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ARTICLE

N-Tosylhydrazone directed annulation *via* C-H/N-N bond activation in Ru(II)/PEG-400 as homogeneous recyclable catalytic system: a green synthesis of isoquinolines†

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A green and sustainable methodology for the synthesis of isoquinolines using Ru(II)/PEG-400 as a homogeneous recyclable catalytic system has been demonstrated. *N*-tosylhydrazone, a rarely explored directing group has been successfully employed for the annulation type of reaction with alkynes *via* C-H/N-N activation. Short reaction time with a simple extraction procedure, wide substrate scope with high yields of products, easily prepared substrates, biodegradable solvent and scalability up to the gram level enhances the efficiency and sustainability of the proposed protocol. Further, the expensive ruthenium based homogeneous catalytic system could be reused up to a fourth consecutive cycle without any loss in its activity.

Introduction

The area of transition-metal-catalyzed direct activation of inert C−H bonds in synthetic organic chemistry has gained considerable attention. Such methodology represents a state-of-the-art for the conversion of organic molecules in account of high atom and step economy, efficiency, environmental impact, and elegance as it reduces the unnecessary prefunctionalization of starting material. Due to the unique advantages offered by this strategy over traditional methods of synthesis, it became a novel toolbox of organic chemists. This approach can also open the doors of new possibilities of retrosynthetic pathways to build complex organic scaffolds.[1]

Homogeneous catalytic systems using organic solvents are well established for C–H functionalization reactions. Still, this approach faces many challenges at the industrial scale as these they require non-reusable, expensive catalyst systems and issues related to the catalyst recovery/recycle. Heterogeneous catalysis for C–H activation can overcomes these disadvantages as it provides the prospect for ease of separation and recycling of the catalyst along with hassle-free product purification and probably continuous or several processing of compounds.[2] Though, leaching of the catalyst into reaction mixture is the serious drawback, thereby limiting its applicability. Moreover, most of the solvents in these systems are volatile organic compounds which are responsible for severe environmental threats. Thus, the development of nonhazardous alternatives avoiding the practice of any perilous and costly solvents became essential for the sustainable advancement of a chemical enterprise.[3] To satisfy both recyclability and environmental concerns, some environmentally benign methodologies like employment of supercritical carbon dioxide[4] (CO_2) and ionic liquids[5] as solvents have been evolved. A major complication associated with supercritical CO_2 is being an "under-pressure" system and also discharges CO_2 gas, so it has limited scope for its application. On the other hand, the main disadvantage which becomes hurdle in the evolvement of the ionic liquids as a solvent is that these compounds are expensive, they have tedious synthetic methods, their environmental safeties and toxicities are still anonymous. To overcome all these constraints, substantial attention has been devoted towards the development of a potent and recyclable catalytic method for C–H activation reactions. In this context, polyethylene glycols (PEGs) can serve as a replacement for traditional solvents in synthetic chemistry. Possessing negligible vapour pressure, inexpensiveness, thermally stable, biodegradable, stable in both acidic and basic media, easily recoverable, relatively low in cost and low toxicity, Polyethylene glycols serve as a compatible reaction medium for environmentally benign and safe organic transformations.[6] In addition, possessing particular properties, PEGs have been employed for catalyst immobilization[7], nanoparticle stabilisation[8], ligand stabilization[9] and as a phase transfer catalysts[10]. The toxicity profile and ecological encumbrance are known for a range of PEG molecular weights. Considering the advantages presented by PEG as a green and sustainable solvent system, our group has come up with several valuable contributions in the area of synthetic methodology as well as catalysis.[11]

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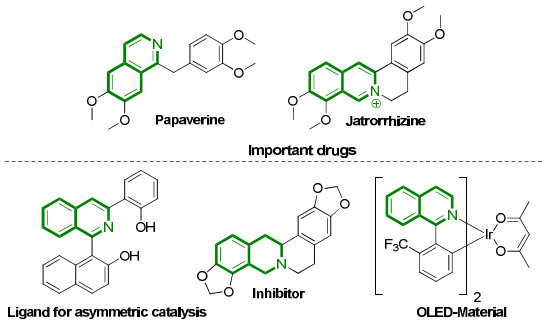
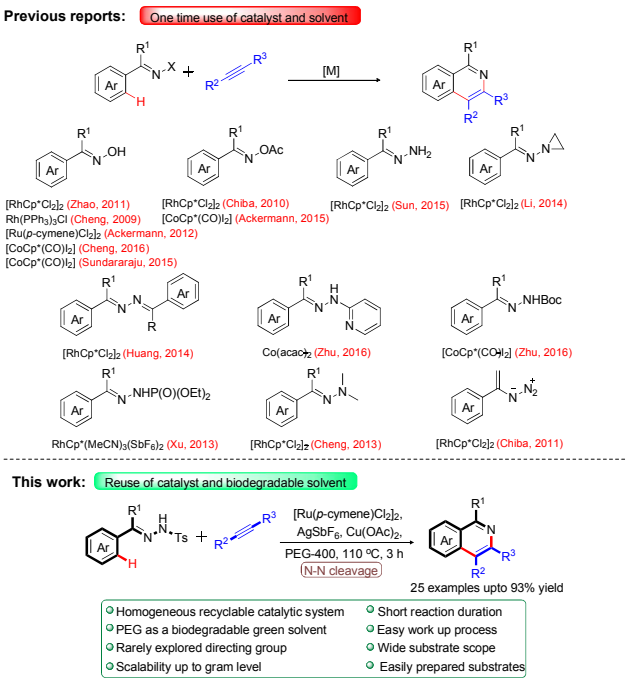


Scheme 1 Examples of important drugs and other useful molecules containing an isoquinoline skeleton.

Heterocyclic compounds with nitrogen as heteroatom are omnipresent in abundant natural, pharmaceutical and synthetic bioactive molecules. Out of them, isoquinolines form one of the most important classes with diverse biological activities like cardiovascular, anti-tumor, anti-HIV, anti-inflammatory, anti-malarial, etc.[12] For instance, papaverine and jatrorrhizine are the molecules containing isoquinoline scaffold and are effective drugs for treatment of erectile dysfunction and anti-inflammatory effect respectively.[13] In addition, isoquinoline derivatives are utilized in the synthesis of various alkaloids, organic light-emitting diodes, ligands, and inhibitors[14] (Scheme 1).

Due to the wealth of isoquinoline skeletons in various molecules, a plethora of multistep synthetic methods has been reported for their generation.[15] However, these suffer from



Scheme 2 Synthesis of isoquinolines *via* transition-metal-catalysed C-H functionalization

several drawbacks like poor yields, low regioselectivity and longer reaction duration in some cases. To overcome these shortcomings, annulation of different aromatic moieties with internal alkynes *via* C–H bond functionalization has become an effective tool for the single step synthesis of substituted isoquinolines. Most of these organic transformations *via* C–H activation are catalyzed by rhodium[16] and cobalt[17] complexes**.**

In recent years, ruthenium complexes have gained renown as promising and economic replacements of rhodium catalysts for C–H bond functionalization reactions.[18] However, only one methodology for the synthesis of isoquinolines by using ruthenium complex as a catalyst in homogeneous media has been reported by Ackermann *et al.*[19]Various directing groups are known for this approach toward substituted isoquinoline synthesis through N–O, N–C and N–N bond cleavage (Scheme 2). In literature, *N*–tosylhydrazone has rarely been explored as a directing group for C–H bond functionalization.[20] To the best of our knowledge, there is no report on *N*–tosylhydrazone directed annulations reaction with internal alkynes. Therefore, an attempt was made to study this directing group for annulations as well as different C–H functionalization reactions. In addition, all the previous protocols for substituted isoquinoline synthesis have been reported in non-reusable homogeneous reaction media. Existing literature lacks a green and sustainable route for this particular synthesis. Earlier we have reported the molecular iodine catalyzed synthesis of quinazolines by benzylic sp^3 C–H bond amination.[21] In continuation to our research work in green and sustainable chemistry, herein, we aimed for the synthesis of isoquinoline using ruthenium catalysed homogeneous recyclable catalytic media.

Results and discussion

We initiated our investigation by choosing the annulation reaction of 4-methyl-*N*′-(1-phenylethylidene)benzenesulfonyl-hydrazide **1a** with diphenylacetylene **2a** for the synthesis of 1-methyl-3,4-diphenylisoquinoline **3aa** as a model reaction (Table 1). At first, three commercially available ruthenium catalysts such as $RuCl_3.H_2O$, Cp*Ru(COD)Cl and $[Ru(p\text{-cymene})Cl_2]_2$ were tested for model reaction at 100 °C for 12 h in the presence of $Cu(OAc)_2$ as an oxidant and $AgSbF_6$ as an additive in 1,2-dichloroethane. Among these three ruthenium catalysts, $[Ru(p\text{-cymene})Cl_2]_2$ exhibited the highest catalytic activity, providing 76% yield of the desired product **3aa** (Table 1; entries 1–3). In order to make proposed protocol more greener and catalytic media reusable, the reaction was attempted in PEG-400 as a biodegradable solvent. Gratifyingly, desired product was obtained giving 74% yield (Table 1, entry 4). PEG–200, PEG–600, PEG–2000 and PEG–6000 were also tested, out of which only PEG-200 and PEG-600 could furnish the reaction to give 57% and 49% product yield respectively (Table 1, entries 6–9). Ultimately, PEG-400 found to be a potent solvent for proposed protocol. Next, a range of additives such as CuO, NaOAc, $Zn(OAc)_2$, AgOAc, CsOAc, KOAc were also screened for this reaction. Among these, except $Zn(OAc)_2$ all other additives were found to be less effective in comparison

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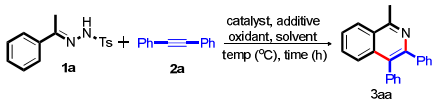
Table 1 Optimization of reaction parameters[a]

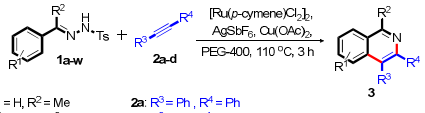


Entry	Catalyst	Solvent	Oxidant	Yield[b](%)
1	$RuCl_3.H_2O$	1,2-DCE	$Cu(OAc)_2$	Trace
2	Cp*Ru(COD)Cl	1,2-DCE	$Cu(OAc)_2$	24
3	$[Ru(p\text{-cymene})Cl_2]_2$	1,2-DCE	$Cu(OAc)_2$	76
4	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-400	$Cu(OAc)_2$	74
6	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-200	$Cu(OAc)_2$	57
7	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-600	$Cu(OAc)_2$	49
8	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-2000	$Cu(OAc)_2$	–
9	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-6000	$Cu(OAc)_2$	–
10	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-400	CuO	trace
11	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-400	NaOAc[k]	21
12	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-400	$Zn(OAc)_2$[k]	62
13	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-400	AgOAc[k]	trace
14	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-400	CsOAc[k]	trace
15	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-400	KOAc[k]	18
16[c]	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-400	$Cu(OAc)_2$	43
17[d]	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-400	$Cu(OAc)_2$	48
18[e]	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-400	$Cu(OAc)_2$	77
19[f]	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-400	$Cu(OAc)_2$	53
20[g]	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-400	$Cu(OAc)_2$	89
21[h]	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-400	$Cu(OAc)_2$	86
22[i]	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-400	$Cu(OAc)_2$	88
23[j]	$[Ru(p\text{-cymene})Cl_2]_2$	PEG-400	$Cu(OAc)_2$	64

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), catalyst (5 mol%), $AgSbF_6$ 10 mol%, oxidant (0.5 mmol), solvent (3.0 mL), 100 °C, 12 h. [b] GC yield. [c] KPF_6 was used as an additive instead of $AgSbF_6$. [d] 3 mol % $[Ru(p\text{-cymene})Cl_2]_2$ was used. [e] 10 mol % $[Ru(p\text{-cymene})Cl_2]_2$. [f] 80 °C, 12h. [g] 110 °C, 12h. [h] 120 °C, 12h. [i] 110 °C, 3 h. [j] 110 °C, 2h. [k] salts used as an additive.

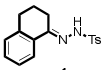
with $Cu(OAc)_2$ (Table 1, entries 10–15). Subsequently, $AgSbF_6$ was replaced by KPF_6 as an additive, however the efficiency of reaction with KPF_6 was found to be less than that of $AgSbF_6$ (Table 1, entry 16). Next, the effect of catalyst loading was determined. Lowering in catalyst concentration to 3 mol% leads to a decrease in the yield of **3aa** whereas with 10 mol% of catalyst no significant increase in yield of **3aa** was noted (Table 1, entries 17 and 18). Later, to study the effect of temperature the reaction was attempted at lower and higher temperatures at a constant duration of 12 hours. When the reaction temperature was decreased to 80 °C, only 53% product yield could be obtained while increasing temperature to 110 °C increased the product yield to 89%. Thereafter, increasing the temperature above 110°C did not produce any significant change in the product yield (Table 1, entries 19–21). Further, reduction in the reaction duration from 12 h to 3 h, did not lead to any remarkable change in the yield, however a subsequent reduction to 2 h decreased the product yield to 64% (Table 1, entries 22 and 23). Thus the optimized reaction conditions are: 4-methyl-*N*′-(1-phenylethylidene)benzenesulfonylhydrazide **1a**: 0.5 mmol, diphenylacetylene **2a**: 0.6 mmol, $[Ru(p\text{-cymene})Cl_2]_2$: 5 mol%, $Cu(OAc)_2$: 1 eqt, $AgSbF_6$: 10 mol%, PEG-400: 3 mL, 110 °C, 3 h.

Table 2 Ruthenium catalyzed annulations of *N*-tosylhydrazone with alkyne[a]



1a: R^1 = H, R^2 = Me
1b: R^1 = 4-Me, R^2 = Me
1c: R^1 = 4-OMe, R^2 = Me
1d: R^1 = 4-Br, R^2 = Me
1e: R^1 = 4-Cl, R^2 = Me
1f: R^1 = 4-F, R^2 = Me
1g: R^1 = 4-NO_2, R^2 = Me
1h: R^1 = 3-Me, R^2 = Me
1i: R^1 = 3-OMe, R^2 = Me
1j: R^1 = 3-NO_2, R^2 = Me
1k: R^1 = 3-Cl, R^2 = Me
1l: R^1 = 4-Cl,3-Me , R^2 = Me
1m: R^1 = 2-Me, R^2 = Me
1n: R^1 = H, R^2 = Et
1o: R^1 = H, R^2 = cyclopropyl
1p: R^1 = H, R^2 = Ph
1q: R^1 = H, R^2 = COPh
1w: R^1 = H, R^2 = H

2a: R^3 = Ph , R^4 = Ph
2b: R^3 = Et , R^4 = Et
2c: R^3 = Et , R^4 = Ph
2d: R^3 = Me , R^4 = Ph
2e: R^3 = Ph , R^4 = H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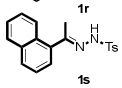
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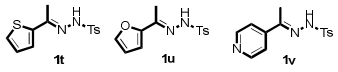
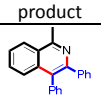
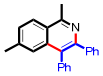
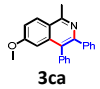
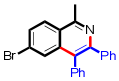
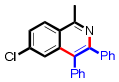
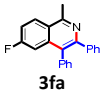
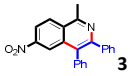
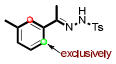
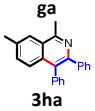
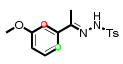
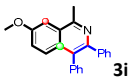
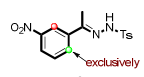
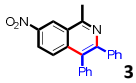

1t **1u** **1v**

Entry	1 *N*-tosylhydrazone	2 alkyne	3 product	Yield[b] (%)
1	**1a**	**2a**	 **3aa**	88
2	**1b**	**2a**	 **3ba**	90
3	**1c**	**2a**	 **3ca**	93
4	**1d**	**2a**	 **3da**	82
5	**1e**	**2a**	 **3ea**	79
6	**1f**	**2a**	 **3fa**	72
7	**1g**	**2a**	 **3ga**	64
8	 **1h**	**2a**	 **3ha**	83
9	 **1i**	**2a**	 **3ia**  **3ia'**	51 38
10	 **1j**	**2a**	 **ja**	59

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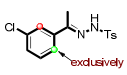
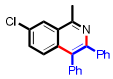
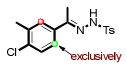
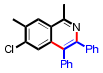
11	 **1k**	**2a**	 **3ka**	75
12	 **1l**	**2a**	 **3la**	80
13	**1m**	**2a**	 **3ma**	73
14	**1n**	**2a**	 **3na**	91
15	**1o**	**2a**	 **3oa**	87
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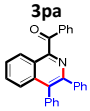
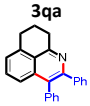
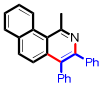
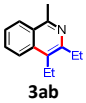
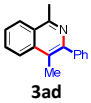
17	**1q**	**2a**	 **3qa**	46
18	**1r**	**2a**	 **3ra**	85
19	**1s**	**2a**	 **3sa**	76
20	**1t**	**2a**	 **3ta**	84
21	**1u**	**2a**	 **3ua**	80
22	**1v**	**2a**	 **3va**	57
23	**1a**	**2b**	 **3ab**	77
24	**1a**	**2c**	 **3ac**	84
25	**1a**	**2d**	 **3ad**	81
26	**1w**	**2a**	 **3wa**	-
27	**1a**	**2e**	 **3ae**	-

Reaction conditions: [a] *N*-tosylhydrazone **1** (0.5 mmol), alkyne **2** (0.6 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%), $AgSbF_6$ 10 mol%, $Cu(OAc)_2$ (0.5 mmol), PEG-400 (3.0 mL), 110 °C, 3 h. [b] GC yield.

With the identified optimized reaction conditions in hand, the synthetic versatility of the proposed protocol is highlighted by screening the compatibility of a diverse set of aromatic *N*-tosylhydrazones bearing both electron donating as well as electron withdrawing substituent (Table 2). The outcomes revealed that, reactions progressed effortlessly and tolerated a varied range of functional groups including methyl, methoxy, chloro, bromo, fluoro and nitro to afford respective products in good to excellent yields. Without any substitution on the phenyl ring of *N*-tosylhydrazone, compound **3aa** was obtained with yield of 88% (Table 2, entry 1). The introduction of electron donating groups like –Me and –OMe at para position of phenyl ring of hydrazones enhanced the corresponding product yields to 90% and 93% respectively (Table 2, entries 2 and 3) while electron withdrawing groups like –Br, –Cl, –F and $–NO_2$ at the para position affected the reaction efficiency and resulted in 82%, 79%, 72% and 64% product yields (Table 2, entries 4–7). The position of the substituent on the phenyl ring of the hydrazine reactant showed only a marginal effect on the product yield. When the substituent at the meta position of hydrazones was screened, it is worth noting that the regioselectivity of the reaction mostly depends on the steric hindrance due to substituent. For instance –Me, $–NO_2$ and –Cl at meta position of hydrazones gave single desired products **3ha**, **3ja** and **3ka** exclusively with 83%, 59% and 75% yield respectively, while –OMe at the meta position of hydrazine gave two different regioselective products **3ia** and **3ia'** with 51% and 38% yields respectively (Table 2, entries 8–11). Disubstituted *N*-tosylhydrazones easily underwent the annulation reaction to give the corresponding products **3la** in 80% yield (Table 2, entry 12). Ortho substituted hydrazone also could be employed successfully for the same reaction to give 73% of **3ma** (Table 2, entry 13). Subsequently, *N*-tosylhydrazones of propiophenone, cyclopropyl phenyl ketone, benzophenone, benzil and 1-tetralone could also be used as substrates, leading to formation of the corresponding substituted isoquinolines **3na**, **3oa**, **3pa**, **3qa** and **3ra** with 91%, 87%, 83%, 46% and 85% product yield respectively (Table 2, entries 14–18). Gratifyingly, *N*-tosylhydrazone of 1-acetylnaphthalene also worked for the proposed reaction giving respective product **3sa** with 76% yield (Table 2, entry 19). Moreover, *N*-tosylhydrazones of heterocyclic ketones also could afford the products **3ta**, **3ua** and **3va** with yields of 84%, 80% and 57% respectively (Table 2, entries 20–22). For further exploration of the substrate scope, we next turned our attention to investigate the scope of internal alkynes for the established annulation reaction. To our delight, 3-hexyne, 1-phenyl-1-butyne and 1-phenyl-1-propyne reacted efficiently with *N*-tosylhydrazone of acetophenone to give desired isoquinoline moieties **3ab**, **3ac** and **3ad** with 77%, 84% and 81% yields respectively (Table 2, entries 23–25). Hydrazone derived from aldehyde and terminal alkynes could not furnish the reaction under proposed protocol (Table 2, entries 26 and 27). This is

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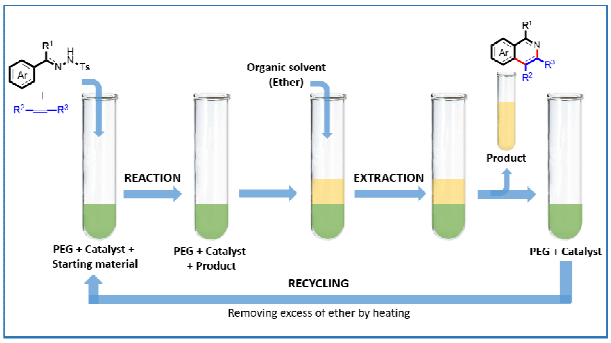
may be due to competitive dimer formation of terminal alkynes in presence of Cu salts.

The evolved synthetic protocol could be scaled up to gram quantity for the synthesis of substituted isoquinolines with no hassle. For example, the reaction of 5 mmol (1.44 g) of **1a** with 6 mmol (1.06 g) **2a** under the optimized reaction conditions produced the corresponding product 1-Methyl-3,4-diphenylisoquinoline **3aa** in 76% yield.

Having gratifying results with Ru(II)/PEG-400 as a green catalytic system, further we examined this for its reusability. For this, annulation reaction of **1a** with diphenylacetylene **2a**

(a)



(b)

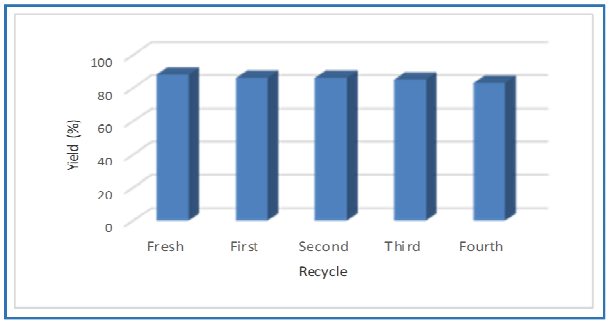
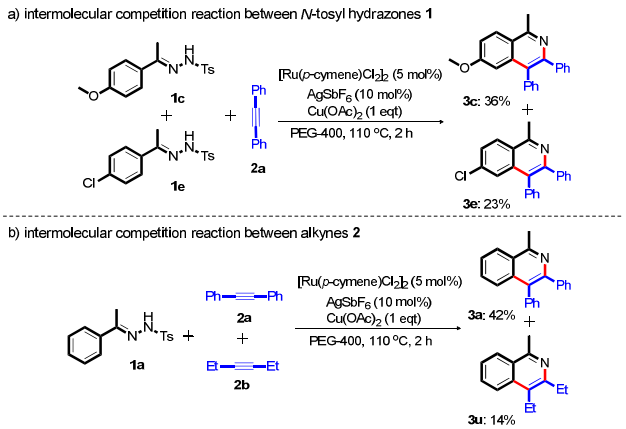


Figure 1 (a) Procedure for the reuse of catalyst and solvent system, (b) The catalyst recyclability study for annulation of 4-methyl-N′-(1-phenylethylidene)benzenesulfonylhydrazide **1a** with diphenylacetylene **2a**.

was conducted using 5 mol% $[Ru(p\text{-cymene})Cl_2]_2$ under the standard reaction conditions. After completion of reaction, the reaction mixture was extracted with 5–7 mL of diethyl ether for three to four times. The extracted diethyl ether contained the product mixture was then subjected for purification. The remaining solvent layer that contained PEG and catalyst could then be reused for the next reaction. The PEG layer was heated at 50–60 ^{o}C for 15 minutes to remove miscible traces of diethyl ether and was then subjected for second run of annulation by charging with the same substrates. The reusability and recyclability was performed following the same procedure for the synthesis of **1a**. The results of this and three successive experiments were consistent in yields 86%, 86%, 85% and 83% respectively (Figure 1). It was observed that the catalyst could work efficiently up to the 4th recycle with negligible loss in its activity and the slight reduction in yield might be due to loss of product during work-up.

Fascinated by the versatility and potency of the ruthenium(II) catalyzed C–H/N–N functionalized annulation reactions, to examine the electronic effects of the two coupling partners on the competence of this catalysis, intermolecular competition reactions were performed. An intermolecular competition experiment between para substituted *N*-tosylhydrazones **1c** and **1e** for the coupling with



Scheme 3 Intermolecular competition reactions

diphenylacetylene **2a** under the standard conditions could provide evidence about the electronic effects of the para-substituent on the reaction. GC study of the crude product exposed that, **3c** and **3e** were obtained with the product yield 36% and 23% respectively (Scheme 3), indicating that the annulation occurred more favourably with the electron-rich *N*-tosylhydrazone **3c**. Likewise, intermolecular competition experiments with diphenylacetylene **2a** and 3-hexyne **2b** with **1a**revealed the aromatic internal alkynes to be inherently much more reactive than aliphatic ones.

On the basis of previous reports and experimental observations[18a, 18c, 18d] a catalytic cycle for the Ru(II) catalyzed oxidative annulation *via* C–H bond functionalization and N–N bond breakage in the presence of $Cu(OAc)_2$ has been proposed (Scheme 4). Initially, –Cl of the catalyst might be removed by silver salt forming AgCl. $Cu(OAc)_2$ functions as a potent additive for the generation of the cationic ruthenium(II) carboxylate with hexafluoroantimonate. The ruthenium-catalyzed oxidative annulation starts from ortho C–H bond activation of **1a** with loss of acetic acid to afford a five-membered ruthenacycle **A**. This is followed by coordination of the metal with diphenylacetylene **2a** forming intermediate B. Subsequently, migratory insertion of the alkyne takes place to generate intermediate **C**. The desired annulated product **3aa** is obtained by the reductive elimination of the intermediate **C** with N–N bond cleavage and regeneration of catalytically active species by the oxidant simultaneously.

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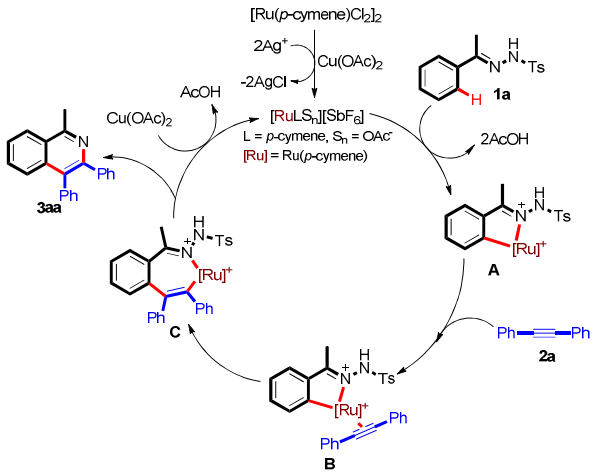

Scheme 4 Plausible reaction mechanism for annulation of *N*-tosylhydrazone with alkyne.

Conclusions

In summary, this work reports *N*-tosylhydrazone directed annulation with alkynes *via* C-H/N-N activation for the synthesis of substituted isoquinolines. The developed methodology is more economical and greener as a homogeneous recyclable catalytic system Ru(II)/PEG-400 efficiently worked for this transformation. This catalytic system could be reused up to fourth cycle with negligible loss in catalytic activity. In addition to that, the proposed protocol could be scaled up to gram level with minimal effect on the product yield. Moreover, a variety of substrates could be successfully employed under a proposed scheme with good to excellent yields.

Experimental section

General experimental details and materials

All chemicals and solvents were purchased with high purities and used without further purification. PEGs were dried prior to use by the literature methods. The progress of the reaction was monitored by gas chromatography (GC) with a flame ionization detector (FID) with a capillary column (30 m × 0.25 mm × 0.25 μm) and thin layer chromatography (using silica gel 60 F-254 plates). The products were visualized with a 254 nm UV lamp. GC-MS (Rtx- 17, 30 m × 25 mm ID, film thickness (df = 0.25 μm) (column flow 2 mL min-1 , 80 °C to 240 °C at 10 °C min-1 rise) was used for the mass analysis of the products. HRMS analysis was done commercially. Products were purified by column chromatography on 100-200 mesh silica gel. The ^{1}H NMR spectras were recorded on 400 MHz and 500 MHz spectrometer using tetramethylsilane (TMS) as an internal standard. The ^{13}C NMR spectras were recorded on 100 MHz and 125 MHz and Chemical shifts were reported in parts per million (δ) relative to tetramethylsilane (TMS) as an internal standard. Coupling constant (*J*) values were reported in hertz (Hz). Splitting patterns of proton are described as s (singlet), d (doublet), dd (doublet of doublet), t (triplet) and m (multiplet) in ^{1}H NMR spectroscopic analysis. The products were confirmed by GCMS, ^{1}H and ^{13}C NMR spectroscopy analysis.

General procedure for the synthesis of isoquinoline derivatives (3)

An oven-dried tube equipped with a magnetic stirrer bar was charged with *N*-tosylhydrazone (0.5 mmol), alkyne (0.6 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (5 mol%), silver hexafluoroantimonate ($AgSbF_6$) (10 mol%) and copper acetate ($Cu(OAc)_2$) (0.5 mmol). Subsequently, the tube was evacuated, purged with nitrogen gas three times and sealed. Then, PEG-400 (3 mL) was added via syringe under nitrogen atmosphere and and the sealed tube was placed in a preheated oil bath at 110 °C for 3h. 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. 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 to afford the desired pure product **3**.

1-Methyl-3,4-diphenylisoquinoline (3aa). Pale yellow solid; mp 154-156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.20 (m, 1H), 7.64 – 7.66 (d, *J* = 3.1 Hz, 1H), 7.57 – 7.59 (m, 2H), 7.36 – 7.32 (m, 5H), 7.24 – 7.15 (m, 5H), 3.07 (s, 3H); GCMS (EI 70 eV) m/z (% rel. inten.) 295 (M+, 51), 294 (100), 252 (21), 146 (13), 139 (9).

1,6-Dimethyl-3,4-diphenylisoquinoline (3ba). White solid; mp 159–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.9 Hz, 1H), 7.42 – 7.29 (m, 7H), 7.24 – 7.13 (m, 5H), 3.04 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.37, 149.55, 141.13, 140.22, 137.72, 136.18, 131.43, 130.23, 128.73, 128.69, 128.15, 127.55, 127.00, 126.81, 125.45, 125.06, 124.52, 22.68, 22.14; GCMS (EI 70 eV) m/z (% rel. inten.) 309 (M+, 52), 308 (100), 252 (14), 146 (17), 139 (10).

6-Methoxy-1-methyl-3,4-diphenylisoquinoline (3ca). Pale yellow solid; m.p. 179-181 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 9.1 Hz, 1H), 7.38 – 7.30 (m, 5H), 7.27 – 7.15 (m, 6H), 6.94 (d, *J* = 4.2 Hz, 1H), 3.74 (s, 3H), 3.04 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.55, 157.02, 150.12, 141.18, 138.06, 137.85, 131.30, 130.22, 128.61, 128.28, 127.57, 217.47, 127.10, 126.88, 121.88, 118.71, 104.47, 55.21, 22.65; GCMS (EI 70 eV) m/z (% rel. inten.) 325 (M+, 52), 324 (100), 281 (24), 154 (9), 146 (10), 139 (8).

6-Bromo-1-methyl-3,4-diphenylisoquinoline (3da). Slightly yellow solid; m.p. 192-194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.9 Hz, 1H), 7.80 (d, *J* = 1.8 Hz, 1H), 7.65 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.37 – 7.33 (m, 5H), 7.24 – 7.16 (m, 5H), 3.04 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.77, 150.58, 140.58, 137.38, 136.79, 131.27, 130.18, 130.01, 128.41, 128.34, 128.30, 127.65, 127.45, 127.30, 127.17, 125.06, 124.57, 22.70; GCMS (EI 70 eV) m/z (% rel. inten.) 375 (M+2, 51), 373 (M+, 53), 374 (100), 372 (95), 293 (20), 292 (21), 277 (7), 252 (17), 250 (8), 147 (41), 139 (18), 125 (9).

6-Chloro-1-methyl-3,4-diphenylisoquinoline (3ea). Pale yellow solid; m.p. 171-173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.9 Hz, 1H), 7.61 (s, 1H), 7.51 (dd, *J* = 8.9, 1.0 Hz, 1H), 7.35 – 7.33 (m, 5H), 7.20 – 7.17 (m, 5H), 3.04 (s, 3H); ^{13}C NMR (101 MHz,

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$CDCl_3$) δ 157.66, 150.58, 140.58, 137.08, 136.84, 136.35, 131.26, 130.17, 128.40, 127.65, 127.42, 127.34, 127.16, 125.09, 124.38 , 22.74; GCMS (EI 70 eV) m/z (% rel. inten.) 331 (M+2, 26), 329 (M+, 79), 330 (63), 328 (100), 293 (12), 252 (24), 146 (35).

6-Fluoro-1-methyl-3,4-diphenylisoquinoline (3fa). White solid; m.p. 145-147 °C; ^{1}H NMR (400 MHz, cdcl$_3$) δ 8.23 – 8.19 (m, 1H), 7.35 – 7.31 (m, 6H), 7.26 – 7.23 (m, 1H), 7.20 – 7.14 (m, 5H), 3.05 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.40, 161.90, 157.49, 150.37, 140.63, 138.08, 137.10, 131.17, 130.17, 128.66, 128.57, 128.38, 127.64, 127.36, 127.13, 123.41, 116.80, 116.55, 109.97, 109.75, 22.85; GCMS (EI 70 eV) m/z (% rel. inten.) 313 (M+, 51), 312 (100), 314 (8), 270 (15), 155 (9).

1,7-Dimethyl-3,4-diphenylisoquinoline (3ha). Slightly yellow solid; 131-133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.42 – 7.32 (m, 6H), 7.22 – 7.16 (m, 5H), 3.04 (s, 3H), 2.56 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.12, 148.76, 141.21, 137.89, 136.50, 134.30, 132.17, 131.51, 130.38, 129.18, 128.26, 127.69, 127.15, 126.91, 126.45, 126.22, 124.62, 22.86, 22.00; GCMS (EI 70 eV) m/z (% rel. inten.) 309 (M+, 77), 308 (100), 252 (18), 146 (25), 139 (10).

7-Methoxy-1-methyl-3,4-diphenylisoquinoline (3ia). Yellow solid; m.p. 121-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 15.2 Hz, 1H), 7.37 – 7.30 (m, 6H), 7.24 – 7.13 (m, 6H), 3.96 (s, 3H), 3.01 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.02, 156.14, 147.90, 141.21, 137.90, 131.50, 131.41, 130.37, 129.31, 128.29, 128.16, 127.70, 127.47, 127.22, 126.86, 122.35, 103.71, 55.64, 23.00; GCMS (EI 70 eV) m/z (% rel. inten.) 325 (M+, 84), 324 (100), 281 (39), 162 (9), 140 (12), 139 (17).

5-Methoxy-1-methyl-3,4-diphenylisoquinoline (3ia'). White solid; mp. 145-147 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 8.1 Hz, 1H), 7.24 – 7.21 (m, 2H), 7.16 – 7.09 (m, 8H), 6.95 (d, *J* = 7.7 Hz, 1H), 3.39 (s, 3H), 3.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.08, 156.83, 151.05, 141.59, 141.41, 130.36, 130.20, 127.90, 127.75, 127.41, 127.29, 127.12, 126.45, 125.61, 118.02, 110.05, 55.53, 23.41; GCMS (EI 70 eV) m/z (% rel. inten.) 325 (M+, 81), 324 (100), 308 (37), 154 (29), 146 (11).

7-Chloro-1-methyl-3,4-diphenylisoquinoline (3ka). White solid; m.p. 143-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 1.2 Hz, 1H), 7.60 (d, *J* = 9.0 Hz, 1H), 7.50 (dd, *J* = 9.0, 1.2 Hz, 1H), 7.34 – 7.33 (m, 5H), 7.24 – 7.17 (m, 5H), 3.03 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.84, 149.75, 140.55, 137.02, 134.39, 132.25, 131.25, 130.68, 130.17, 128.99, 128.32, 128.15, 127.65, 127.36, 127.11, 126.82, 124.50, 22.70; GCMS (EI 70 eV) m/z (% rel. inten.) 331 (M+2, 18), 329 (M+, 56), 330 (42), 328 (100), 293 (10), 252 (14), 146 (24).

6-Chloro-1,7-dimethyl-3,4-diphenylisoquinoline (3la). Slightly yellow solid; m.p. 158-160 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.47 (s, 1H), 7.32 (d, *J* = 5.7 Hz, 5H), 7.21 – 7.10 (m, 5H), 3.01 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.53, 149.69, 140.74, 138.69, 137.23, 134.71, 133.71, 131.29, 130.16, 128.41, 128.27, 127.60, 127.49, 127.24, 126.99, 125.65, 125.06, 22.62, 20.96; HRMS (ESI) calcd. For $C_{23}H_{18}ClN$ [M+H]: 344.1206, found: 344.1202.

1-Ethyl-3,4-diphenylisoquinoline (3na). White solid; m.p. 114-116 °C; ^{1}H NMR (400 MHz, cdcl$_3$) δ 8.26 – 8.24 (m, 1H), 7.67 – 7.66 (m, 1H), 7.58 – 7.56 (m, 2H), 7.41 – 7.32 (m, 5H), 7.25 – 7.16 (m, 5H), 3.45 (q, *J* = 7.6 Hz, 2H), 1.54 (t, *J* = 7.6 Hz 3H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 162.27, 149.26, 141.11, 137.73, 136.32, 131.39, 130.34, 129.70, 128.94, 128.21, 127.56, 127.09, 126.88, 126.43, 126.40, 125.27, 125.14, 28.83, 14.01; GCMS (EI 70 eV) m/z (% rel. inten.) 309 (M+, 55), 308 (100), 293 (13), 280 (7), 154 (7), 146 (8), 139 (6).

1-Cyclopropyl-3,4-diphenylisoquinoline (3oa). White solid; m.p. 149-151 °C; ^{1}H NMR (400 MHz, cdcl$_3$) δ 8.49 – 8.47 (m, 1H), 7.65 – 7.63 (m, 1H), 7.61 – 7.54 (m, 2H), 7.37 – 7.33 (m, 5H), 7.23 – 7.20 (m, 2H), 7.16 – 7.15 (m, 3H), 2.85 – 2.79 (m, 1H), 1.39 – 1.37 (m, 2H), 1.14 – 1.12 (m, 2H); ^{13}C NMR (101 MHz, cdcl$_3$) δ 160.55, 148.66, 141.14, 137.97, 136.11, 131.43, 130.42 , 129.59, 128.24, 128.01, 127.33, 127.04, 126.81, 126.33, 126.26, 126.22, 124.83, 13.62, 9.38; GCMS (EI 70 eV) m/z (% rel. inten.) 321 (M+, 68), 320 (100), 243 (11), 152 (10).

1,3,4-Triphenylisoquinoline (3pa). Yellow solid; m.p. 169-171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.3 Hz, 1H), 7.85 – 7.83 (m, 2H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.62 – 7.49 (m, 5H), 7.46 – 7.35 (m, 5H), 7.33 – 7.31 (m, 2H), 7.24 – 7.16 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.81, 149.64, 140.90, 139.81, 137.55, 136.97, 131.36, 130.46, 130.24, 129.96, 129.78, 128.55, 128.33, 127.56, 127.51, 127.30, 127.00, 126.60, 126.03, 125.44; GCMS (EI 70 eV) m/z (% rel. inten.) 357 (M+, 95), 171 (100), 145 (5), 118 (8).

1-Methyl-3,4-diphenylbenzo[h]isoquinoline (3sa). Slightly yellow solid; mp 142-144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 7.3 Hz, 1H), 7.78 – 7.71 (m, 2H), 7.66 – 7.63 (m, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.42 (d, *J* = 4.5 Hz, 2H), 7.34 (s, 3H), 7.25 – 7.19 (m, 5H), 3.43 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.40, 150.90, 140.59, 138.01, 137.20, 132.95, 131.65, 131.12, 130.19, 129.64, 128.72, 128.25, 127.64, 127.28, 127.17, 127.14, 126.84, 126.60, 124.20, 123.92, 30.52; GCMS (EI 70 eV) m/z (% rel. inten.) 345 (M+, 61), 344 (100), 302 (17), 171 (9), 164 (16).

7-Methyl-4,5-diphenylthieno[2,3-c]pyridine (3ta). White solid; m.p. 145-147 °C; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.03 (d, *J* = 5.4 Hz, 1H), 7.33 – 7.25 (m, 5H), 7.20 – 7.08 (m, 6H), 2.77 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d6) δ 151.24, 150.46, 145.76, 140.65, 138.19, 133.93, 133.49, 130.66, 130.50, 128.83, 128.10, 127.89, 127.76, 127.44, 123.95, 23.62; GCMS (EI 70 eV) m/z (% rel. inten.) 301 (M+, 57), 300 (100), 285 (4), 258 (16), 150 (12), 149 (9).

3,4-Diethyl-1-methylisoquinoline (3ab). Yellow liquid; b.p. 140-142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.3 Hz, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.6 Hz, 1H), 3.03 (q, *J* = 7.6 Hz, 2H), 2.95 (q, *J* = 7.6 Hz, 2H), 2.90 (s, 3H), 1.33 (t, *J* = 7.6 Hz, 3H), 1.27 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.75, 152.52, 135.11, 129.48, 127.17, 126.12, 126.05, 125.25, 123.32, 28.47, 22.33, 20.66, 15.24, 14.95; GCMS (EI 70 eV)

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m/z (% rel. inten.) 199 (M+, 45), 198 (100), 184 (25), 170 (10), 128 (14), 115 (9), 91 (10).

4-ethyl-1-methyl-3-phenylisoquinoline (3ac). White solid; m.p. 121-123 ^{o}C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.3 Hz, 1H), 8.07 (d, J = 8.3 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.51 – 7.36 (m, 5H), 3.01– 2.96 (m, 5H), 1.25 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.82, 150.69, 141.83, 135.12, 129.80, 129.17, 128.52, 128.13, 127.37, 126.68, 126.28, 126.14, 124.12, 22.48, 21.64, 15.67; GCMS (EI 70 eV) m/z (% rel. inten.) 247 (M+, 56), 246 (100), 232 (17), 231 (21), 230 (13), 217 (7), 115 (14).

Conflicts of interest

There are no conflicts to declare.

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N-Tosylhydrazone directed annulation *via* C-H/N-N bond activation in Ru(II)/PEG-400 as homogeneous recyclable catalytic system: a green synthesis of isoquinolines

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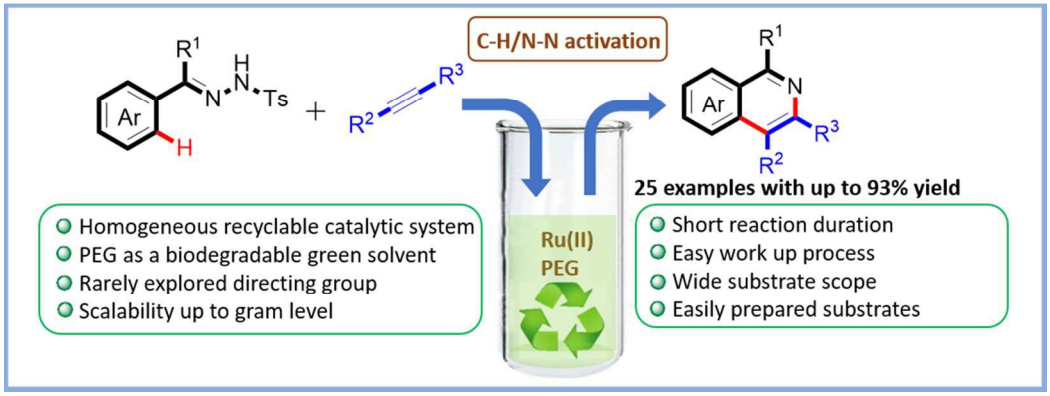

A green and sustainable methodology for the synthesis of isoquinolines using Ru(II)/PEG-400 as homogeneous recyclable catalytic system and *N*-tosylhydrazone, a rarely explored directing group has been reported.