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A green synthesis of isoquinolines using Ru(II)/peg-400 as homogeneous recyclable catalyst *via* C-H/N-N bond activation

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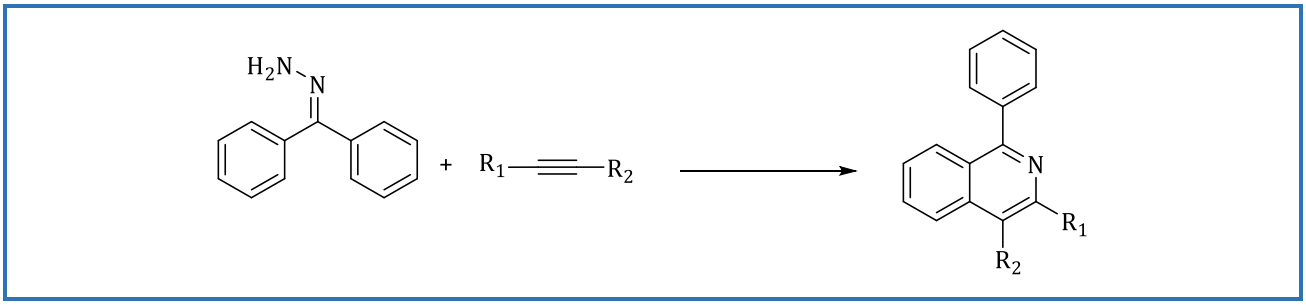
ABSTRACT

A novel and green synthesis of 1-phenyl isoquinoline derivatives has been developed using $[Ru(p\text{-cymene})Cl_2]_2$, as a homogeneous recyclable catalyst, with $Cu(OAc)_2$ and $AgSbF_6$ as oxidant and additive respectively, in PEG-400 biodegradable and green solvent *via* C-H/N-N functionalization of 1-(diphenylmethylene) hydrazine and aryl substituted acetylene. This protocol gives a simple extraction procedure, biodegradable and green solvent, high atom economy, reusable catalytic system and wide substrate scope with high yield of the product for the synthesis of isoquinoline derivatives.

Graphical Abstract



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Introduction

Isoquinoline ring has been found to possess a wide range of biological and pharmacological applications such as antimalarial, anti-HIV, insect growth retarding antitumor, antimicrobial, antileukmic antibacterial and anti-parkinson's disease activity and is also a scaffold for chiral ligands. Isoquinoline is an important source of leads for drug discovery [1]. In addition, isoquinoline represents one of the most important structural scaffolds found in various natural products and pharmaceutical compounds [2, 3]. In order to investigate this chemical space, several protocols have been developed for the synthesis of isoquinoline ring.

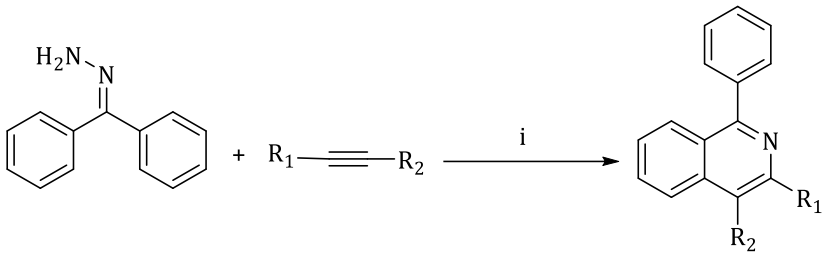
Bische-Napieralski, Pictet-Spengler, and Pomeranz–Fritsch reactions which are traditional methods for the synthesis of isoquinolines often suffer from some drawbacks such as low yields, a narrow substrate scope, and drastic reaction conditions [4]. There are certain reactions in which a pre-activated halogen group such as I or Br was used to activate the ortho-carbon of the aromatic imines. In such reactions, cyclization of *o*-halobenzimines with carbon-carbon π-components using Palladium- or nickel-catalysis is one of the challenging methods to synthesize isoquinoline derivatives [5–12]. Nowadays, C–H activation reactions [13–20] have exchanged route for accessing isoquinoline scaffolds with a more concise manner [21]. These methods provide straightforward way to isoquinolines synthesis, but they often require the use of a precious transition metal. The mentioned methodology represents one of the best strategies for the conversion of organic molecules in account of high atom and step economy, efficiency and environmental impact.

In recent years, utilization of the first row transition metals has focused on the area of C–H functionalization [22–25]. In this context, research workers independently reported Co(III)-catalyst for C–H/N–O bond functionalization of oximes with alkynes [26–29], oxidative annulations of N–H imines with alkynes in the presence of an external oxidant [30], an elegant C–H/N–H bond functionalization of amidines with diazo compounds [31], C–H/N–S bond functionalization of *N*-sulfonyl imines with alkynes [32] and recently C–H/N–N functionalization [4] of aryl hydrazones for the synthesis of isoquinoline.

Ellman et al. [33–42] reported the Rhodium(I)-catalyzed chelation-assisted C-H bond activation of aromatic imines or oximes with alkynes. Similarly, Chiba's group reported an Rh(III)-catalyzed cyclization of aryl ketone *O*-acyloximes with alkynes by C-H bond activation [43–45], *Rovis* et al. and *Li* et al., also demonstrated a rhodium-catalyzed cyclization of aromatic ketoximes with alkynes using C-H bond activation [46–48].

Recently, a less-expensive ruthenium catalyst has been widely used in the cyclization reaction rather than rhodium catalyst because of its remarkable regioselectivity and the economy [49–56]. *Jaganmohan* et al. [57, 58] reported the complete regioselective synthesis of isoquinolines by the

cyclization of ketoximes with unsymmetrical alkynes in the presence of catalytic amount of Ru(II) and NaOAc and also reported an unprecedented redox-free Ru(II)-catalysis of benzimidates with alkenes in green ethanol solvent. Recently, *Bhanage* et al. [59] reported *N*–tosylhydrazone directed annulations reaction with internal alkynes for the synthesis of isoquinoline using a ruthenium-catalysed, homogeneous and recyclable catalytic media. According to the best of our knowledge, there is no report on simple and easy availability, without any leaving group, of the substituted hydrazine directed annulations reaction with internal alkynes in green protocol.



1 **2(a-n)** **3(a-n)**

Scheme 1. Reagent and conditions: i) [Ru(*p*-cymene)Cl_2]$_2$, Cu (OAc)$_2$, $AgSbF_6$, PEG-400, 110 °C, air atm, 10-12 hrs, 85-95%

Experimental

Materials and methods

All chemical and solvents were used as commercial anhydrous grade without further purification. PEGs were dried prior to use by the literature methods [59]. Aluminum sheets 20×20 cm, silica gel 60 $F_{254,}$ and Merck grade were used for thin layer chromatography to determine progress of reaction. Melting points were determined in open capillary tube and are uncorrected. IR, ^{1}H and ^{13}C NMR spectra were recorded on a Brucker AV-400 MHz and 100 MHz spectrometer in $CDCl_3$, DMSO solvent. Mass spectra were taken on Polaris-*Q* Thermo scintific MS.

Experimental procedure

In a screw capped vial a spinevane triangular shaped teflon stirrer bar, aryl hydrazine (38.8 mg), diphenylacetate (53.4 mg), [Ru(p-cymene)Cl_2]$_2$ (10 mol%), silver hexafluoroantimonate ($AgSbF_6$) (10 mol%) and copper acetate (Cu(OAc)$_2$) (36.4 mg, 0.5 mmol) and PEG 400 (0.5 mL) were added under the air atmosphere.

The reaction mixture was stirred at 110 °C in oil bath for 12 hours. After completion of the reaction, the reaction mixture was allowed to cool down to room temperature and then extracted with 5–7 mL of diethyl ether for three to four times. The extracted diethyl ether was concentrated

under reduced pressure to get the crude residue, which was then purified by silica gel column chromatography using pet ether/ethyl acetate as eluent in order to afford the desired pure isoquinoline product.

*1,3,4-triphenylisoquinoline (**3a**)*

White solid, yield 90%, mp 187–191 °C, ^{1}H NMR (300 MHz, $CHCl_3$): δ 7.16-7.18 (m, 3H), 7.30-7.31 (d, 2H), 7.36-7.50 (m, 5H), 7.50-7.57 (m, 5H), 7.80-7.81 (d, 1H), 7.83-7.84 (d, 1H), 8.16-8.19 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.1, 149.6, 140.8, 139.7, 137.5, 136.9, 131.3, 130.4, 130.2, 129.8, 129.7, 128.4, 128.2, 127.5, 127.4, 127.2, 126.9, 126.5, 125.9, 125.4.

*3,4-bis(4-fluorophenyl)-1-phenylisoquinoline (**3b**)*

White solid, yield 88%, mp 183–184 °C, ^{1}H NMR (300 MHz, $CHCl_3$): δ 7.12-7.17 (dd, 2H), 7.34-7.38 (dd, 2H), 7.48-7.52 (m, 2H), 7.62-7.76 (m, 2H), 7.77-7.80 (m, 4H), 7.82-7.86 (m, 1H), 7.93-8.04 (d, 1H), 8.05-8.06 (d, 2H), 8.43-8.45 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3, 163.2, 160.9, 160.7, 160.0, 148.8, 132.9, 132.8, 132.1, 132.0, 130.1, 130.1, 128.6, 128.3, 127.6, 125.6, 115.6, 115.4, 114.7, 114.7, 114.4, 77.3, 77.0, 76.6.

*3,4-bis(4-(trifluoromethyl)phenyl)-1-phenylisoquinoline (**3c**)*

White solid, yield 85%, mp 208–210 °C, ^{1}H NMR (300 MHz, $CHCl_3$): δ 7.43-7.79 (m, 10H), 7.80-7.89 (m, 4H), 7.98-8.00 (d, 2H), 8.40-8.43 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.8, 148.1, 143.9, 141.0, 139.2, 136.5, 131.6, 130.6, 130.1, 129.8, 129.4, 129.1, 128.8, 128.8, 128.4, 127.8, 127.3, 125.6, 125.5, 124.7, 123.0, 122.9, 77.2, 77.0, 76.7.

*Diethyl 4,4-(1-Phenylisoquinoline-3,4-diyl)dibenzoate (**3d**)*

White solid, yield: 86%, mp 173–176 °C, ^{1}H NMR (300 MHz, $CHCl_3$): δ 1.54-1.65 (t, 6H), 4.50-4.66 (q, 4H), 7.57-7.60 (d, 2H), 7.66-7.85 (m, 6H), 8.00-8.08 (m, 4H), 8.27-8.30 (q, 2H), 8.40-8.43 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 166.3, 160.5, 148.4, 144.8, 142.0, 139.2, 136.4, 131.3, 130.5, 130.4, 130.1, 129.7, 129.6, 129.4, 129.0, 128.9, 128.8, 128.4, 127.7, 127.2, 125.6, 125.6, 77.3, 77.0, 76.6, 61.1, 60.9, 14.3, 14.2.

*3,4-bis(4-methoxyphenyl)-1-phenylisoquinoline (**3e**)*

White solid**,** yield: 91%, mp 175–176 °C, ^{1}H NMR (300 MHz, $CHCl_3$): δ 3.99 (t, 3H), 4.10 (t, 3H), 6.96-6.99 (d, 2H), 7.17-7.20 (m, 2H), 7.44-7.47 (m, 2H), 7.48-7.62 (d, 2H), 7.65-7.96 (m, 5H), 7.99-8.03 (d, 1H), 8.04-8.07 (t, 2H), 8.38-8.40 (d, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.7, 159.6, 158.8,

149.2, 142.1, 139.7, 138.9, 136.9, 130.2, 128.5, 128.5, 128.2, 122.9, 116.7, 115.3, 113.6, 113.1, 77.4, 77.0, 76.5, 55.2, 55.0.

*3,4-bis(4-chlorophenyl)-1-phenylisoquinoline (**3f**)*

White solid, yield: 90%, mp 189–191 °C, ^{1}H NMR (300 MHz, $CHCl_3$): δ 7.98-8.80 (q, 1H), 8.09-8.16 (q, 3H), 8.23-8.48 (q, 3H), 8.49-8.55 (q, 5H), 8.58-8.61 (q, 2H), 8.71-8.74 (d, 2H), 9.10-9.13 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.4, 148.1, 142.2, 139.3, 139.0, 136.5, 134.3, 133.7, 131.1, 130.4, 130.4, 130.1, 129.8, 129.5, 128.7, 128.6, 128.4, 128.3, 127.8, 127.6, 127.4, 127.0, 125.6, 125.5, 77.2, 77.0, 76.7.

*1-phenyl-3,4-dim-tolylisoquinoline (**3g**)*

White solid, yield 88%, mp 224–226 °C, ^{1}H NMR (300 MHz, $CHCl_3$): δ 2.57 (s, 3H), 2.66 (s, 3H), 7.28-7.41 (q, 1H), 7.46 (s, 1H), (q, 2H), 7.49-7.92 (m, 5H), 8.03-8.06 (d, 1H), 8.13-8.16 (d, 2H), 8.47-8.50 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 149.6, 140.7, 139.8, 137.7, 137.4, 137.0, 136.9, 131.9, 131.1, 130.2, 129.8, 129.7, 128.4, 128.3, 128.2, 128.1, 127.8, 127.6, 127.4, 127.3, 127.1, 126.4, 126.1, 125.3, 77.4, 77.0, 76.5, 21.4.

*1-phenyl-3,4-dip-tolylisoquinoline (**3h**)*

White solid, yield 92%, mp 218–220 °C, ^{1}H NMR (300 MHz, $CHCl_3$): δ 3.79 (s, 3H), 3.90 (s, 3H), 6.90-7.12 (q, 1H), 7.18 (s, 1H), 7.28-7.42 (t, 2H), 7.67-7.47 (q, 1H), 7.69-7.80 (m, 5H), 7.93-7.96 (d, 1H), 7.98-8.01 (d, 2H), 8.34-8.37(d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 156.0, 155.3, 145.7, 138.6, 136.2, 135.4, 133.3, 126.7, 125.0, 125.0, 124.7, 119.4, 113.2, 111.8, 110.1, 109.6, 73.9, 73.4, 73.0, 51.7, 51.5.

*3,4-bis(3-methoxyphenyl)-1-phenylisoquinoline (**3i**)*

White solid, yield 95%, mp 194–196 °C, ^{1}H NMR (300 MHz, $CHCl_3$): δ 4.95 (s, 3H), 5.06 (s, 3H), 8.06-8.26 (m, 1H), 8.28 (s, 1H), 8.34-8.60 (m, 1H), 8.68 (s, 2H), 8.83-8.85 (m, 1H), 8.86-8.87 (m, 1H), 8.87-8.96 (m, 5H), 9.14 (d, 1H), 9.16-9.17 (d, 2H), 9.50-9.53 (d, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.4, 160.3, 159.5, 149.9, 142.8, 140.4, 139.6, 137.6, 130.9, 130.0, 129.2, 129.2, 128.9, 123.6, 117.4, 116.0, 114.3, 113.8, 78.1, 77.7, 77.2, 55.9, 55.7.

*3,4-bis(3-chlorophenyl)-1-phenylisoquinoline (**3j**)*

White solid, yield 87%, 213–215 °C, ^{1}H NMR (300 MHz, $CHCl_3$): δ 7.46-7.51 (t, 1H), 7.55-7.58 (q, 3H), 7.59-7.73 (q, 3H), 7.75-7.95 (m, 5H), 7.97-8.08 (q, 2H), 8.18-8.21 (d, 2H), 8.57-8.80 (d, 2H). ^{13}C

NMR (75 MHz, $CDCl_3$): δ 158.0, 145.7, 139.8, 136.9, 134.1, 131.9, 131.3, 128.7, 128.0, 127.7, 127.3, 127.0, 126.3, 126.2, 126.0, 125.9, 125.4, 125.2, 124.9, 124.6, 123.2, 123.1, 74.8, 74.8, 74.5, 74.3.

Results and Discussion

In order to optimize the isoquinoline synthesis (Scheme 1), various catalysts were initially tested for the model reaction of benzophenone hydrazone **1** as a starting substrate and diphenylacetylene **2a** as a coupling partner. A summary of the experiment optimization is provided in Table 1. It was found that [Ru (*p*-cymene)Cl_2]$_2$ was the most efficient catalyst as compared to $SnCl_4$, $InCl_3$, DMAP and *L*-Proline which exhibited catalytic properties from moderate to poor yields. According to the fact that benzophenone hydrazone **1** was treated with diphenylacetylene **2a** in the absence of any other catalyst and we used $Cu(OAc)_2$ and NaOAc as a oxidants and $AgSbF_6$ (20 mol%) as additive in EtOH, it was only $Cu(OAc)_2$ which gave better yield than NaOAc as oxidant (entry 1, 2). Consequently, we further used $Cu(OAc)_2$ as oxidant for different catalysts and solvents. When the reaction was performed using [Ru(*p*-cymene)Cl_2]$_2$ (5 mole%) as catalyst, $Cu(OAC)_2$ as oxidant and $AgSbF_6$ as additive in PEG-400 as a green solvent, it gave the isoquinoline with good yield (90%) within 10 hrs at 110 °C in an air atm pressure. When reaction was performed using $SnCl_4$ as catalyst, $Cu(OAc)_2$ and NaOAc as oxidants and $AgSbF_6$ as additive in EtOH and toluene, it furnished the desired isoquinoline **3a** in low yield but better than NaOAc (Table 1, entry 3 and 4). Therefore, according to the results illustrated in (entries 1-4), it was concluded that $Cu(OAc)_2$ acted as a better oxidizing agent than NaOAc. Gratifyingly, introducing catalysts like $InCl_3$, DMAP, and *L*-Proline was found to promote the reaction (Table 1, entries 5-9) in solvents such as EtOH, DCM, toluene and PEG-400. More pleasingly, when solvents were tested (Table 1, entries 5-7), it was found that the use of PEG-400 furnished the required isoquinoline in almost a same quantitative yield (Table 1, entry 10).

Table 1. Optimization of reaction parameters

Catalyst	Solvent	Oxidant	Catalytic loading (mol %)	Additives	Tempt (°C)	Time (h)	Yield (%)
1	-	EtOH	$Cu(OAc)_2$	--	$AgSbF_6$	110	20	56
2	-	EtOH	NaOAc	--	$AgSbF_6$	110	23	45
3	$SnCl_2$	EtOH	NaOAc	5	$AgSbF_6$	110	20	60
4	$SnCl_2$	Toluene	$Cu(OAc)_2$	5	$AgSbF_6$	110	18	62
5	*L*-Proline	EtOH	$Cu(OAc)_2$	5	$AgSbF_6$	110	19	65
6	*L*-Proline	DCM	$Cu(OAc)_2$	5	$AgSbF_6$	110	21	63

7	$InCl_3$	EtOH	$Cu(OAc)_2$	5	$AgSbF_6$	110	25	70
8	$InCl_3$	DCM	$Cu(OAc)_2$	5	$AgSbF_6$	110	24	50
9	DMAP	EtOH	$Cu(OAc)_2$	5	$AgSbF_6$	110	16	68
10	DMAP	PEG-400	$Cu(OAc)_2$	5	$AgSbF_6$	110	15	75
11	[Ru(*p*-cymene)Cl_2]$_2$	DCM	$Cu(OAc)_2$	5	$AgSbF_6$	110	14	60
12	[Ru(*p*-cymene)Cl_2]$_2$	PEG-400	$Cu(OAc)_2$	5	$AgSbF_6$	110	11.3	85
13	[Ru(*p*-cymene)Cl_2]$_2$	EtOH	$Cu(OAc)_2$	5	$AgSbF_6$	110	13	80
14	[Ru(*p*-cymene)Cl_2]$_2$	Toluene	$Cu(OAc)_2$	5	$AgSbF_6$	110	14.3	78

After the optimization effect of the catalyst concentration has been studied (Table 2), it was found that loading of 10 mol% of the catalyst gave 90% of the yield in the stipulated time (Table 2, entry 2). Increase and decrease of the catalytic concentration decreases the percentage of the yield. With this optimization in our hand, we also studied the effect of decrease and increase of the reaction temperature resulted in a diminished yield of the product (Table 2, entry 6 and 7).

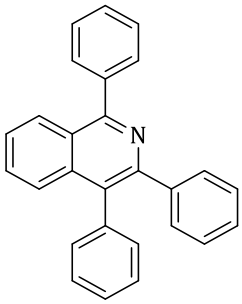
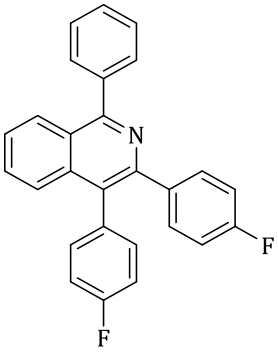
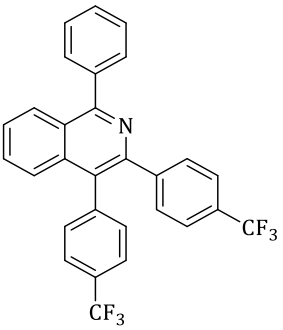
After determining the optimized condition, we investigated the scope and generality of the reaction using different internal alkynes. It was found that diarylalkyne having an electron-donating functional group on the aromatic ring furnished the corresponding isoquinoline in good yield. Interestingly, the disubstituted alkyne also participated in the annulation reaction, producing the corresponding product in moderate yield. The alkynes bearing electron-withdrawing groups such as Cl, F, CF_3, and ester on the aromatic ring also furnished the corresponding isoquinolines in good to excellent yields. When meta-substituted diarylalkynes were employed, the reaction also delivered the products in high yields. The sterically hindered *O*-substituted diarylalkyne was also found to be companionable under our reaction conditions. Analytical data for all the synthesised isoquinoline derivatives have been matched with literature value (Table 3).

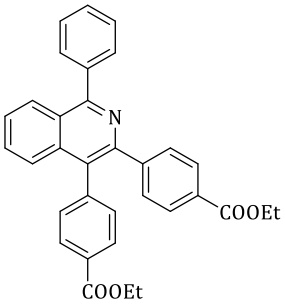
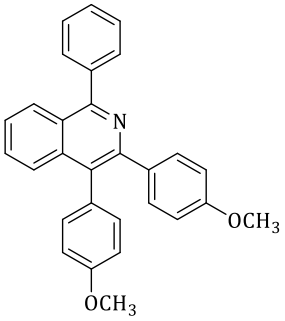
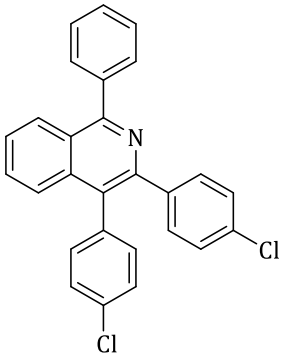
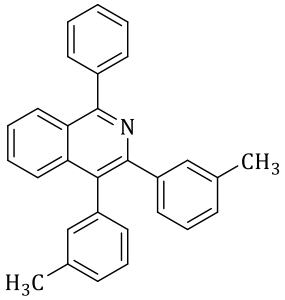
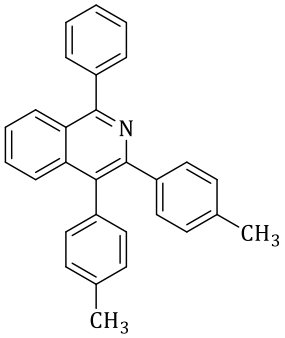
Table 2. Effect of catalyst concentration [Ru(*p*-cymene) Cl_2]$_2$ in solvent PEG-400

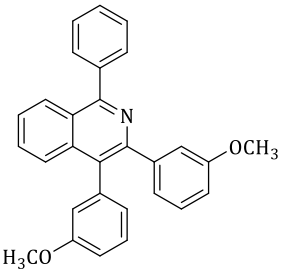
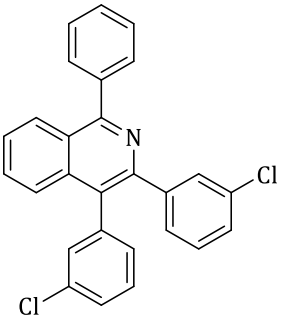
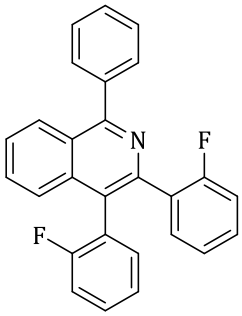
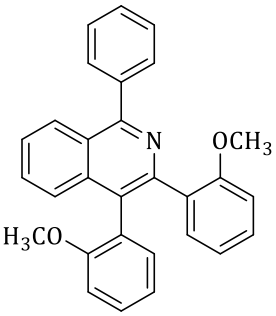
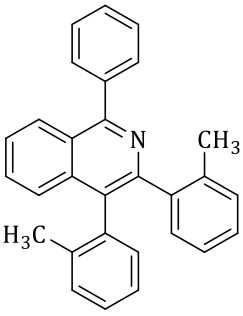
Entry	Catalyst (mole %)	Time (h)	Temperature (°C)	Yield[a] (%)
1	5	11.30	110	85
2	10	10	110	90
4	15	15	110	86
5	20	18	110	80
6	10	13	100	70
7	10	09	120	75

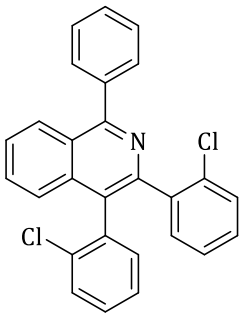
[a] Isolated yield

Table 3. Exploration of the substrate scope for the synthesis of isoquinoline derivatives

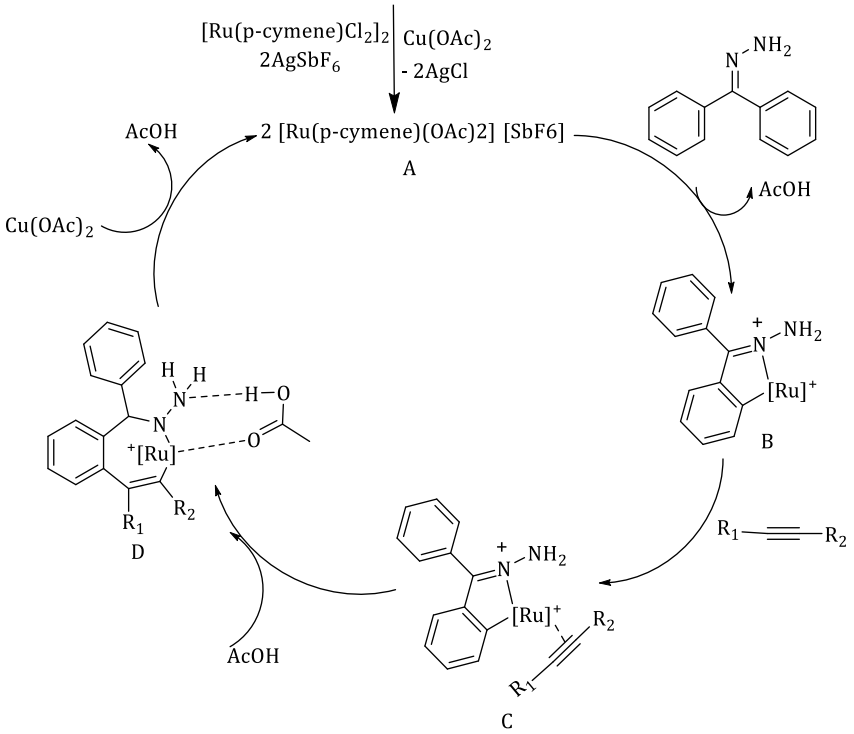
Entry	Substituted Phenyl acetylene	Time (h)	Product	M.P (°C) (Lit.)		Yield (%)
3a	H	10		187-191	[60]	90
3b	4-F	11		183-185	[60]	88
3c	4-CF_3	12		208-210	[4]	85

3d	4-COOEt	11		173-175	[4]	86
3e	4-OMe	10		175-177	[61]	91
3f	4-Cl	10.5		189-191	[60]	90
3g	3-CH_3	10		224-226	[60]	88
3h	4-CH_3	10		218-220		92

3i	3-OCH_3	11.5		194- 196	[62]	95
3j	3-Cl	12		213-215	[4]	87
3k	2-F	11		203-206		88
3l	2-OCH_3	10.5		208- 210	[62]	90
3m	2-CH_3	10		194-196		87

3n	2-Cl	11		233-235	89

On the basis of the organized experiments described above and related Ru(II)-catalyzed annulations reactions, a plausible mechanism is proposed as outlined in Scheme 2. Initially, [Ru(*p*-cymene)Cl_2]$_2$ reacted with AgSbF6 in the presence of Cu(Ac)$_2$ to generate the catalytically active complex A. Then, complex A undergoes cyclometalation with **1a** to generate B. This is followed by the migratory insertion of alkyne **2a** into B to form seven-membered Ru-cyclic intermediate C, which, upon acetic acid-assisted proton transfer, generates intermediate D. In this sense, it eventually underwent intramolecular substitution resulting in the formation of a C–N bond and the breakage of a N–N bond to furnish isoquinoline **3a** with attendant regeneration of catalytically active Ru(II) species A.



Scheme 2. Plausible mechanism for the formation of isoquinoline derivatives

Conclusions

A series of 1-Phenyl Isoquinoline derivatives has been synthesized using extraordinary ruthenium-catalyzed, homogeneous and recyclable catalytic media in PEG-400 as a green and sustainable solvent with $Cu(OAc)_2$ as oxidant and $AgSbF_6$ as additive at ambient temperature, starting with hydrazine and substituted alkynes. This methodology accounts for high atom economy, efficiency, environmental impact, and elegance as it reduces the unnecessary prefunctionalization of the starting material.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

Supporting Information

Additional supporting information related to this article can be found, in the online version, at DOI: 1022034/AJGC/2020.2.4

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