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Ru(II)/PEG-400 as a Highly Efficient and Recyclable Catalytic Media for Annulation and Olefination Reactions *via* C-H Bond Activation

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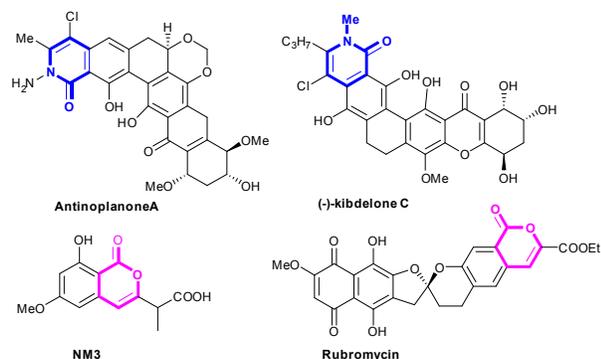
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In this report synthesis of isoquinolinones, isocoumarins, N-methyl isoquinolinones and olefination of Weinreb amides by C-H bond activation using Ru(II)/PEG-400 as green and recyclable media is documented. This developed methodology is capable for the regioselective and stereoselective construction of new C-C, C-O and C-N bonds by the one step cleavage of C-H, N-H, O-H and N-O bonds. This method is environmentally benign due to its peculiar characteristics such as i) high atom economy, ii) reuse of expensive ruthenium based homogeneous catalytic system, iii) mild reaction conditions with simple extraction process and, iv) importantly, all the systems derived from this protocol are scalable up to gram level.

Introduction

Isoquinolinones and isocoumarins are the six membered lactams and lactones which are useful intermediates in organic synthesis.¹ Isoquinolinone is the class of the most powerful heterocycle, which is found in many natural products as well as biologically active molecules.² For instance, natural product Antinoplanone A and (-)-kibdelone C, as an anticancer polyketide which were isolated from a rare Australian actinomycete and both have the isoquinolinone skeleton (Scheme 1).³

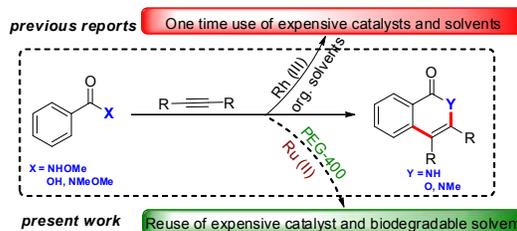


Scheme 1. Examples of important drug molecules containing isoquinolinone and isocoumarin skeleton.

As well as, isocoumarins have also the greatest attention to synthetic and medicinal chemists due to their diverse

biological activities, including antifungal, antiallergic, antitumor, phytotoxic, antimicrobial, anti-inflammatory, antidiabetic, and immunomodulatory activities.⁴ The isocoumarin framework also represents one of the advantaged structures for the development of natural product inspired compounds of biological interest (Scheme 1).⁵ Traditionally, multistep synthesis of isoquinolinone and isocoumarin has reported by many groups.⁶ However, remain some limitations such as low yields, poor regioselectivity, and harsh reaction conditions in some cases.

For the last decade, research is focused to avoid the multistep synthesis. The transition metal-catalyzed direct C-H bond functionalization is one of the key emerging strategies that is currently attracting tremendous attention to provide alternative environmentally friendly and efficient ways for one step construction of C-C, C-O and C-N bonds.⁷ Recently, some groups like Fagnou's group and Wang's group have reported the isoquinolinone synthesis by Rh(III)/Ru(II) catalyzed *ortho*-C-H bond activation of amides.⁸ Whereas, some groups like Miura's group and Ackermann's group reported the isocoumarin synthesis from acid using Rh(III)/Ru(II) catalytic system.⁹



Scheme 2. Previous reports and Ru(II) catalysed annulations *via* C-H bond activation.

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† Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available:

This method compares favorably with conventional transformations in terms of atom and step-economy. Mostly, the homogeneous transition metals like Pd(II),¹⁰ Ru(II)¹¹ and Rh(III)¹² homogeneous complexes have attracted considerable attention for C–H bond activation. Nevertheless, the use of homogeneous catalytic system in industrial scale is challenging because they are highly expensive and one time use. The separation of homogeneous catalyst from the reaction mixture is also the serious issue in the pharmaceutical industries. The main drawback is the wastage of rarely available and expensive metal precursor. With these great importance, some groups reported the heterogeneous recyclable catalytic system for the C–H bond activation,¹³ but they have limited scope. The leaching of metal catalyst into the reaction mixture causes the serious problem. In order to gratify recyclability and environmental concerns, more facile and efficient approach is to immobilize the catalyst in a liquid phase by dissolving it into a nonvolatile and non mixing liquid, such as ionic liquids¹⁴ and poly (ethylene glycols) (PEGs). Although ionic liquids provide some disadvantages, such as a complicated method for the synthesis of ionic liquids as well as their environmental safety is still debated because the toxicity and environmental issues.

It is well documented that PEG is stable at high temperature, easily available, inexpensive, recoverable, biodegradable and nontoxic material.¹⁵ PEG also serves as an efficient medium for environmentally friendly and safe chemical reactions. In recent years, PEGs have been successfully utilized as reaction media for the metal-catalyzed cross-coupling reactions with facile recyclability of solvents as well as catalysts.¹⁶ Considering the importance of Ru(II)/PEG as green, environmentally and economically benign catalytic system for the development of C–C and C–O bond formations.¹⁷ Herein we report the Ru(II)/PEG catalytic system for the synthesis of isoquinolinones, isocoumarin, *N*-methyl isoquinolinones and *ortho*-olefinated products via C–H bond activation of aromatic amides and acids.

Results and discussion

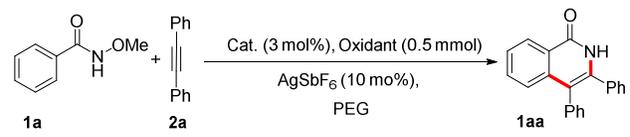
For initial tests, we chose the *N*-methoxybenzamide **1a** and diphenylacetylene **2a** as model substrates for the annulation reaction using RuCl₃·3H₂O (3 mol%), Cu(OAc)₂·H₂O (0.5 mmol), AgSbF₆ (10 mol%), PEG-400 (4 mL) at 100 °C for 24 h and trace amount of isoquinolinone product **1aa** was observed (Table 1). Next, different Ru-catalysts were tested, and series of experiments were extended out to examine the essence of various reaction parameters such as solvents, oxidants, temperature, time and catalyst loading on the takings of the desired product. The Ru based catalysts were screened such as Cp*Ru(COD)Cl, and [{RuCl₂(*p*-cymene)}₂] (Table 1, entries 2–3). It was observed that [{RuCl₂(*p*-cymene)}₂] catalysts showed best catalytic activity for the annulations and forms isoquinolinone **1aa** with maximum yield (Table 1, entry 3). The product was purified and confirmed by the characterisation of ¹H and ¹³C NMR.

Among the various PEG solvents, it was found that PEG-400 is superior to PEG-200, PEG-600, PEG-2000 and PEG-6000

(Table 1, entries 4–7). The mixture of PEG-400 and H₂O was not set up to be more effective than PEG-400 (Table 1, entry 8). Instead of Cu(OAc)₂·H₂O, other oxidants such as CuO, NaOAc, AgOAc and CsOAc were also tested during the screening of the reaction and all these oxidants are found to be ineffective for this transformation (Table 1, entries 9–12). The effect of temperature was studied (110, 80, 60 and 50 °C), in between 110 °C - 60 °C showed the best result (Table 1, entries 13–15). The yield of product **1aa** decreased with time decreases less than 12 h. (Table 1, entries 16–18). Thus, the final optimized reaction conditions for isoquinolinone synthesis are: **1a** (0.5 mmol), **2a** (0.5 mmol), [{RuCl₂(*p*-cymene)}₂] (3 mole%), Cu(OAc)₂·H₂O (0.5 mmol), AgSbF₆ (10 mol%), PEG-400 (4 mL) at 60 °C for 12 h.

Later on the synthesis of isoquinolinones, we went towards the optimization study for synthesis of isocoumarin from aromatic benzoic acid. With changes of optimization parameters like temperature, oxidant concentration and time. In the full optimization condition, the isocoumarin synthesis requires 80 °C temperature and 18 h, this might be due to the weak directing group properties of –OH group of acid. The final optimized reaction conditions for isocoumarin synthesis from acid are: **8a** (0.5 mmol), **2a** (0.5 mmol), [{RuCl₂(*p*-cymene)}₂] (3 mol%), Cu(OAc)₂·H₂O (0.5 mmol), AgSbF₆ (10 mol%), PEG-400 (4 mL) at 80 °C for 18 h. Evaluation of the C–H bond activation for annulations strategy examined by the coupling of diphenylacetylene **2a** with various amides and acid derivatives (Table 3). Firstly, to investigate the scope of *N*-substituted benzamides such as the amide containing N–O and N–H bond, such as NHOMe **1a**, NHOBn **2a**, NHOH **3a**, provided

Table 1. Optimization of reaction parameters^a



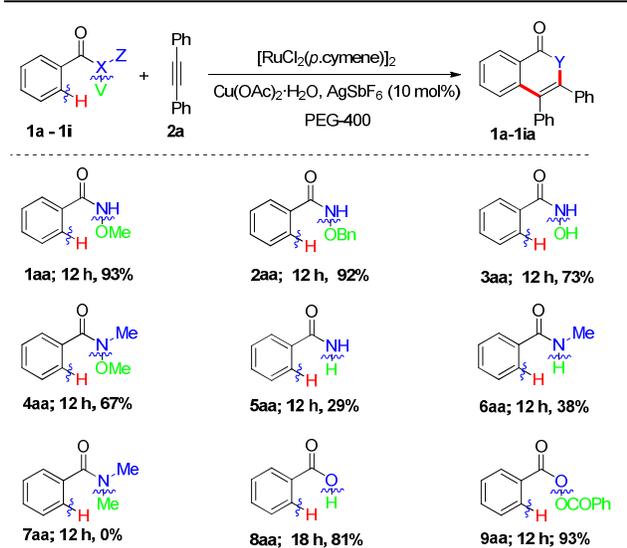
Entry	Catalyst	Solvent	Oxidant	Yield (%) ^b
1	RuCl ₃ ·3H ₂ O	PEG-200	Cu(OAc) ₂ ·H ₂ O	trace
2	Cp*Ru(COD)Cl	PEG-200	Cu(OAc) ₂ ·H ₂ O	15
3	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	PEG-200	Cu(OAc) ₂ ·H ₂ O	61
4	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	PEG-400	Cu(OAc) ₂ ·H ₂ O	93
5	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	PEG-600	Cu(OAc) ₂ ·H ₂ O	37
6	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	PEG-2000	Cu(OAc) ₂ ·H ₂ O	-
7	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	PEG-6000	Cu(OAc) ₂ ·H ₂ O	-
8	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	PEG-400/H ₂ O (3:1)	Cu(OAc) ₂ ·H ₂ O	23
9	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	PEG-400	CuO	trace
10	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	PEG-400	NaOAc	trace
11	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	PEG-400	AgOAc	trace
12	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	PEG-400	CsOAc	trace
13 ^c	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	PEG-400	Cu(OAc) ₂ ·H ₂ O	93
14 ^d	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	PEG-400	Cu(OAc) ₂ ·H ₂ O	93
15 ^e	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	PEG-400	Cu(OAc) ₂ ·H ₂ O	81
16 ^f	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	PEG-400	Cu(OAc) ₂ ·H ₂ O	93
17 ^g	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	PEG-400	Cu(OAc) ₂ ·H ₂ O	93
18 ^h	[[RuCl ₂ (<i>p</i> -cymene)] ₂]	PEG-400	Cu(OAc) ₂ ·H ₂ O	87

^aReaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), catalyst (3 mol%), oxidant (0.5 mmol), solvent (4.0 mL), 100 °C, 24 h, ^bGC yield, ^c80 °C, ^d60 °C, ^e50 °C, ^f18 h, ^g12 h, ^h10 h.

excellent yields of product **1aa-3aa** and this is due to good leaving group (–OR) of the N–O bond. Interestingly, in the absence of N–H bond like NMe (OMe) of **4a**, the –OMe also acts as a good leaving group and resulted in *N*-methyl isoquinolinone product **4aa**. It indicates that the high activity of the Ru(II) catalyst for the N–O insertion. Also, amide containing N–H bond like NH₂ **5a** and NHMe **6a** shown lower yield of **5aa** and **6aa**. However, in the absence of N–H and N–O bond, such as N(Me)₂ amide **7a** is difficult to convert into the desired product **7aa**. Parallel to amide, the same catalytic system shows great use for isocoumarin synthesis from aromatic acid derivatives. The Benzoic acid **8a** requires 80 °C temperature for 18 h to the maximum conversion of **8aa**. However, acid derivatives containing good leaving group like benzoyl peroxide **9a** showed an excellent yield of **9aa**.

With optimal reaction conditions at hand, we explored the detail substrate scope with Ru(II)/PEG catalyzed annulations of *N*-methoxy aromatic amides and acids with respect to the alkyne (Table 3). The reaction tolerates a remarkably broad range of functional groups. Amides/Acid containing neutral, electron-donating and electron-withdrawing groups afforded the desired products in excellent yields. The model reaction for the synthesis of isoquinolinone and isocoumarin showed an excellent yield of products **1aa** and **8aa** respectively. The effects of electron donating and withdrawing groups on *N*-

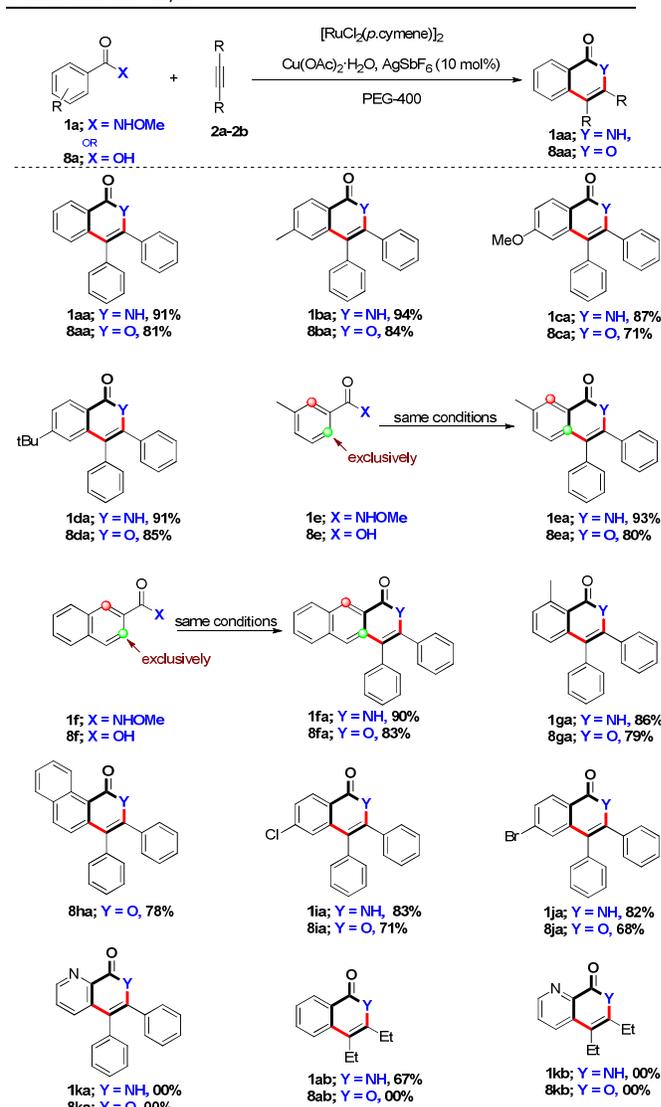
Table 2. Ruthenium-catalyzed reactivity of different amide and acid derivatives with diphenylacetylene



^aReaction conditions: amide/acid derivatives **1a-9a** (0.5 mmol), diphenylacetylene **2a** (0.5 mmol), [[RuCl₂(*p*-cymene)]₂] (3 mol %), Cu(OAc)₂·H₂O (0.5 mmol), PEG-400 (4.0 mL), 60 °C ^bGC yield.

methoxybenzamide **1a** and benzoic acid **8a** were studied. It was found that electron donating groups such as –Me, –OMe and –*t*butyl produced corresponding products **1ba-1da** and **8ba-8da** in good to excellent yields. Next, the regioselectivity of substituted amide and acid **1e-1f** and **8e-8f** was examined.

Table 3. Ruthenium catalyzed oxidative annulations of *N*-methoxybenzamides and benzoic acids with alkyne



^aReaction conditions: *N*-methoxy-*N*-methyl benzamide (**1a**, 0.5 mmol), diphenylacetylene **2a** (0.5 mmol), [[RuCl₂(*p*-cymene)]₂] 3 mol%, PEG-400 (4 mL), Cu(OAc)₂·H₂O (0.5 mmol), PEG-400 (4 mL), 60 °C, 12 h, for acid derivatives 80 °C, 18 h, ^bYield of isolated product.

The *meta*-substituted *N*-methoxybenzamide **1e** and benzoic acid **8e** regioselective coupled with **2a** at the less hindered C–H bond of **1e** and **8e** exclusively to give coupling product **1ea** and **8ea** in 93 and 80% yields respectively. The regioselective reactivity of alkyne toward less hindered side was confirmed by ¹H NMR spectroscopy. The singlet present at 8.27 ppm of **1ea** and singlet at 8.20 ppm of **8ea** indicate that exclusively formation of **1ea** and **8ea** (ESI, S2). Similarly, *N*-methoxy-2-naphthamide **1f** and 2-naphthoic acid **8f** also underwent the annulation reaction regioselectively with **2a** and exclusively formation of isoquinolinone **1fa** [confirmed by singlet at 9.08 ppm] and isocoumarin **8fa** [confirmed by singlet at 9.01 ppm] in 90 and 83% yield, respectively. In addition, the catalytic

reaction proceeded very well with *ortho*-substituted aromatic *N*-methoxyamide such as *N*-methoxy-2-methylbenzamide **1g** and 2-methylbenzoic acid **8g**, which yielded coupling products **1ga** and **8ga** in 86 and 79% yield, respectively. To explore the scope of the coupling reaction, various substituted aromatic *N*-methoxyamides **1i–1k** and acids **8h–8k** were examined and provided **1ia–1ka**, **8ha–8ka** in excellent to good yields, respectively. The heterocyclic amides are not reactive, products of **1la** and **8la** were not observed. The catalytic system is selectively important for annulations of aliphatic internal alkyne and *N*-methoxyamide to give the product **1ab** and the **8ab**, **1kb** and **8kb** were not observed. Unfortunately, under the reported reaction conditions, terminal alkynes failed to afford the corresponding cyclist products.

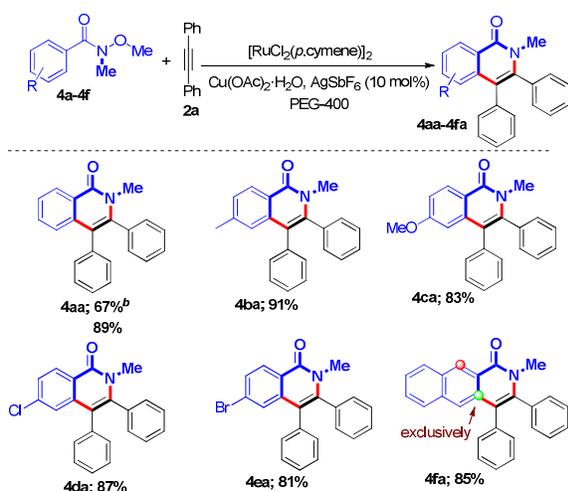
To extend the scope of catalytic system, for the C–H activation/cyclization of *N*-methoxy-*N*-methylbenzamide (W. A.) **4a** with diphenylacetylene **2a** was investigated. The reaction was performed at previously reported optimized parameters, unfortunately 67% yield of product **4aa**. Importantly, the product **4aa** is nothing but the industrially important *N*-protected cyclic amide and number of groups have synthesized using *N*-alkyl amide.¹⁸ With the existing reports *N*-methoxy-*N*-methylbenzamide acts as a good directing group and also provides good leaving group (–OMe).¹⁹ To increase the yield of product, studied reaction parameters such as concentration of oxidizing agent, temperature and time. Finally, 100 °C temperature is a key point for maximum conversion at optimized reaction condition and 89% yield of product **4aa** was observed. The results demonstrated that the oxidative annulation process smoothly occurred with internal alkynes. We observed that the desired 89% product **4aa**. The optimized reaction conditions are: **4a** (0.5 mmol), **2a** (0.5 mmol), $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ 3 mol%, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1 mmol%), AgSbF_6 (10 mol%) and PEG-400 (4 mL) at 100 °C for 12 h. To

explore the substrate scope, diphenylacetylene as the internal alkyne was studied under the optimized reaction conditions. It was observed that diphenylacetylene reacts with different substituted *N*-methoxy-*N*-methyl amides to furnish respective products in good yield. The *N*-methoxy-*N*-methyl amides containing electron-donating groups like –Me and –OMe provided excellent yields of **4ba** and **4ca**. Weak electron withdrawing groups –Cl and –Br gave the respective products **4da** and **4ea**. In the regioselective annulations of *N*-methoxy-2-naphthamide, in ¹H spectrum the singlet at 9.20 ppm confirms the exclusive synthesis of 3,4-diphenylbenzo[*g*]isoquinolin-1(2*H*)-one **4fa** instead of 1,2-diphenylbenzo[*f*]isoquinolin-4(3*H*)-one (ESI, S2).

After the successful synthesis of isoquinolinones, isocoumarin, and *N*-methyl isoquinolinones, we extended this protocol for the olefination reaction of W.A and alkene to synthesize (*E*)-*N*-methyl-2-styrylbenzamide **4aa**. The metal catalyzed *ortho*-olefination of W.A. to (*E*)-*N*-methyl-2-styrylbenzamide using alkene *via* C–H activation have great intense interest due its importance in pharmaceuticals.^{19,20} Under the optimized reaction condition, the olefination reaction of *N*-methoxy-*N*-methylbenzamide **4a** using styrene **2a'** as a model reaction was performed (Table 5). With screening of different reaction parameters like oxidant temperature and time, the 0.1 mmol of oxidant is sufficient for the maximum conversion of product (*E*)-*N*-methyl-2-styrylbenzamide **4aa'**. In ¹H spectroscopy, the coupling constant more than 12 Hz clearly indicates the stereoselectivity towards the *trans*-olefinated products (ESI, S2). With optimization condition in hand, we moved towards the olefination of various derivatives of *N*-methoxy-*N*-methyl amides and styrene (Table 5). It was observed that, the styrene derivatives having electron donating substituents such as –CH₃ and –OCH₃ results in good yields of **4ab'** and **4ac'**. While, weak electron-withdrawing groups such as –Br on the aromatic ring of styrene provide excellent yields of products **4ad'**. The strong electron withdrawing group (–NO₂) containing styrene also provided an excellent yield of **4ae'**. After studying different styrene derivatives, the reactivity of different *N*-methoxy-*N*-methyl amide derivatives were also investigated. The electron rich *N*-methoxy-*N*,4-dimethylbenzamide **4b** and *N*, 4-dimethoxy-*N*-methylbenzamide **4c** were smoothly reacting with styrene and provided the excellent yield products **4ba'** and **4ca'**. The *N*-methoxy-*N*-methyl benzamide derivatives with weak electron withdrawing substituents such as –Br results in better yield of **4da'**. The *N*-methoxy-*N*,3-dimethylbenzamide **4e** regioselectively coupled with **2e'** towards less hindered side exclusively and provides 89% yield of **4ee'** which was confirmed by ¹H spectroscopy shown singlet at 7.60 ppm (ESI, S2). Unfortunately, a strong electron withdrawing group containing Weinreb Amide **4f** and pyridine derivatives of amide and styrene does not provide the yield of **4fa–4af'**.

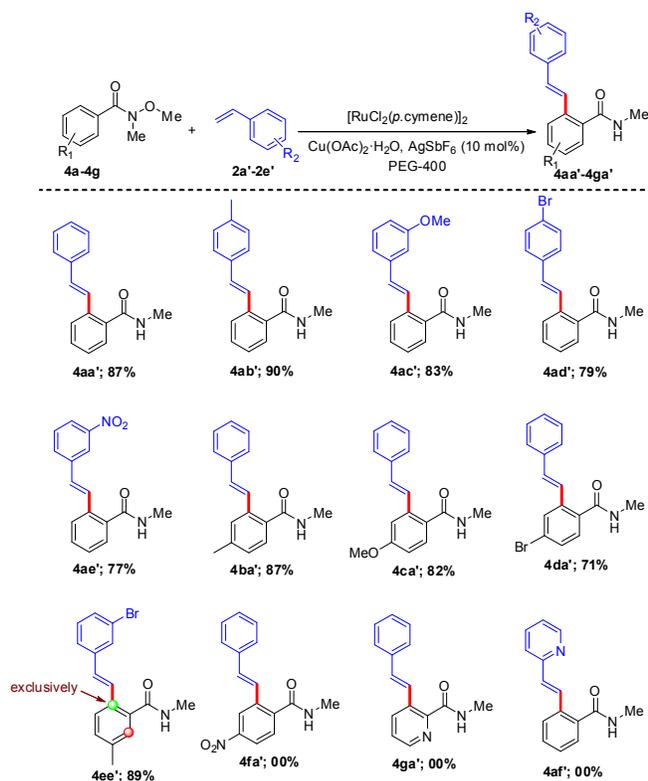
After all the study of annulation and olefination reactions, to show the consistency of this one-pot protocol we moved towards exploration this methodology for gram scale level (Table 6). In annulation reaction, at optimized reaction

Table 4. Scope on the ruthenium-catalyzed annulations of *N*-methoxy-*N*-methylbenzamide derivatives^a



^aReaction conditions: *N*-methoxy-*N*-methyl benzamide **4a–4f** (0.5 mmol), diphenylacetylene **2a** (0.5 mmol), $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ 3 mol%, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1 mmol), PEG-400 (4 mL), 100 °C, 12 h, ^b80 °C, ^cisolated yields.

Table 5. Substrate scope of ruthenium-catalyzed oxidative olefination



^aReaction conditions: **4a-4g** (0.5 mmol), **2a'-2e'** (0.7 mmol), $[RuCl_2(p-cymene)]_2$ (3 mol%), $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol), PEG-400 (4 mL), 100 °C, 16 h. ^bIsolated yield.

condition 1.06 g (7 mmol) of **1a**, 1.10 g (9 mmol) **3a** and 1.16 g (7 mmol) of **4a** has taken as starting substrate and 1.54 g (74 %) of **1aa**, 1.79 g (67%) of **8aa** and 1.58 g (73%) of **4aa** observed respectively. After the successful gram scale study of annulations moved towards gram scale study of *ortho*-olefination reaction. The 1.16 gm (7 mmol) of **4a** provided 1.17 gm (71%) of product **4aa'**. To investigate the reusability of the catalyst and solvent for annulation and *ortho*-olefination reactions of amide with alkyne and styrene at the optimized reaction conditions. The observations of recyclability are demonstrated in Fig. 1, before the reaction brown colour of mixture **1** was observed, while after completion of the reaction

Table 6. Gram scale study

Amide/Acid	Reaction conditions	Product
1a (7 mmol) 1.06 g	$[RuCl_2(p-cymene)]_2$ (3 mol%), $Cu(OAc)_2 \cdot H_2O$ (3.5 mmol), $AgSbF_6$ (10 mol%), PEG-400 (10 mL), 60 °C, 12 h.	1aa 74% 1.54 g
3a (9 mmol) 1.10 g	$[RuCl_2(p-cymene)]_2$ (3 mol%), $Cu(OAc)_2 \cdot H_2O$ (4.5 mmol), $AgSbF_6$ (10 mol%), PEG-400 (10 mL), 80 °C, 18 h.	8aa 67% 1.79 g
4a (7 mmol) 1.16 g	$[RuCl_2(p-cymene)]_2$ (3 mol%), $Cu(OAc)_2 \cdot H_2O$ (7 mmol), $AgSbF_6$ (10 mol%), PEG-400 (10 mL), 100 °C, 12 h.	4aa 73% 1.58 g
4a (7 mmol) 1.16 g	$[RuCl_2(p-cymene)]_2$ (3 mol%), $Cu(OAc)_2 \cdot H_2O$ (0.7 mmol), $AgSbF_6$ (10 mol%), PEG-400 (10 mL), 100 °C, 16 h.	4aa' 71% 1.17 g

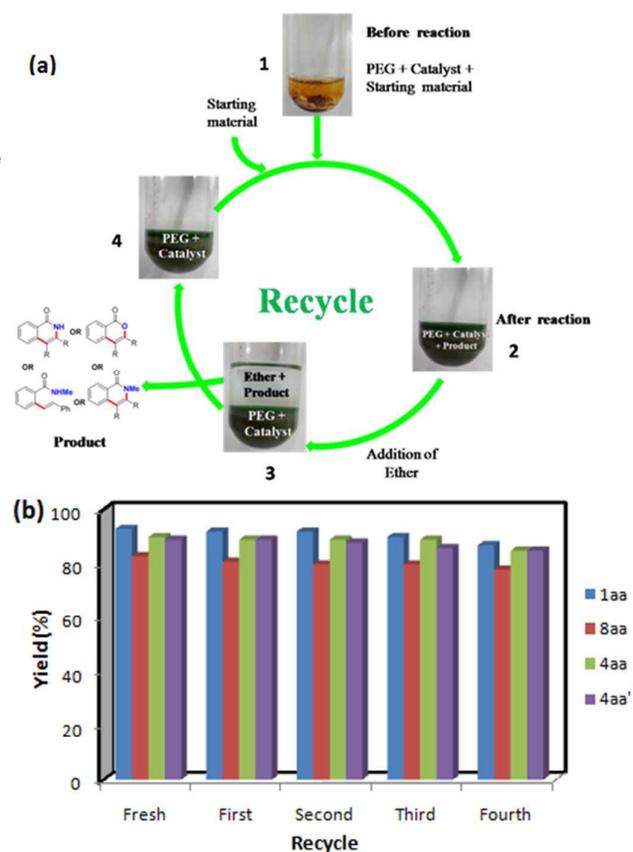
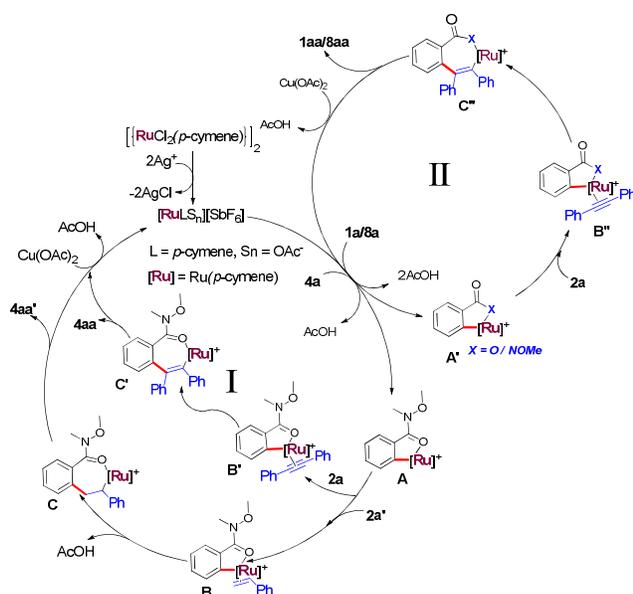


Fig.1 a) Procedure for reuse of catalyst and solvent system, b) catalyst recyclability study for the annulations and olefination reactions.

the color changed to blue **2**. With cooling the reaction mixture at room temperature, 5-7 mL of diethyl ether was added and shakes, the two layers **3** were generated. The upper layer of diethyl ether contains a product mixture directly uses for purification and the lower layer contains PEG with catalytic system. The PEG layer was heated to 40-50 °C for 10 min to remove the miscible quantity of ether. The cooled PEG-catalytic system used for the next cycle. With the same procedure, the recyclability and reusability were performed for the synthesis of **1aa** (93, 92, 92 and 90%), **8aa** (83, 81, 80 and 80%), **4aa** (90, 89, 89 and 87%) and **4aa'** (89, 89, 88 and 86%) (Fig 1). It was observed that the catalyst was effective to 4th recyclability without much loss in its activity and the decrease in yield might be loss during work up.

On the basis of experimental observations and previous reports,^{11,20a} a proposed mechanism for the Ru(II) catalyzed oxidative annulation and *ortho*-olefination by C-H bond activation as well N-O bond cleavage in the presence of $Cu(OAc)_2 \cdot H_2O$ is depicted in Scheme 3. As below, the proposed mechanism shown in two paths like the path **I** and path **II**. The path **I** is annulations and olefination of *N*-Methoxy-*N*-methyl benzamide **4a** and path **II** is the annulations of *N*-Methoxy benzamide **1a** and benzoic acid **8a** with diphenylacetylene **2a**. The first step of the transformation is unknown. It might be -Cl of catalyst absorbs by Ag salt and form $AgCl$.²¹



Scheme 3. Plausible reaction mechanism, I) for annulations and olefination of *N*-methoxy-*N*-methylbenzamide, II) annulations of *N*-methoxybenzamide and benzoic acid with alkyne.

In path **I**, the Ru(II) forms complex with hexafluoroantimonate and which made complex **A** by *ortho*-C–H bond activation with the release of protons and coordination with carbonyl of **4a**.^{19,21} This is followed by coordination of the metal to the alkene/alkyne **B/B'** and subsequent carbometallation and generates intermediate **C** and **C'**.^{19,21} The β hydride elimination of **C** gives the product **4aa'** and reductive elimination of **C'** affords the product **4aa** and. In path **II**, the Ru(II) forms complex with hexafluoro antimonate and which made complex **A** by *ortho*-C–H bond activation of **1a** and **8a** with the release of protons. This is followed by coordination of the metal to the diphenylacetylene **2a** forms **B''** and subsequent carbometallation and generates intermediate **C''**.^{8b} The reductive elimination of **C''** gives annulated product **1aa/8aa**. The Ru⁰ generates final step of path path **I** and **II**, which is oxidized by Cu(II) to regenerate a Ru(II) catalyst for the next catalytic cycle. In the developed protocol of annulations and olefinations, only 0.1 mmol to 1 mmol of Cu(OAc)₂ is used as the internal oxidant, the remaining amount of Cu(OAc)₂ might be regenerated in the presence of oxygen or air from the reduced CuOAc as a copper source.²²

Conclusions

In summary, we utilized Ru(II)/PEG-400 as a reusable catalytic system for the construction of C–C, C–O and C–N bond formations *via* C–H bond activations. This developed protocol is superior than previous methods due its advantageous features such as i) cost effective, ii) recyclibility of homogeneous catalyst, iii) multitasking catalyst for C–H activations, iv) mild reaction conditions, v) wide range of the substrate scope with excellent yield, vi) scalable up to gram level, and vii) simple work up process. The C–H bond activation

and high atom economy are the most attractive part of this reaction. The developed protocol is also constructive for the of stereoselective synthesis of *trans-ortho*-olefinated products.

Experimental

General experimental procedure:

All reactions were carried out in oven-dried glassware. All acid derivatives, styrene derivatives, diphenyl acetylene, [{RuCl₂(*p*-cymene)}₂], AgSbF₆, Cu(OAc)₂·H₂O and all the solvents were purchased from Aldrich, Alfa Aesar, Spectrochem or Thomas Baker. All W.A. derivatives were synthesized by reported method.²³ Analytical TLC was performed with 60 F254 silica gel plates (0.25 mm thickness). Column chromatography was performed with silica gel (100–200 mesh). NMR spectra were recorded with Agilent Technologies (¹H NMR at 500 or 400 MHz, ¹³C NMR at 125 or 100 MHz) spectrometer. The chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard and the coupling constant in Hz. The High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Q-Exactive with Accela 1250 pump, LRMS analysed by Agilent Tripal-Quard LC MS 6520. GC-MS-QP 2010 instrument (Rtx-17, 30 m × 25 mm ID, film thickness (df) = 0.25 μ m) (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. GC yields were obtained using Perkin Elmer Clarus 400 instruments with an ELITE-1 column.

Experimental procedure for the ruthenium catalyzed isoquinolinone, isocoumarin and *N*-methyl isoquinolinone synthesis

A 15 mL pressure tube containing *N*-methoxybenzamide **1a** (0.5 mmol, 76 mg)/Benzoic acid **8a** (0.5 mmol, 61 mg)/W.A. **4a** (0.5 mmol, 83 mg), diphenylacetylene (0.5 mmol, 89 mg), [{RuCl₂(*p*-cymene)}₂] (3 mol% 18 mg), Cu(OAc)₂·H₂O (as mentioned above) and AgSbF₆ (10 mol%, 34 mg) was added. To the tube 4 mL of PEG-400 was added. The reaction mixture was allowed to stir at mentioned temperature for 12–18 h. At the end of the reaction, the reaction mixture was diluted with diethyl ether. The upper layer of diethyl ether contains a product mixture directly uses for purification. The product was purified through a silica gel column using toluene and ethyl acetate as eluent to give pure **1aa/8aa/4aa**.

Experimental procedure for the ruthenium catalyzed *ortho*-olefination of aromatic W.A.

A 15 mL pressure tube containing W.A. **4a** (0.5 mmol, 83 mg) [{RuCl₂(*p*-cymene)}₂] (3 mol%, 18 mg), Cu(OAc)₂·H₂O (0.1 mmol, 20 mg), AgSbF₆ (10 mol%) were added. To the tube, 4 mL of PEG-400 solvent was added and styrene **2a'** (0.7 mmol, 73 mg) *via* a syringe. The reaction mixture was allowed to stir at 100 °C for 16 h. At the end of the reaction, the reaction mixture was diluted with diethyl ether. The upper layer of diethyl ether contains a product mixture directly uses for purification. The product was purified through a silica gel

column using toluene and ethyl acetate as eluent to give pure **4aa'**.

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Graphical Abstract

Ru(II)/PEG-400 as a Highly Efficient and Recyclable Catalytic Media for Annulation and Olefination Reactions *via* C-H Bond Activation

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