic ring region 125 – 150 ppm. Also shown below is the mass spectrum (Fig. 19) of the purified product with the observed molecular ion peak at 280 *m/z*, indicating that the reaction had proceeded efficiently. The infrared (IR) spectrum (Fig. 20), revealed the presence of the aromatic C=C stretch in the region $\tilde{\nu}_{max}$ = 1500 – 1700 cm^{-1}, as well aromatic C-H stretch at $\tilde{\nu}_{max}$ = 1000 – 700 cm^{-1}.



Scheme 28: Synthesis of disubstituted quinolines using $FeCl_3$ as a catalyst.

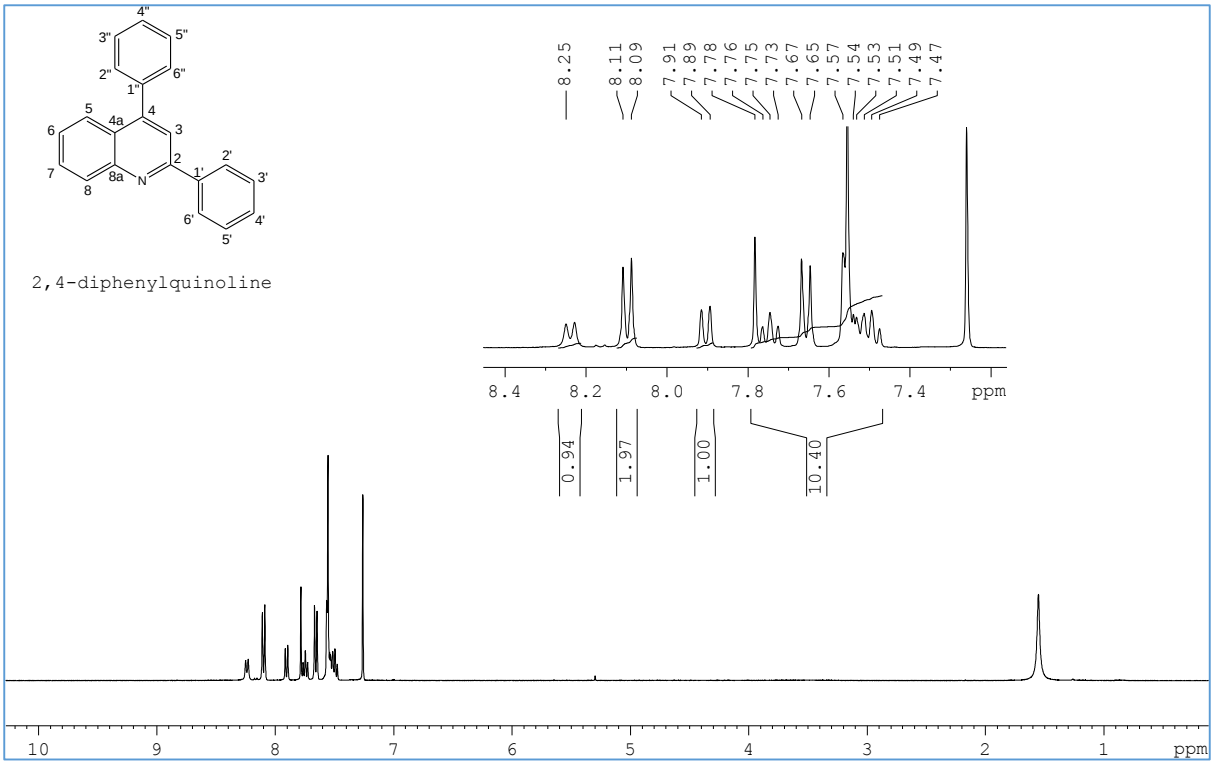


Figure 17: ^{1}H NMR spectrum of 2,4-diphenylquinoline.

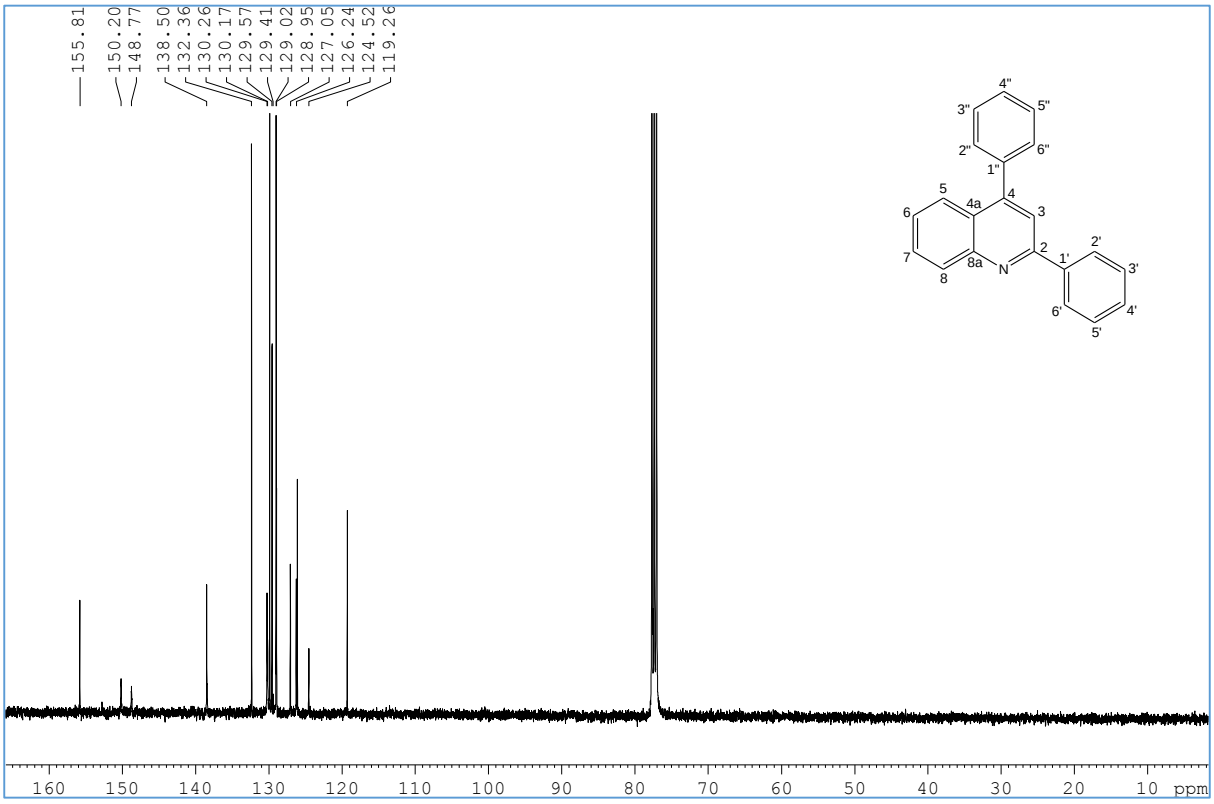


Figure 18: ^{13}C NMR spectrum of 2,4-diphenylquinoline.

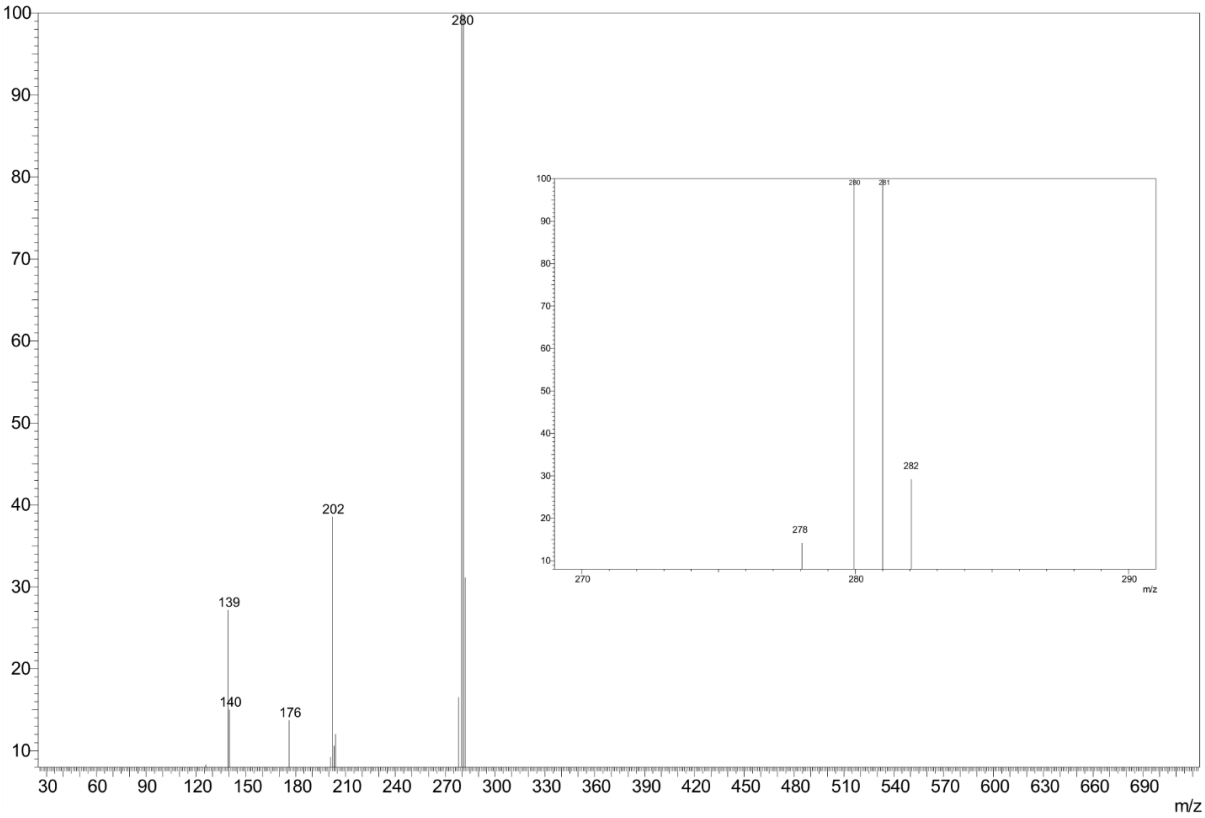


Figure 19: GC-MS spectrum of 2,4-diphenylquinoline.

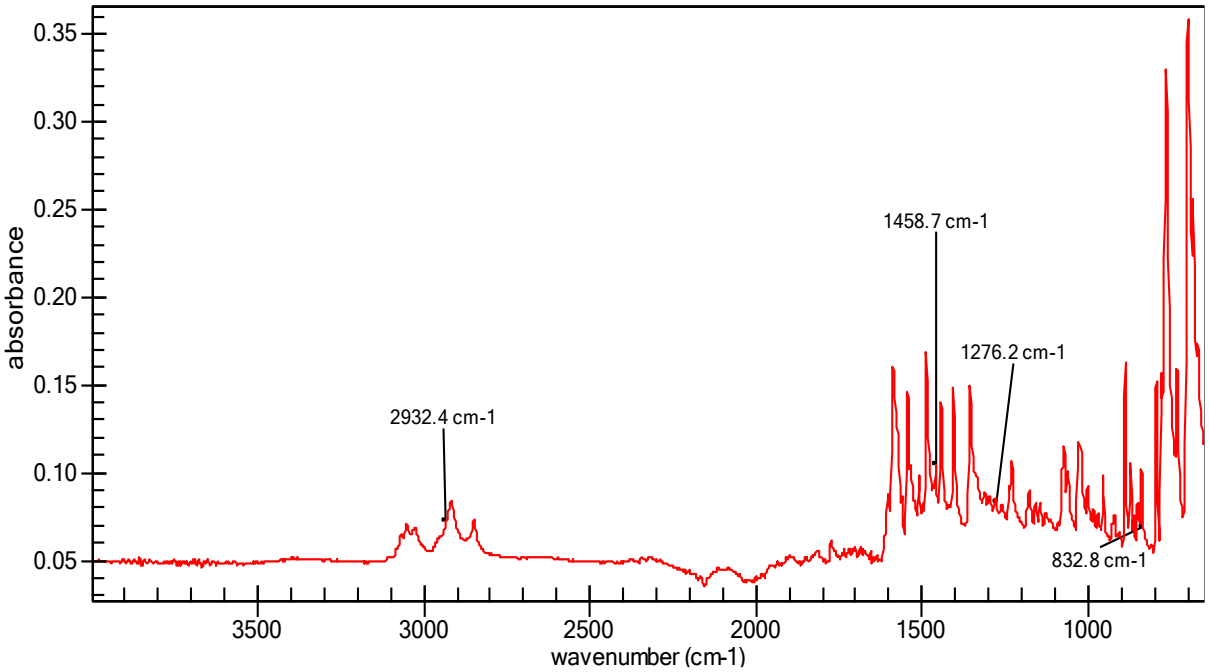
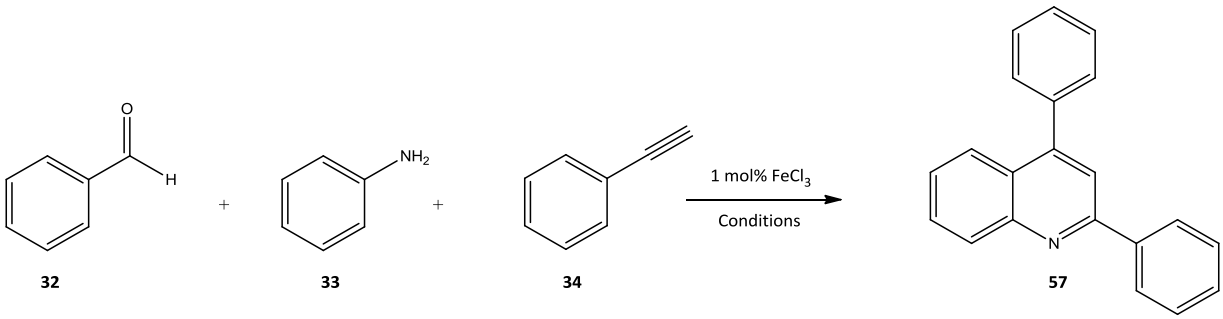


Figure 20: IR spectrum of 2,4-diphenylquinoline.

Inspired by the results obtained, we then focussed our attention on using the 1 mol% $FeCl_3$ catalyst system under MAOS conditions, with different solvents to increase the yield. The first solvent tested was dichloromethane, this was reacted with reagents and 1 mol% $FeCl_3$, the reaction mixture was irradiated for 40 minutes in an open-vessel (Fig. 21, experiment 3). Unfortunately, TLC analysis and the ^1H NMR spectrum of the crude mixture indicated that no reaction occurred. It was then decided to use more environmentally friendly solvents such as water and toluene. Water was added to the reagents in the presence 1 mol% $FeCl_3$ as a catalyst and irradiated for 40 minutes (Fig. 21, experiment 4). The desired product was isolated in a yield of 15%. Toluene was then used as a solvent with the reagents and 1 mol% of $FeCl_3$ as a catalyst and reacted for 40 minutes (Fig. 21, experiment 5), which led to a 40% yield of the isolated product.

From our previous conventional heating reaction, we explored solvent-free reactions as microwave assisted chemistry is known to benefit under these conditions (Chapter 1). The first solvent-free reaction was conducted in a closed-vessel to enable rapid heating of reaction mixtures to high temperatures.[73] Benzaldehyde, aniline, and phenylacetylene were reacted in the presence of 1 mol% $FeCl_3$ as a catalyst, for 40 minutes (Fig. 21, experiment 6). However, the desired product was formed in a mediocre yield of 51%. Next a similar reaction was carried out under open-vessel conditions (Fig. 21, experiment 7) and, to our delight, the desired compound was formed in a **91%** isolated yield.

A catalyst and solvent-free reaction was carried out with just the use of the reagents and irradiated for 40 minutes (Fig. 21, experiment 8), however as expected no reaction took place indicating the need for a catalyst to allow for 2,4-diphenylquinoline formation.



Scheme 28: Synthesis of 2,4-diphenylquinoline using 1 mol% $FeCl_3$ as a catalyst.

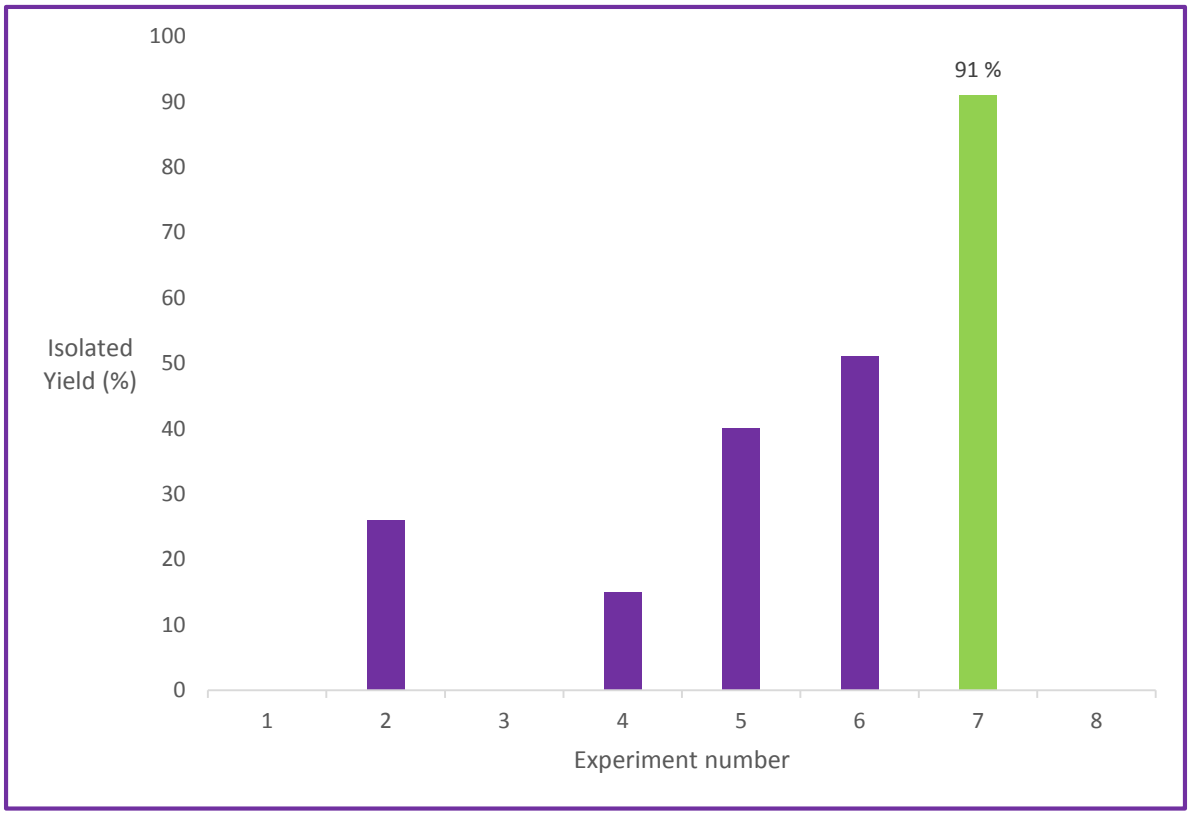
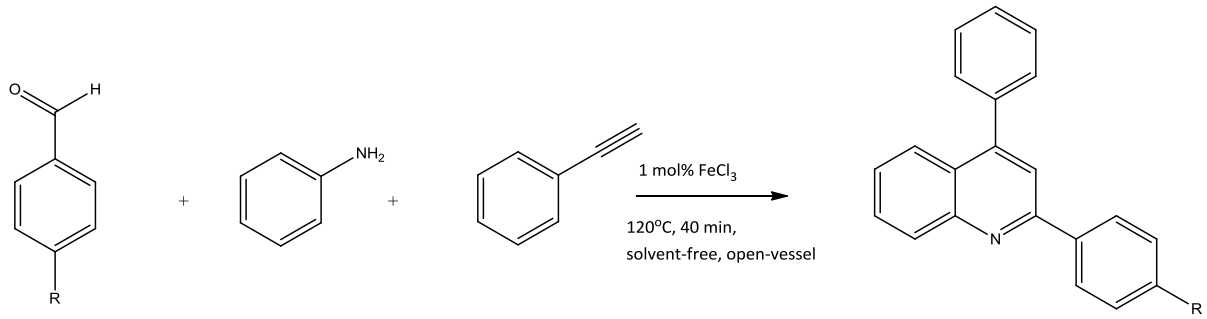


Figure 21: Summary of optimized reactions

Optimization study for the synthesis of 2,4- diphenylquinoline via A^3-coupling : **1a** (1 mmol), **2a** (1 mmol), **3a** (1 mmol), $FeCl_3$ (1 mol %). Experiments: (1) Sonication, room temperature, 3 hours, solvent-free, 0%; (2) Conventional heating, 120°C, 3 hours, solvent-free, 26%; (3) Microwave conditions: Open-vessel, 35°C, 40 min, Dichloromethane, 0%; (4) Open-vessel, 110°C, 40 min, Water, 15%; (5) Open-vessel, 110°C, 40 min, Toluene, 40%; (6) Closed-vessel, 120°C, 40 min, Solvent-free 51%; **(7) Open-vessel, 120°C, 40 min, solvent free 91%**; (8) Open-vessel, 120°C, 40 min, catalyst and solvent free, 0%.

2.5.2 Variation of aldehydes



Compound	R	Yield (%)
59	Br	80
60	CH_3	93
61	NO2	55

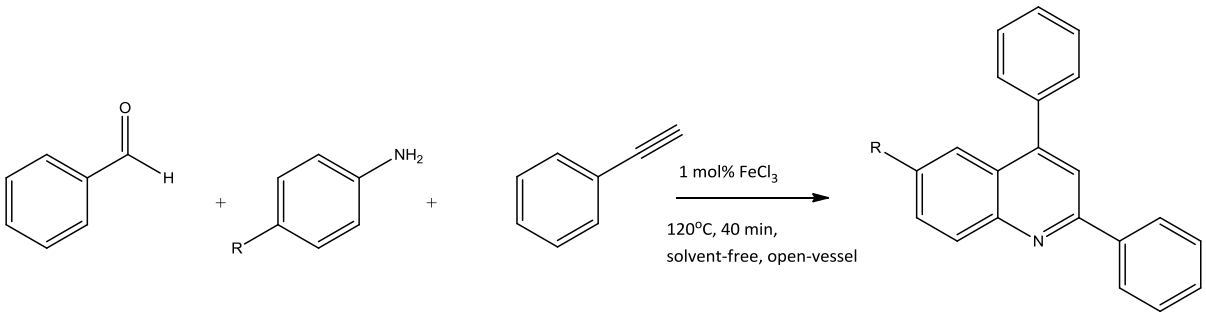
Synthesis of 2-aryl-4-phenylquinolines

With the optimized reaction conditions in hand, we then decided to vary the benzaldehyde derivatives, anilines and phenylacetylenes used. Various substituted benzaldehydes were first tested. 4-Bromobenzaldehyde was reacted with aniline and phenylacetylene in the presence of 1 mol % $FeCl_3$ at 120°C for 40 minutes (Scheme 36) to afford 2-(4-bromophenyl)-4-phenylquinoline **59**, with an isolated yield of 80%. The GC/MS spectrum showed one distinct peak in the gas chromatogram indicating that the desired product was synthesized while the mass spectrum showed a molecular ion (M^+) peak of 360 *m/z* (100%) corresponding to the product.

We then reacted 4-methylbenzaldehyde with aniline and phenylacetylene to produce 2-(4-methylphenyl)-4-phenylquinoline **60**, as a pale yellow solid, with an isolated yield of 93%. The ^1H NMR spectrum showed a distinct singlet at 2.44 ppm, which integrated for three protons, indicating the presence of the methyl substituent. A melting range of 115-116°C was observed, which closely correlated to the literature melting point range of 116-117°C.[87]

Thereafter, 4-nitrobenzaldehyde was reacted with aniline and phenylacetylene to afford 2-(4-nitrophenyl)-4-phenylquinoline **61**, as a pale yellow solid, with an isolated yield of 55%. The GCMS spectrum displayed one distinct peak indicating the purity of the product while the mass spectrum showed the molecular ion peak of 326 *m/z* (100%). The presence of the NO_2 group showed an absorption band at $\tilde{\nu}_{max}$ = 1622 cm^{-1} on the IR spectrum.

2.5.3 Variation of anilines



Compound	R	Yield (%)
62	Cl	90
63	CH_3CH_2	71
64	OCH_3	71

Synthesis of 6-aryl-2,4-diphenylquinolines

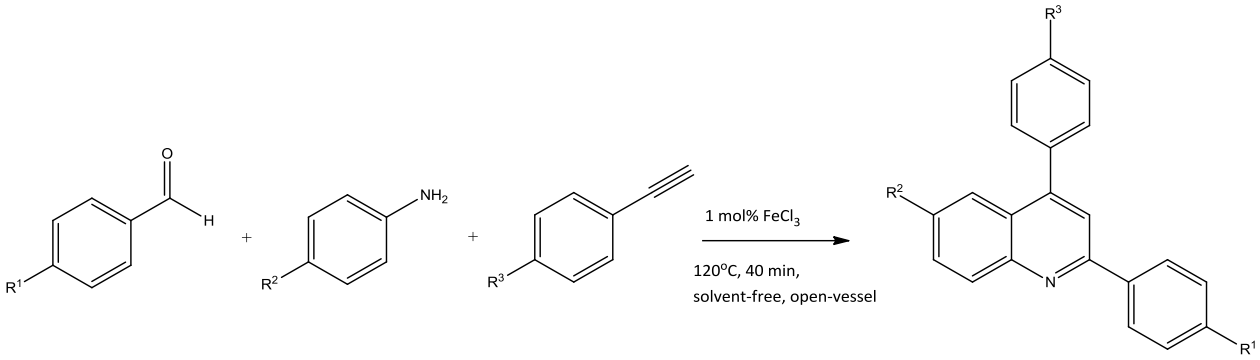
To further test the applicability of the method we then decided to introduce various substituted anilines into the optimized reaction conditions. 4-Chloroaniline was reacted with benzaldehyde and phenylacetylene under the same reaction conditions described for the synthesis of the 2-(4-substituted phenyl)-2-phenylquinolines (**59 – 61**) to afford 6-chloro-2,4-diphenylquinoline **62**, as a pale yellow solid with an excellent isolated yield of 90%. The GCMS spectrum showed one peak present on the chromatogram indicating the purity of the sample while the mass spectrum showed a molecular ion peak of 315 *m/z* (100%). A melting point

range of 129-130°C was observed which closely correlated to the literature melting point range of 130-132°C.[88]

Thereafter, 4-ethylaniline was reacted with benzaldehyde and phenylacetylene to produce 6-ethyl-2,4-diphenylquinoline **63**, as a brown oil, with an isolated yield of 71%. The ^{1}H NMR spectrum showed the presence of the methyl signal (triplet) at *ca*. 1.29 ppm, integrating for 3H and the ethyl signal (quartet) at 2.79 ppm that integrates for 2H. The ^{13}C NMR spectrum also showed the desired methyl and ethyl peaks at 15.87 and 29.49 ppm respectively, with the aromatic peaks between 140-160 ppm. The IR spectrum, showed C-H stretches at $\tilde{\nu}_{max}$ = 2850 and 2932 cm^{-1}, as well as C=C stretches at $\tilde{\nu}_{max}$ = 1622 cm^{-1}. This reaction was particularly satisfying due to the purity of the sample as evident from spectra.

We then examined the reaction between *p*-anisidine with benzaldehyde and phenylacetylene, which produced 6-methoxy-2,4-diphenylquinoline **64** as a brown oil with an isolated yield of 71%, the addition of the methoxy group showed a slight decrease in the quinoline yield. The ^{13}C NMR spectrum showed a prominent methyl peak (singlet) at 55.73 ppm, integrating for 3H. The mass spectrum showed a distinct molecular ion peak at 311 *m/z* (100%).

2.5.4 Variation of benzaldehyde, aniline and phenylacetylene



Compound	R^1	R^2	R^3	Yield (%)
65	H	Cl	CH_3	86
66	Br	Br	H	95
67	Br	OCH_3	H	83

To further investigate our method, we then decided to vary two reactants in the desired quinoline synthesis. We first decided to react benzaldehyde, 4-chloroaniline and 4-etynyltoluene, under optimized conditions to afford 6-chloro-2-phenyl-4-*p*-tolylquinoline **65** (Table 10, entry 8), as a pale yellow oil with an isolated yield of 86%. The ^{1}H NMR spectrum showed the methyl peak (singlet) at 2.50 ppm, which integrated for 3H. The mass spectrum showed the molecular ion peak at 329 *m/z* (100%).

Thereafter, 4-bromobenzaldehyde was reacted with 4-bromoaniline and phenylacetylene to produce 6-bromo-2-(4-bromophenyl)-4-phenylquinoline **66**, as a pale yellow oil, with an isolated yield of 95%, the addition of the bromo substituents increased the yield greatly. The structure was confirmed by mass spectroscopy, with a prominent molecular ion peak of 439 *m/z* (100%). The IR spectrum showed C-H stretches at $\tilde{\nu}_{max}$ = 2850 and 2932 cm^{-1} and a C=C stretch at $\tilde{\nu}_{max}$ = 1628 cm^{-1}.

Lastly, 4-bromobenzaldehyde was reacted with p-anisidine and phenylacetylene, to produce 2-(4-bromophenyl)-6-methoxy-4-phenylquinoline **67**, as a light yellow solid with an isolated yield of 83%. The mass spectrum shows a molecular ion peak at 390 *m/z* (41%). A melting range was observed between 134-136°C, which correlated to the literature melting range of 135-136°C.[89]

The disubstituted quinolines were synthesized in good to excellent yields with the results summarized in the table below. Variation of the benzaldehyde substituent produced the desired quinoline derivatives in moderate to excellent yields, 55-93% (Table 14, entries 2-4). With the varying aniline substituents, to produce the coveted disubstituted quinolines resulted in good to excellent yields of, 71-90% (Table 14, entries 5-7). Lastly, two reactants were then varied during the disubstituted quinoline synthesis and once again excellent yields of 83-95% were obtained (Table 14, entries 8-10).

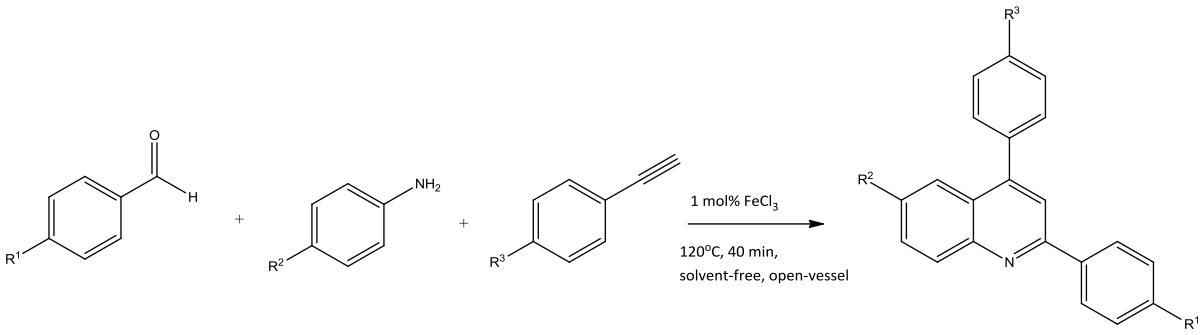
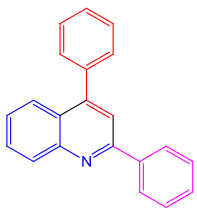
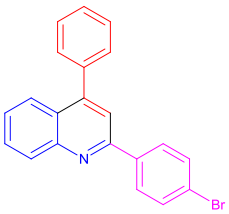


Table 14: Summary of substituted 2,4-diphenylquinolines using substituted benzaldehydes, anilines and phenylacetylene



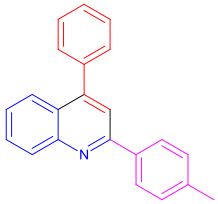
1

91%



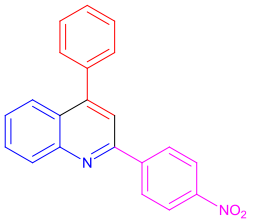
2

80%



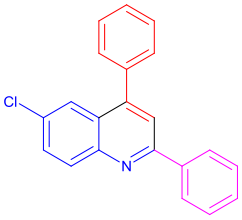
3

93%



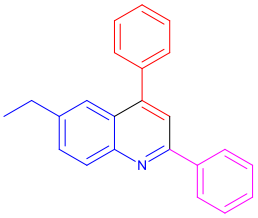
4

55%



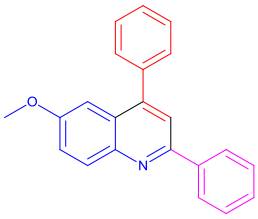
5

90%



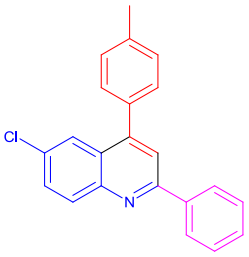
6

71%



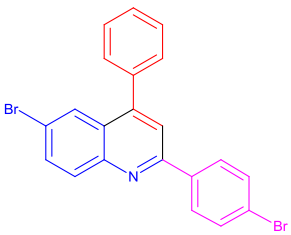
7

71%



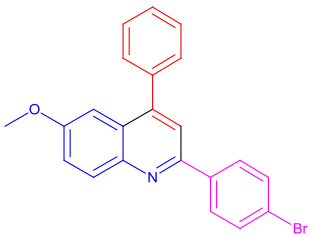
8

86%



9

95%



10

83%

Compared to techniques mentioned previously in the literature, our optimized system deems most superior due to its' low catalyst loading, solvent-free nature, short reaction times and high product yields. For the synthesis of 2,4-diphenylquinoline, our system proved to yield greater results compared to the 10 mol% system used by Tu and co-workers (Table 15, entry 1). However, their system seemed to obtain greater yields for the synthesis of 6-methoxy-2,4-

diphenylquinoline (Table 15, entry 7) but this system required a longer reaction time, 24 hours compared to our 40 mins, in a solvent and with 10 times more catalyst than our system.

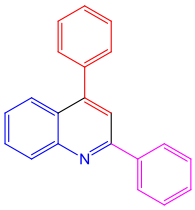
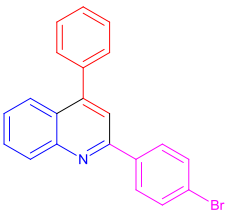
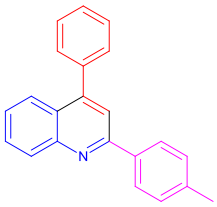
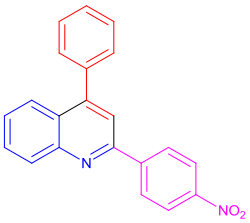
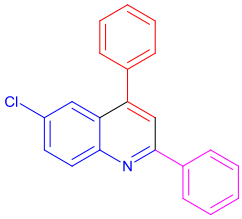
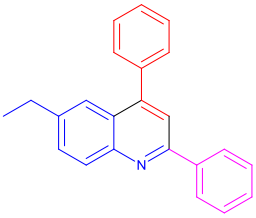
A similar result was observed for the synthesis of 2-(4-bromophenyl)-4-phenylquinoline (Table 15, entry 2), Wang and co-workers obtained a product yield of 89% compared to our yield 80%, however, their catalytic system required 10 times more catalyst compared to our system, their reaction times were also longer and required the use of chlorinated solvent (dichloroethane).

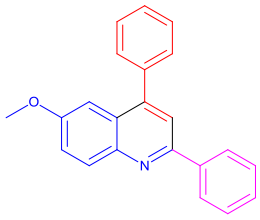
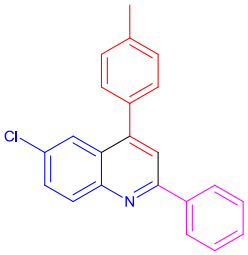
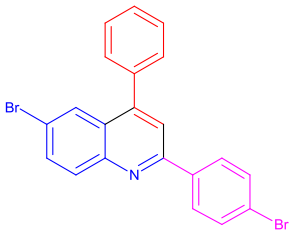
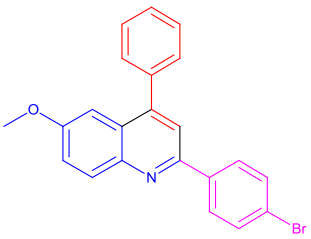
For the synthesis of 2-(4-methylphenyl)-4-phenylquinoline and 6-chloro-2,4-diphenylquinoline (Table 15, entries 3 and 5), our system proved to be more efficient compared to that proposed by Yao and co-workers, that required 5 mol% $Fe(OTf)_3$ which is extremely expensive compared to $FeCl_3$, a longer reaction time was also required and a tedious time-consuming catalyst recover and reuse experiment had to be conducted.

The mont.K-10 system used by Kulkarni and Torök showed superior results for the synthesis of 2-(4-nitrophenyl)-4-phenylquinoline (Table 15, entry 4) and 6-ethyl-2,4-diphenylquinoline (Table 15, entry 6), however, our system showed a greater yield for the synthesis of 6-chloro-2-phenyl-4-p-tolylquinoline. The system used by Kulkarni and Torök requires a larger catalyst loading for a 1 mmol reaction scale, due to this a tedious catalyst recover and reuse study was undertaken.

For the synthesis of 6-bromo-2-(4-bromophenyl)-4-phenylquinoline (Table 15, entry 9) our optimized system proved to be more efficient, 83 %, compared to the system used by Song and co-workers, 80%. Their system required 0.1-0.5 mol equivalents of diphenyl phosphate (DPP) and reactions were conducted in a domestic microwave oven. Lastly, our optimized system showed greater results for the synthesis of 2-(4-bromophenyl)-6-methoxy-4-phenylquinoline compared to the work by Li and co-workers, reactions required longer times (12 hours) in nitromethane.

Table 15: Comparison of the optimized system of this project compared to literature.

Entry	Product	Isolated Yields (%)		Conditions of Literature Exp.
		This project	Literature	
1		91	70 [55]	$FeCl_3$ (10mol%), toluene, 100°C, 24 hr
2		80	89 [56]	$FeCl_3$ (10mol%), DCE, 120°C, 12 hr
3		93	86 [57]	$Fe(OTf)_3$(5mol%), solvent-free, 100°C, 3 hr
4		55	81 [75]	K-10 (500mg), solvent-free, 100°C, 10 min
5		90	82 [57]	$Fe(OTf)_3$(5mol%), solvent-free, 100°C, 3 hr
6		71	88 [75]	K-10(500mg), solvent-free, 100°C, 10 min

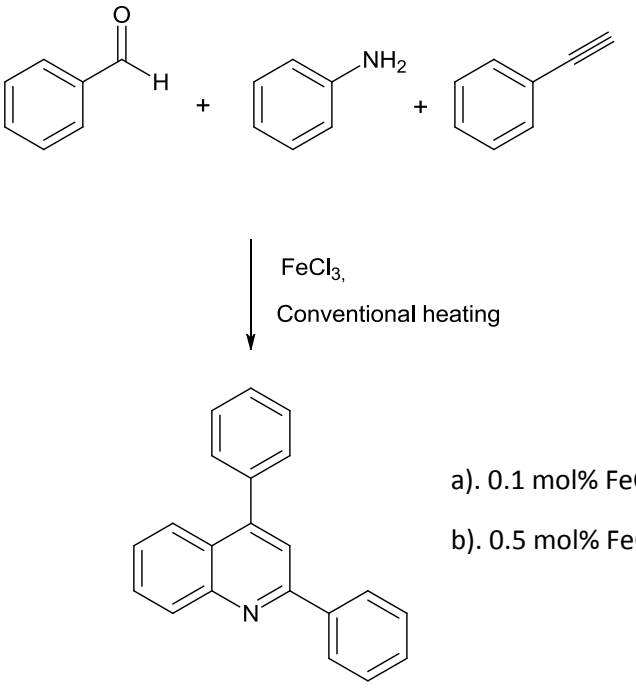
7		71	83 [55]	$FeCl_3$(10mol%), toluene, 100°C, 24 hr
8		86	83 [75]	K-10(500mg), solvent-free, 100°C, 10 min
9		95	85 [90]	(DPP)(0.1-0.5 mol eq.), 4 min, solvent-free
10		83	80 [89]	Iodine (0.1 mmol), CH_3NO_2, r.t., 12 hr

2.6 Lower catalyst loading study

The use of microwave chemistry has a number of advantages such as high yields and short reaction times and the benefits of this approach have been well documented in the literature.[72],[91],[92] There are however limitations to microwave chemistry such as; scale-up applicability and consequently, synthetic microwave reactors cannot be run for hours on end and these factors must be considered when choosing reaction conditions.[93],[94] In an effort to complement our studies above, we were interested in further decreasing the amount of catalyst and due to the limitations of microwave chemistry highlighted above, we chose to

exploit our earlier observation in which 26% of the desired quinoline was formed in 3 hours of conventional heating, as it is not feasible to run a microwave reaction for that long.

In a preliminary study, the catalyst loading was further decreased and evaluated using 0.1 and 0.5 mol% $FeCl_3$. Benzaldehyde, aniline and phenylacetylene were reacted with 0.1 mol% $FeCl_3$ and left to react for 7 days under solvent-free conditions at 120°C, unfortunately only trace amounts of the product was observed (Scheme 29 a). The amount of catalyst was then increased to 0.5 mol%, this followed the same reaction conditions mentioned above and left to react for 72 hours, however only trace amounts of the product was observed (Scheme 38 b). The same reaction was repeated, this time, the reaction was left to react for 7 days, and a 73% isolated yield was obtained (Scheme 29 b). We were elated that these results indicate that with sufficient time, the catalyst loading can be further decreased using an alternate energy source and still produce the desired product in satisfactory yields.



Scheme 29

Compared to the previous catalytic systems previously used in A^3-coupling, our system was most superior due to the low catalyst loading (1 mol%), short reaction times (40 mins),

inexpensive nature of the catalyst, solvent-free conditions and no catalyst recover and reuse study had to be conducted (Table 16).

Table 16: Comparison of catalytic systems.

Entry	Catalyst	Catalyst Loading	Reaction Time	Cost	Recover and Reuse
1	CuCl	×	×	✓	✓
2	$AuCl_3$/CuBr	×	×	×	×
3	CuCl-Mont.	×	✓	✓	✓
4	$FeCl_3$	×	×	✓	✓
5	$Fe(OTf)_3$	✓	✓	×	×
6	$Cu(OTf)_2$	✓	✓	×	✓
7	$Yb(Pfb)_3$	✓	×	×	×
8	$K_5CoW_{12}O_{40}.3H_2O$	×	✓	×	×
9	Fe_3O_4	✓	✓	×	×
10	**$FeCl_3$ (1 mol%)**	✓	✓	✓	✓

Key:

- Catalyst loading: ✓- low catalyst loading < 10 mol%
  ×- high catalyst loading > 10 mol%
- Reaction time: ✓- reaction time < 5 hours
  ×- reaction time > 5 hours
- Cost: ✓- inexpensive
  ×- expensive
- Recover and reuse study: ✓- No recover and reuse study conducted
  ×- Recover and reuse study conducted

The developed system thus adheres to the following goals of Green Chemistry, which are highlighted below:

1. Prevention: It is better to prevent waste than to treat or clean up waste after it has been created.

2. **Atom economy:** Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.

3. Less hazardous chemical syntheses: Synthetic methods should be designed to use and generate substances that possess little or no toxicity to the human health and the environment.

4. Designing safer chemicals: Chemical products should be designed to effect their desired function while minimizing toxicity.

5. Safer solvents and auxiliaries: The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible.

6. Design for energy efficiency: Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

7. Use of renewable feedstocks: A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

8. Reduce derivatives: Unnecessary derivatization (use of blocking groups, protection/deprotection, temporary modification of physical/ chemical processes) should be minimized or avoided if possible because such steps require additional reagents and can generate waste.

9. Catalysis: Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. Design for degradation: Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

11. Real-time analysis for pollution prevention: Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

12. Inherently safer chemistry for accident prevention: Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

The results of this study have been drawn up for a publication to be submitted to an appropriate journal. A copy of the paper is attached in the Appendix.

Conclusions

Disubstituted quinoline derivatives are important compounds due to their broad range of biological activity. The results described in this research project display a more environmentally friendly approach towards the synthesis of 2,4-disubstituted quinoline derivatives using an A^3-coupling approach as other methods require large amounts of expensive reagents/catalysts, environmentally unfriendly solvents and long reaction times.

Reaction conditions were optimized by using just 1 mol% $FeCl_3$ as a catalyst to obtain 2,4-diphenylquinoline via microwave irradiation under solvent-free conditions in short reaction times (40 minutes). Using the optimized reaction conditions, a series of 2,4-disubstituted quinolines were synthesized in good to excellent yields (55-95%).

The catalyst loading was further decreased to 0.5 mol% $FeCl_3$, and 2,4-diphenylquinoline was still obtained in a satisfactory yield (73%). The application of very low catalyst loadings, no ligands or additives, solvent-free conditions coupled with the inexpensive nature of $FeCl_3$ makes this a very attractive route towards quinolines. The developed system is appealing as it adheres to some of the twelve principles of Green Chemistry.

Future research extending from this investigation:

- This research project focussed on quinoline moieties that contained aromatic substituents (good to excellent yields were obtained), it would be interesting to apply aliphatic substituents to the system and pay particular attention to the chain length of the aldehyde and alkyne substituents. This would be exciting as aliphatic substituted quinolines have numerous biological activities and could form the basis of another synthetic study.
- Metal-mediated catalysis is an important part of organic chemistry however most protocols require the use of expensive metals, this catalytic system could be applied to other metal mediated catalytic systems other than A^3-coupling.

- It would also be interesting to test this 1 mol% $FeCl_3$ catalytic system on another A^3-coupled (aldehyde, alkyne and 2-aminopyridine) reaction to synthesize biologically active compounds such as, Zolpidem, a hypnotic drug used for the treatment of insomnia.

CHAPTER 3

Experimental

General information:

All starting reagents were purchased from Sigma-Aldrich and used without further purification. $CDCl_3$ (99.8%) (Magnisolv) was used as solvent for NMR studies. Other solvents used had a minimum purity of 99.5%. The silica gel (130 – 270 mesh) was used for column chromatography.

All products are known and their spectroscopic data compared with literature.

Microwave Reactions: All microwave synthesis was carried out on a CEM Focused Microwave™ which uses an infrared sensor located below the microwave cavity floor to measure temperature. All microwave reactions were performed under opened- vessel conditions.

NMR Analysis: The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance III 400 or Bruker Avance III 500 spectrometer operating at 400 MHz or 100 MHz. NMR spectra were referenced against the residual $CDCl_3$ present in δ_H 7.26 ppm or the δ_C 77.0 ppm. *NMR abbreviations:* s-singlet, d-doublet, m-multiplet, q-quartet, t-triplet

GC-MS Analysis: The mass spectrometric identification of the products have been carried out using a Perkin Elmer Spectra One.

IR Analysis: IR spectra were recorded on a Smiths IdentifyIR Spectrometer.

Melting Points: All melting points were determined using a Kofler hot-stage melting apparatus and are uncorrected.

All spectra referred to in the discussion have been included within the text with supplementary spectra included in electronic format. NMR, IR and GC-MS have been assigned a folder with its designated IUPAC name as it appears in the text. The appropriate ^{1}H and ^{13}C NMR FID files are also attached.

3.1 Procedures and general methods

3.1.1 Using montmorillonite-K10

A mixture of benzaldehyde (102 µL, 1 mmol), aniline (100 µL, 1 mmol) and phenylacetylene (110 µL, 1 mmol) was stirred with 0.5 g mont.K-10 under solvent-free conditions at room temperature for 30 minutes. The free flowing powder was then irradiated at 120 °C for 10 minutes in the microwave. Thereafter the reaction mixture was quenched with ethyl acetate (10 ml). The mixture was then passed through a short silica plug and the filtrate was concentrated under reduced pressure. The crude mixture was analyzed by ^{1}H NMR spectroscopy, however, no peaks corresponding to the product were observed.

3.1.2 Using $HClO_4$-K10

Preparation of $HClO_4$-K10

$HClO_4$ (1.25 g, 12.5 mmol as a 70% aqueous solution) was added to a suspension of mont.K-10 (20 g) in diethyl ether (50 ml). The mixture was concentrated (open to the atmosphere) and the residue was heated at 100 °C for 72 hours to afford $HClO_4$-K10 as a free flowing powder.

Benzaldehyde (102 µL, 1 mmol), aniline (100 µL, 1 mmol) and phenylacetylene (110 µL, 1 mmol) were added to 0.5 g $HClO_4$-K10 in DCM. The reaction was irradiated for 30 minutes in the microwave at 85 °C, and the resulting mixture was thereafter quenched with diethyl ether (10 ml) and passed through a short silica plug. The resulting residue was analyzed by ^{1}H NMR spectroscopy. The crude NMR showed peaks for the imine and starting material, no product

peaks were observed. The reaction was thereafter carried out under various reaction conditions.

Preparation of $HClO_4$-SiO_2 [82]

$HClO_4$ (1.25 g, 12.5 mmol as a 70% aqueous solution) was added to a suspension of silica gel (23.75 g, 230-400 mesh) in diethyl ether (50 ml). The mixture was concentrated (open to the atmosphere) and the residue was heated at 100 °C for 72 hours to afford $HClO_4$-SiO_2 as a free flowing powder.

Benzaldehyde (102 µL, 1 mmol), aniline (100 µL, 1 mmol) and phenylacetylene (110 µL, 1 mmol) were added to 0.5 g $HClO_4$-SiO_2 in DCM (1 ml). The reaction was irradiated for 30 minutes at 85 °C, and the resulting mixture was thereafter quenched with diethyl ether (10 ml) and passed through a short silica plug. The solvent was evaporated and the resulting residue was subjected to ^{1}H NMR spectroscopy. Unfortunately, no product was detected in the crude mixture. The reaction was thereafter carried out under various reaction conditions.

3.1.3 Using Ag^I-K10 clay

Preparation of Ag^I-K10 clay

The silver ions were exchanged onto montmorillonite K-10 clay (5 g) by stirring $AgNO_3$ (21.24 g, 0.13 mol) in distilled water (125 ml), at room temperature for 72 hours. The clay was filtered and washed thoroughly with distilled water. The adsorbed clay was then left to dry in air for 24 hours.

Benzaldehyde (102 µL, 1 mmol), aniline (100 µL, 1 mmol) and phenylacetylene (110 µL, 1 mmol) were reacted in the presence of Ag^I-K10 clay (0.5 g) together with DCM (1 ml). The reaction was irradiated for 30 minutes at 50 °C in the microwave and thereafter quenched with ethyl acetate and passed through a short silica plug. The filtrate was concentrated and the residue was analyzed with ^{1}H NMR spectroscopy. However, the NMR showed only peaks

for the starting material peaks present. This method was thereafter tested under various reaction conditions.

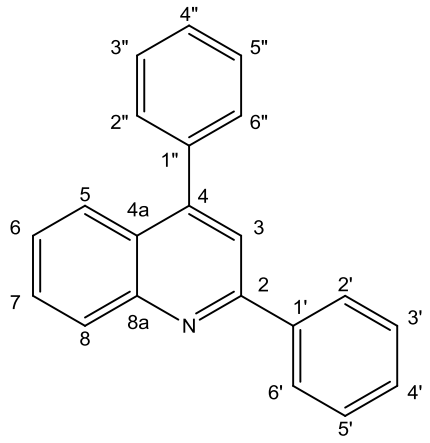
3.2 Using Ag(OTf)

A mixture of benzaldehyde (102 µL, 1 mmol), aniline (100 µL, 1 mmol) and phenylacetylene (110 µL, 1 mmol) was reacted in the presence of Ag(OTf) (0.051 g, 20 mol%) under solvent-free conditions. The reaction was irradiated for 30 minutes at 110 °C in the microwave. After the reaction was completed ethyl acetate was added to the reaction mixture and the mixture filtered. The filtrate was concentrated under reduced pressure and the resulting residue was subjected to column chromatography (30:1 petroleum ether-ethyl acetate, v/v) to afford the pure product however in a 10% isolated yield.

3.3 Using copper catalysts

Benzaldehyde (102 µL, 1 mmol), aniline (100 µL, 1 mmol) and phenylacetylene (110 µL, 1 mmol) were reacted in the presence of CuCl (0.027 g, 30 mol%) under solvent-free conditions. The reaction was irradiated for 30 minutes at 110 °C in the microwave. After the reaction was completed ethyl acetate was added to the reaction mixture and the mixture was filtered through a short silica plug. The filtrate was concentrated under reduced pressure and analyzed with ^{1}H NMR spectroscopy. However, NMR spectrum of the crude mixture showed propargylamine and imine peaks, with traces of product peaks. This method was thereafter tested under various reaction conditions using other copper catalysts such as CuI, $Cu(CH_3COO)_2$), $CuCl_2$ and CuBr, however with unsatisfactory results obtained.

3.4 Generalized procedure using 1 mol % $FeCl_3$



Benzaldehyde (102 µL, 1 mmol), aniline (100 µL, 1 mmol), phenylacetylene (110 µL, 1 mmol) and $FeCl_3$ (1 mol %, 1.62 mg) were added to a microwave reaction vessel and irradiated for 40 minutes at 120 °C under open-vessel conditions. After the reaction was completed, ethyl acetate was added to the reaction mixture and thereafter filtered. The filtrate was concentrated under reduced pressure and the resulting residue was subjected to column chromatography (30:1 petroleum ether-ethyl acetate, v/v) to afford the pure product as a light yellow solid (0.256 g, 91%).

^{1}H NMR (400 MHz, $CDCl_3$), δ(ppm) 8.30-8.27 (d, 1H, *J* = 8.62, 5-H), 8.23-8.20 (m, 2H, 2'-H, 6'-H), 7.93-7.90 (d, 1H, *J*=8.33, 8-H), 7.83 (s, 1H, 3-H), 7.77-7.72 (m, 1H, 7-H), 7.58-7.46 (m, 9H, 6-H, 3'-H, 4'-H, 5'-H, 2"-H, 3"-H, 4"-H, 5"-H, 6"-H).[55]

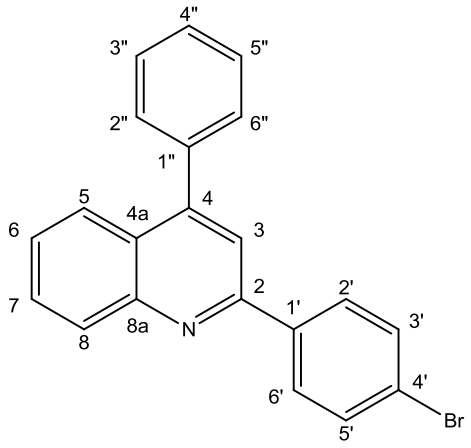
^{13}C NMR (100 MHz, $CDCl_3$), δ(ppm) 156.9 (2-C), 149.3 (4-C), 148.7 (8a-C), 139.6 (1"-C), 138.4 (1'-C), 130.1 (8-C), 129.6 (3"-C, 5"-C), 129.4 (2"-C, 6"-C), 129.3 (4'-C), 128.9 (4"-C), 128.6 (3'-C, 5'-C), 128.5 (7-C), 127.7 (6-C), 127.5 (2'-C, 6'-C), 126.4 (5-C), 125.8 (4a-C), 119.3 (3-C).[55]

IR: ṽ: 2932, 1458, 1276 cm^{-1}.[95]

GC-MS: *m/z* (%) = 282 (29), 281 (M^+) (100), 280 (100), 278 (15).[55]

m.p: 110 – 111 °C (Lit. 111 – 112 °C).[95]

3.4.1 Preparation of 2-(4-bromophenyl)-4-phenylquinoline



4-Bromobenzaldehyde (0.185 g, 1mmol), aniline (100 µL, 1 mmol), phenylacetylene (110 µL, 1 mmol) and $FeCl_3$ (1 mol%, 1.62 mg) was added to a microwave reaction vessel and irradiated for 40 minutes at 120 °C in the microwave. After the reaction was completed, ethyl acetate was added to the reaction mixture and thereafter filtered. The filtrate was concentrated. The resulting residue was subjected to column chromatography (30:1 petroleum ether-ethyl acetate, v/v), to afford a pure product as white crystals (0.289 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.25 (d, 1H, *J* = 8.52, 5-H), 8.10 (d, 2H, *J* = 8.73, 2”-H, 6”-H), 7.91 (d, 1H, *J* = 8.51, 8-H), 7.77-7.53 (m, 10H, 3-H, 6-H, 7-H, 2’-H, 3’-H, 5’-H, 6’-H, 3”-H, 4”-H, 5”-H).[96]

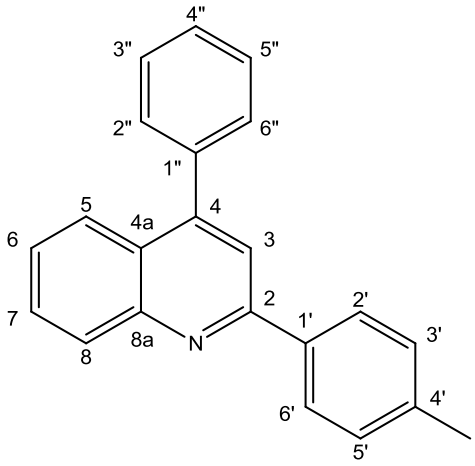
^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 155.8 (2-C), 152.5 (4-C), 150.2 (1’-C), 148.8 (1”-C), 138.5 (8a-C), 132.4 (2’-C, 6’-C), 130.3 (3’-C, 5’-C), 130.2 (8-C), 129.6 (2”-C, 6”-C), 129.4 (4”-C), 129.1 (7-C), 129.0 3”-C, 5”-C), 127.1 (6-C), 126.2 (4a-C), 124.5 (4’-C), 124.2 (5-C), 119.3 (3-C).[53]

IR: ṽ 1458, 1276, 1054, 758 cm^{-1}.[53]

GC-MS: *m/z* (%) = 360 (100), 359 (M^+) (82), 278 (41), 139 (41).[53]

m.p: 113 – 114 °C (Lit. 121 – 122 °C).[96]

3.4.2 Preparation of 2-(4-methylphenyl)-4-phenylquinoline



A mixture of *p*-tolualdehyde (116 µL, 1mmol), aniline (100 µL, 1 mmol), phenylacetylene (110 µL, 1 mmol) and $FeCl_3$ (1 mol%, 1.62 mg) was added to a microwave reaction vessel and irradiated for 40 minutes at 120 °C in the microwave. After the reaction was completed, ethyl acetate was added to the reaction mixture and thereafter filtered. The filtrate was concentrated. The resulting residue was subjected to column chromatography (30:1 petroleum ether-ethyl acetate, v/v) to afford the pure product as a pale yellow solid (0.336 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.29 (d, 1H, *J* = 8.32, 8-H), 8.11 (d, 2H, *J* = 8.32, 3'-H, 5'-H), 7.91 (d, 1H, *J* = 8.46, 5-H), 7.81 (s, 1H, 3-H), 7.77-7.72 (m, 1H, 7-H), 7.58-7.50 (m, 5H, 2"-H, 3"-H, 4"-H, 5"-H, 6"-H), 7.50-7.45(m, 1H, 6-H), 7.35 (d, 2H, *J* = 8.21, 2'-H, 6'-H), 2.44 (s, 3H).[55]

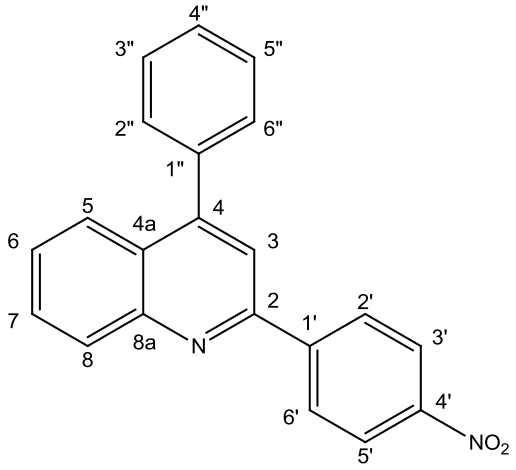
^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 157.2 (2-C), 149.6 (4-C), 149.0 (8a-C), 139.9 (4'-C), 138.8 (1"-C), 137.0 (1'-C), 130.3 (3'-C, 5'-C), 129.9 (8-C) , 129.8 (2"-C, 6"-C), 128.9 (3"-C, 4"-C, 5"-C), 128.7 (2"-C, 6"-C), 127.9 (7-C), 126.5 (6-C), 126.1 (5-C), 126.0 (4a-C), 119.6 (3-C), 21.7.[55]

IR: ṽ 2932 2932, 1738, 1622, 1458 cm^{-1}.[95]

GC-MS: *m/z* (%) = 295 (M^+) (100), 294 (100), 202 (35).[95]

m.p: 115 – 116 °C (Lit. 116 -117 °C).[87]

3.4.3 Preparation of 2-(4-nitrophenyl)-4-phenylquinoline



A mixture of 4-nitrobenzaldehyde (0.151 g, 1mmol), aniline (100 µL, 1 mmol), phenylacetylene (110 µL, 1 mmol) and $FeCl_3$ (1 mol%, 1.62 mg) was added to a microwave reaction vessel and irradiated for 40 minutes at 120 °C in the microwave. After the reaction was completed, ethyl acetate was added to the reaction mixture and thereafter filtered. The filtrate was concentrated. The resulting residue was subjected to column chromatography (30: 1 petroleum ether-ethyl acetate, v/v) to afford the pure product as a pale yellow solid (0.180 g, 55%).

^{1}H NMR (400 MHz,$CDCl_3$): δ(ppm) 8.41-8.36 (m, 4H,2'-H, 3'-H, 5'-H, 6'-H), 8.28 (d, 1H, *J* = 8.59, 5-H), 7.94 (d, 1H, *J* = 8.63, 8-H), 7.86 (s, 1H, 3-H), 7.79 (t, 1H, *J* = 8.14, 6-H), 7.58-7.53 (m, 6H, 7-H, 2"-H, 3"-H, 4"-H, 5"-H, 6"-H).[96]

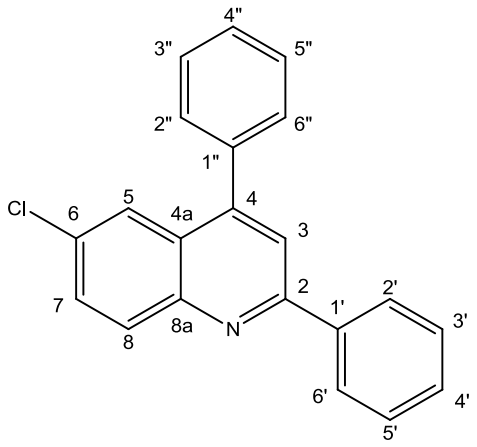
^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 154.4 (2-C), 150.4 (4-C), 149.0 (8a-C), 148.8 , 145.7 (4'-C), 138.2 (1"-C), 130.6 (1'-C), 130.5 (4"-C), 129.9 (8-C), 129.1 (7-C), 128.7 (3"-C, 5"-C), 127.7 (6-C), 126.6 (5-C), 126.2 (4a-C), 124.3 (3'-C, 5'-C), 119.4 (3-C).[96]

IR: ṽ 2850, 1738, 1622 cm^{-1}.[97]

GC-MS: *m/z* (%) = 326 (M^+) (100), 280 (44), 279 (38), 139 (29).[97]

m.p: 155 – 156 °C (Lit. 160 – 161 °C).[59]

3.4.4 Preparation of 6-chloro-2, 4-diphenylquinoline



A mixture of benzaldehyde (102 µL, 1 mmol), 4-chloroaniline (0.128 g, 1 mmol), phenylacetylene (110µL, 1 mmol) and $FeCl_3$ (1 mol%, 1.62 mg) was added to a microwave reaction vessel and irradiated for 40 minutes at 120 °C in the microwave. After the reaction was completed, ethyl acetate was added to the reaction mixture and thereafter filtered. The filtrate was concentrated. The resulting residue was subjected to column chromatography (30:1 petroleum ether-ethyl acetate, v/v) to afford the pure product as a pale yellow solid (0.285 g, 90%).

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.20-8.18 (m, 3H, 5-H, 2'-H, 6'-H), 7.87 (d, 1H, *J* = 2.09, 8-H), 7.84 (s, 1H, 3-H), 7.66-7.67 (m, 1H, 4'-H), 7.60-7.48 (m, 8H, 7-H, 3'-H, 5'-H, 2"-H, 3"-H, 4"-H, 5"-H, 6"-H).[95]

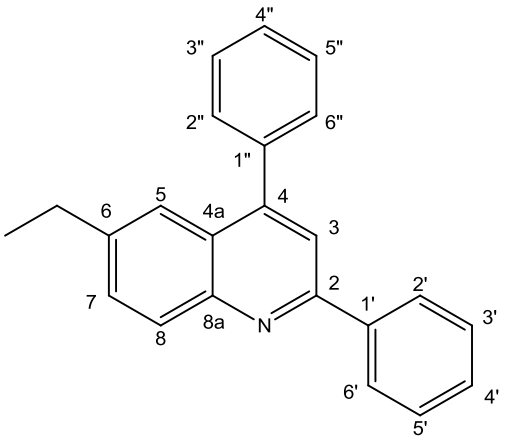
^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 157.4 (2-C), 149.0 (4-C), 147.4 (8a-C), 139.4 (4"-C), 138.1 (1'-C), 132.6 (4'-C), 132.0 (6-C), 130.9 (7-C), 130.0 (3'-C, 5'-C), 129.8 (6"-C), 129.3 (2"-C), 129.2 (2'-C, 6'-C), 129.1 (8-C), 127.9 (5-C), 126.9 (4a-C), 124.9 (3"-C, 5"-C), 120.4 (3-C).[95]

IR: ṽ 2932, 1738, 1054cm^{-1}.[88]

GC-MS: *m/z* (%) = 317 (33), 316 (60), 315 (M^+) (100), 314 (100).[88]

m.p: 129 - 130 °C (Lit. 130- 132 °C).[95]

3.4.5 Preparation of 6-ethyl-2, 4-diphenylquinoline



A mixture of benzaldehyde (102 µL, 1 mmol), 4-ethylaniline (124 µL, 1 mmol), phenylacetylene (110 µL, 1 mmol) and $FeCl_3$ (1 mol%, 1.62 mg) was added to a microwave reaction vessel and irradiated for 40 minutes at 120 °C in the microwave. After the reaction was completed, ethyl acetate was added to the reaction mixture and thereafter filtered. The filtrate was concentrated. The resulting residue was subjected to column chromatography (30:1 petroleum ether-ethyl acetate, v/v) to afford the pure product as a brown oil (0.220 g, 71%).

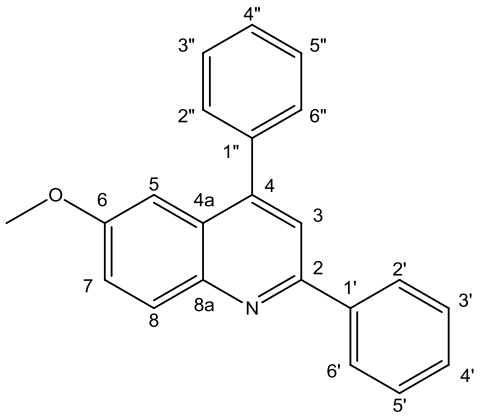
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.20 (d, 2H, *J* = 7.40, 2'-H, 6'-H), 7.80 (s, 1H, 3-H), 7.69 (s, 1H, 5-H), 7.55 (m, 10H, 7-H, 8-H, 3'-H, 4'-H, 5'-H, 2"-H, 3"-H, 4"-H, 5"-H, 6"-H), 2.79 (q, 2H, *J* = 7.40), 1.29 (t, 3H, *J* = 7.52).[75]

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 156.4 (2-C), 149.1 (4-C), 147.9 (8a-C), 142.9 (6-C), 140.1 (4"-C), 139.0 (1'-C), 131.0 (1"-C), 130.3 (3"-C), 130.0 (5"-C), 129.5 (2"-C, 5"-C), 129.2 (4'-C), 128.9 (3'-C, 5'-C), 128.7 (8-C), 127.9 (7-C), 126.1 (4a-C), 123.6 (2'-C, 6'-C), 119.8 (3-C), 29.5, 15.9.[75]

IR: ṽ 2964, 1574, 1276, 1255 cm^{-1}.[75]

GC-MS: *m/z* (%) = 309 (M^+) (100), 294 (89), 280 (71), 139 (19).[75]

3.4.6 Preparation of 6-methoxy-2, 4-diphenylquinoline



Benzaldehyde (102 µL, 1 mmol), *p*-anisidine (0.123 g, 1 mmol), phenylacetylene (110 µL, 1 mmol) and $FeCl_3$ (1 mol%, 1.62 mg) was added to a microwave reaction vessel and irradiated for 40 minutes at 120 °C in the microwave. After the reaction was completed, ethyl acetate was added to the reaction mixture and thereafter filtered. The filtrate was concentrated. The resulting residue was subjected to column chromatography (30:1 petroleum ether-ethyl acetate, v/v) to afford the pure product as a brown oil (0.220 g, 71%).

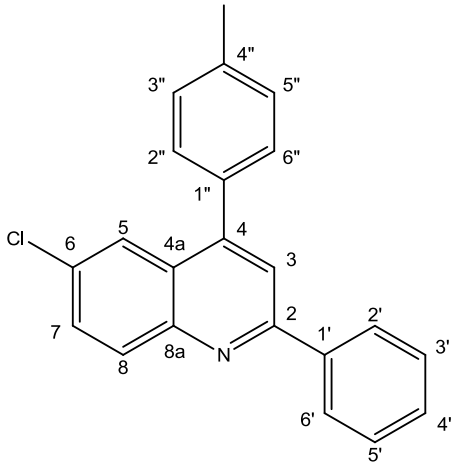
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.18-8.17 (m, 3H, 5-H, 2'-H, 6'-H), 7.78 (s, 1H, 3-H), 7.58-7.47 (m, 7H, 7-H, 3'-H, 4'-H, 5'-H, 3"-H, 4"-H, 5"-H), 7.45-7.40 (m, 2H, 2"-H, 6"-H), 7.20 (d, 1H, *J* = 2.75, 8-H), 3.81 (s, 3H).[89]

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 158.1 (2-C), 154.9 (6-C), 148.1 (4-C), 145.2 (8a-C), 140.0 (1"-C), 139.1 (1'-C), 131.9 (4"-C), 129.7 (3"-C, 5"-H), 129.3 (2"-C, 6"-C), 129.1 (5'C), 129.0 (4'-C), 128.7 (3'-C), 127.6 (6'-C), 127.0 (2'-C), 122.1 (7-C), 119.9 (3-C), 104.0 (5-C), 55.7.[89]

IR: ṽ 2932, 1738, 1622, 1054, 1022, 758 cm^{-1}.[89]

GC-MS: *m/z* (%) = 312 (20), 311 (M^+)(100), 310 (27).[89]

3.4.7 Preparation of 6-chloro-2-phenyl-4-p-tolylquinoline



Benzaldehyde (102 µL, 1 mmol), 4-chloroaniline (0.128 g, 1 mmol), 4-ethynyltoluene (127 µL, 1 mmol) and $FeCl_3$ (1 mol%, 1.62 mg) was added to a microwave reaction vessel and irradiated for 40 minutes at 120 °C in the microwave. After the reaction was completed, ethyl acetate was added to the reaction mixture and thereafter filtered. The filtrate was concentrated. The resulting residue was subjected to column chromatography (30:1 petroleum ether-ethyl acetate, v/v) to afford the pure product as a pale yellow oil (0.285 g, 86%).

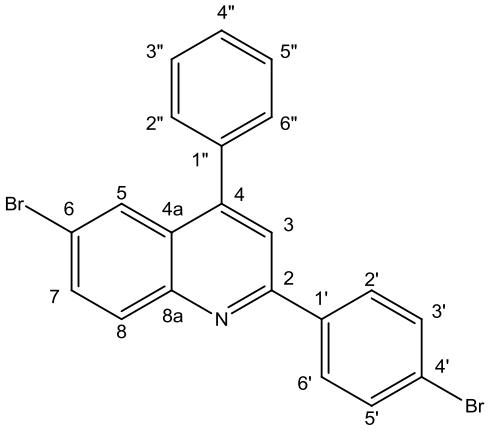
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.19 (m, 3H, 5-H, 2'-H, 6'-H), 7.90 (d, 1H, *J* = 2.19, 8-H), 7.83 (s, 1H, 3-H), 7.67 (dd, 1H, *J* = 9 and 2.38 Hz, 7-H), 7.46 (m, 7H, 3'-H, 4'-H, 5'-H, 2"-H, 3"-H, 5"-H, 6"-H), 2.50 (s, 3H).[89]

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 157.4 (2-C), 148.9 (4-C), 147.5 (8a-C), 139.6 (1"-C), 139.0 (4"-C), 135.2 (1'-C), 132.5 (3"-C, 5"-C), 132.0 (6-C), 130.7 (7-C), 129.9 (4'-C), 129.7 (3'-C, 5'-C), 129.3 (8-C), 127.9 (5-C), 127.0 (2'-C, 6'-C), 126.4 (4a-C), 124.9 (2"-C, 6"-C), 120.4 (3-C), 21.6.[89]

IR: ṽ 2850, 2432, 1738, 1622, 1244 cm^{-1}.[89]

GC-MS: *m/z* (%): 330 (38), 329 (M^+) (100), 328 (52).[89]

3.4.8 Preparation of 6-bromo-2-(4-bromophenyl)-4-phenylquinoline



4-Bromobenzaldehyde (0.185 g, 1 mmol), 4-bromoaniline (0.172 g, 1 mmol), phenylacetylene (110 µL, 1 mmol) and $FeCl_3$ (1 mol%, 1.62 mg) was added to a microwave reaction vessel and irradiated for 40 minutes at 120 °C in the microwave. After the reaction was completed, ethyl acetate was added to the reaction mixture and thereafter filtered. The filtrate was concentrated. The resulting residue was subjected to column chromatography (30:1 petroleum ether-ethyl acetate, v/v) to afford the pure product as a pale yellow oil (0.419 g, 95%).

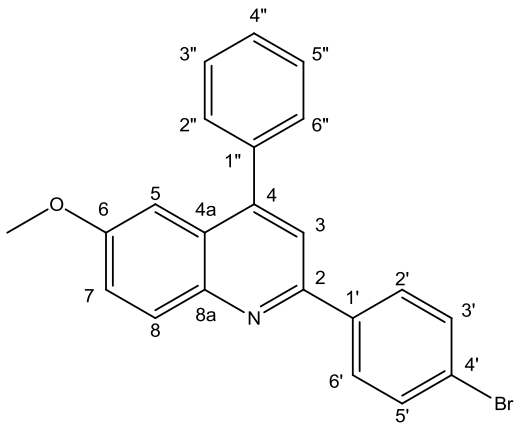
^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.14-8.08 (d, 3H), 8.04-8.03 (d, 1H), 7.82 (s, 2H), 7.67-7.60 (d, 2H), 7.59-7.52 (m, 5H).[90]

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 156.2 (2-C), 137.9 (4-C, 8a-C, 1'-C, 1"-C), 133.7 (7-C), 132.5 (8-C), 132.0 (5-C, 3'-C, 5'-C), 129.8 (2'-C, 6'-C), 129.5 (4"-C), 129.3 (3"-C, 5"-C), 128.3 (2"-C, 6"-C), 127.4 (6-C), 124.7 (4a-C), 121.2 (4'-C), 119.9 (3-C).[90]

IR: ṽ 2932, 2850 (CH), 1738 (phenyl), 1628, 1244 (CN) cm^{-1}.[90]

GC-MS: *m/z* (%) = 439 (M^+)(100), 358 (29), 278 (41), 139 (64).[90]

3.4.9 Preparation of 2-(4-bromophenyl)-6-methoxy-4-phenylquinoline



A mixture of 4-bromobenzaldehyde (0.185 g, 1 mmol), p-anisidine (0.123 g, 1 mmol), phenylacetylene (110 µL, 1 mmol) and $FeCl_3$ (1 mol%, 1.62 mg) was added to a microwave reaction vessel and irradiated for 40 minutes at 120 °C in the microwave. After the reaction was completed, ethyl acetate was added to the reaction mixture and thereafter filtered. The filtrate was concentrated. The resulting residue was subjected to column chromatography (petroleum ether: ethyl acetate, 30:1) to afford the pure product as light yellow solid (0.326 g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.16 (d, 1H, *J* = 9.14, 8-H), 8.06 (d, 2H, *J* = 8.60, 2”-H, 6”-H), 7.73 (s, 1H, 3-H), 7.64(d, 2H, *J* = 8.48, 2’-H, 6’-H), 7.56-7.52 (m, 5H), 7.42 (q, 1H, *J* = 6.49), 7.19 (d, 1H, *J* = 2.68, 7-H), 3.81 (s, 3H).[89]

^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 158.5 (2-C), 153.5 (6-C), 148.9 (4-C), 144.8 (8a-C), 138.8 (1’-C, 1”-C), 132.4 (8-C), 131.6 (3’-C, 5’-C), 129.7 (2’-C, 6’-C), 129.4 (4”-C), 129.2 (3”-C, 5”-C), 128.9 (6”-C), 127.3 (2”-C), 126.8 (4a-C), 124.2 (4’-C), 122.7 (7-C), 119.6 (3-C), 104.2 (5-C), 55.9.[89]

IR: ṽ 2932, 2850, 1738, 1622, 1054, 1022 cm^{-1}.[89]

GC-MS: *m/z* (%) = 390 (41), 389 (M^+) (100), 388 (18).[89]

m.p: 134-136 °C (Lit. 135-136 °C).[89]

3.5 Preliminary study

3.5.1 Using 0.1 mol% $FeCl_3$

Benzaldehyde (102 µL, 1 mmol), aniline (100 µL, 1 mmol) and phenylacetylene (110 µL, 1 mmol) were reacted with $FeCl_3$, (0.162 g, 0.1 mol%) under solvent-free conditions at 120 °C seven days. The reaction mixture was quenched with 10 mL ethyl acetate and was then passed through a short silica plug and the resulting mixture was concentrated. The concentrated filtrate was then subjected to ^1H NMR spectroscopy, however, the crude NMR spectrum showed trace amount of product.

3.5.2 Using 0.5 mol% $FeCl_3$

Benzaldehyde (102 µL, 1 mmol), aniline (100 µL, 1 mmol) and phenylacetylene (110 µL, 1 mmol) were reacted with $FeCl_3$ (0.810 g, 0.5 mol%) under solvent-free conditions at 120 °C seven days. The reaction mixture was quenched with 10 mL ethyl acetate and was then passed through a short silica plug and the resulting mixture was concentrated. The resulting residue was subjected to column chromatography (30:1 petroleum ether-ethyl acetate, v/v) to afford the pure product as a light yellow solid (0.201 g, 73%).

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