

Synthesis of pyrazolo [5,1-*a*]isoquinolines via C-H/N-H annulation of pyrazoles and alkynes with ruthenium(II) catalysts

Keisham Sarjit Singh,^{1,*} Ramila R. Goankar,¹ Kushal Banerjee,¹ Werner kaminsky²

¹ Bio-organic Chemistry Laboratory, CSIR-National Institute of Oceanography,
Dona Paula-403004, Goa, India

² Department of Chemistry, University of Washington, Seattle, Washington-98195, USA

*Email: keisham@nio.org

Abstract

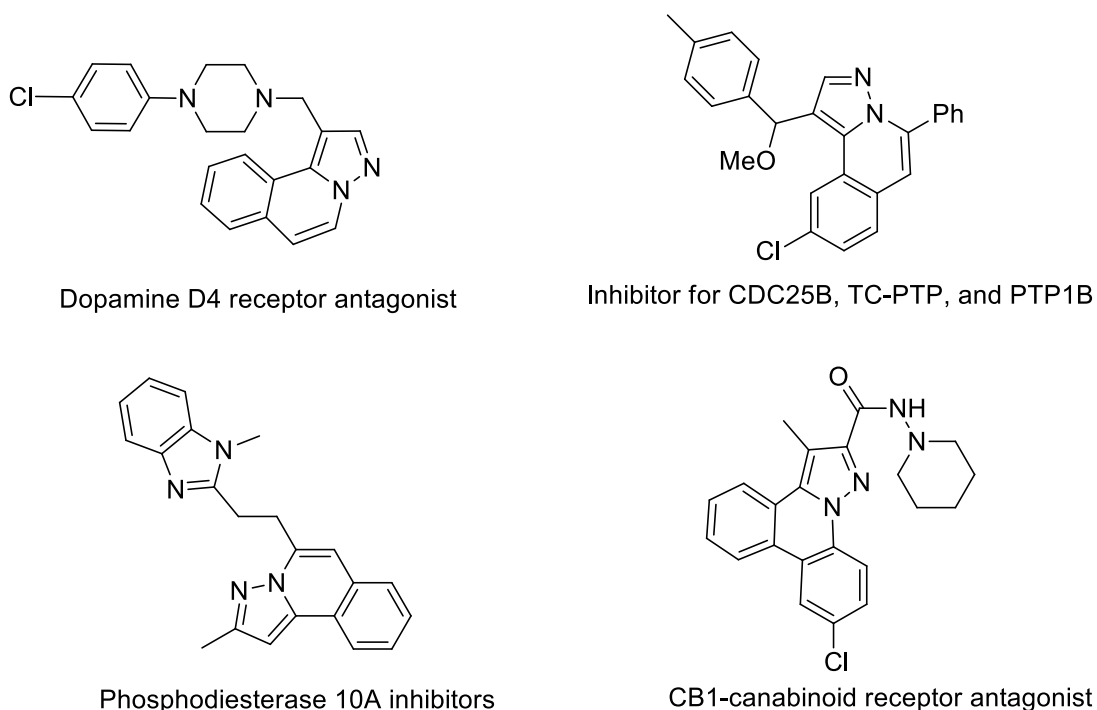
A series of pyrazolo[5,1-*a*]isoquinolines have been synthesized by ruthenium(II)-catalyzed annulation of pyrazole derivatives with alkynes in the presence of Cu(OAc)₂.H₂O and AgSbF₆ producing pyrazolo[5,1-*a*]isoquinolines. The reaction proceeded efficiently in water under nitrogen atmosphere leading to an excellent yield of the products. This annulation process can also be performed in alcohol at a lower temperature without Cu(OAc)₂.H₂O and silver salt but in the presence of a carboxylate ligand under air. The compounds were characterized based on spectroscopic data and the crystal structure of one of the representative compound, pyrazolo[5,1-*a*]isoquinoline derivative has been determined by single-crystal X-ray crystallography..

Keywords: Regioselective, C-H/N-H annulation , One-pot synthesis , Homogeneous catalysis, NMR spectroscopy , X-Ray structure determination.

Introduction

Heterocyclic compounds containing a pyrazole ring exhibit various biological properties such as antagonists [1], anti-hyperglycemic [2], anti-inflammatory [3], antipyretics [4] and anti-hypertension [5-6]. Specifically, functionalized pyrazolo [5,1-*a*]isoquinolines [7] and pyrazolo[1,5-*a*]pyridine [8] moieties constitute a crucial structure unit of several biologically active compounds and pharmacophores. It is well-known that compounds with pyrazolo[1,5-*a*]pyridine moiety exhibited potent p38 kinase inhibition [9], antiviral activity against HSV-1 and HSV-2 [10] (HSV = Herpes Simplex Virus) and also they are promising agent for melatonin receptor (MT1/MT2) ligands [11]. Further, a significant enhancement of bioactivity was noticed as a result of pyrazole ring fusion with other heterocycles such as pyrazolopyrimidines [12], pyrazolopyridines [13] and pyrazolopiperidines [14]. The pyrazolo[5,1-*a*]isoquinolines are class of pyrazole compounds that contained both the pyrazolo skeleton and isoquinoline. They exhibited biological properties including dopamine D4 receptor antagonist [15], CDC25B inhibitor [7], phosphodiesterase 10A inhibitors [16], and CB1 receptor antagonist [17] (Figure 1).

Figure 1. Representative examples of pyrazolo[5,1-*a*] isoquinolines with their bioactivities.

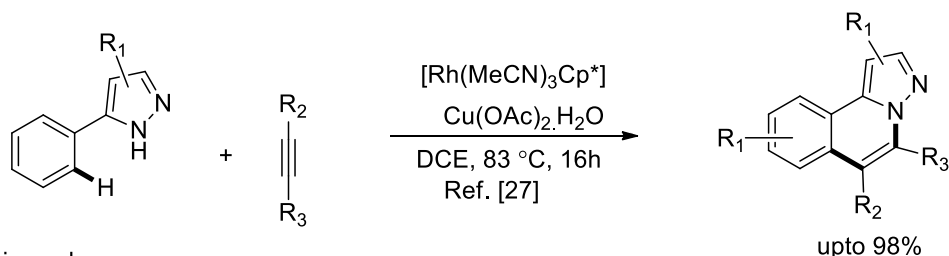
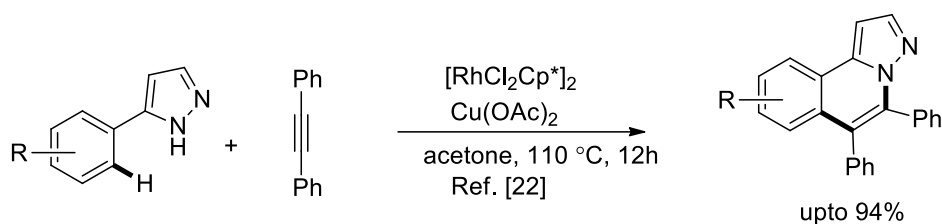
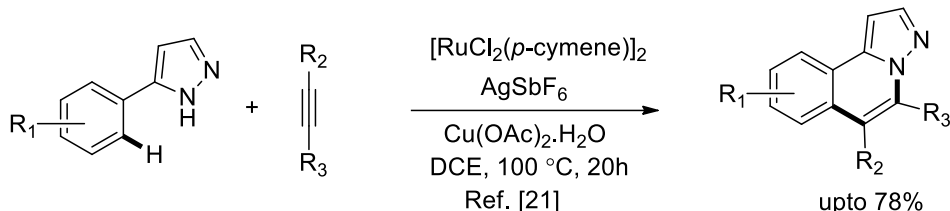
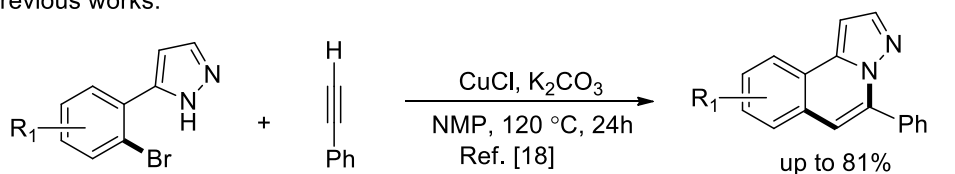


Owing to their promising bioactivity, synthesis of pyrazolo[5,1-*a*]isoquinolines and their derivatives have been a subject to considerable interest [18]. In 2013, Yang et al. [19] reported a copper-catalyzed synthesis of pyrazolo[5,1-*a*]isoquinoline by the annulation of brominated pyrazole with an alkyne. Very recently, Wen et al. [20] described another copper-catalysed synthesis of

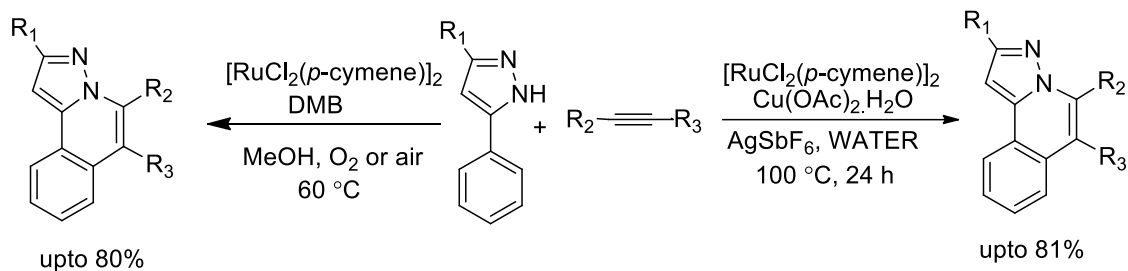
pyrazolo[5,1-*a*]isoquinolenes through the annulation of a brominated pyrazole amine derivative with an activated acetonitrile in the presence of heterocyclic ketene amins as ligand. Ackerman and Li described the synthesis of pyrazolo[5,1-*a*]isoquinolenes by oxidative coupling in the presence of Ru [21] and Rh-catalysts [22], respectively. However, most of these syntheses were carried out in organic solvents at high temperature (Figure 2). It is noteworthy that the synthesis of heterocycles *via* ruthenium-catalyzed intermolecular [23-27] and intramolecular [28-30] C-H bond activation is an attractive for a ready access to diverse heterocycles.

Figure 2. Overview for the synthesis of pyrazolo[5,1-*a*]-ioquinolines

Previous works:



This work:



- *Excellent Yield*
- *Low temperature*
- *No silver salts*
- *Free of chemical oxidant*

- *Excellent yield*
- *Water is used as solvent*
- *Product formed Regioselectively with unsymmetrical alkyne*

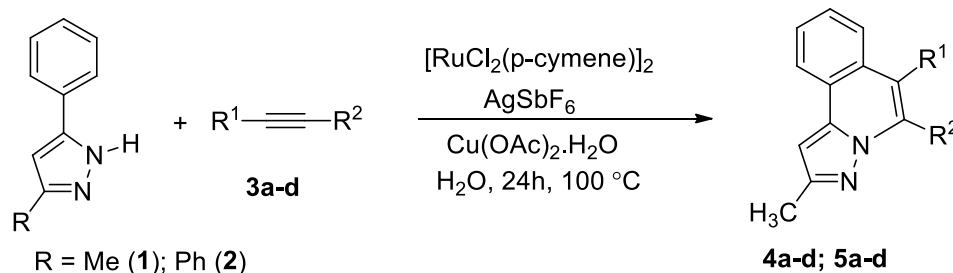
The stable ruthenium(II) complexes allowed various C-H bond functionalization reactions leading to heteroarenes to operate in water is cheap and non-toxic is attractive approach [31-33]. Although annulation of pyrazole derivatives with alkynes has been reported by several groups in

organic solvents [21, 22], to the best of our knowledge the reaction is not explored yet in water. Recently, we reported an efficient synthesis of isocoumarins via the annulation of carboxylic acids and alkynes in water through ruthenium(II)-catalysed C-H/O-H bond cleavage reaction [34]. In the continuation of our studies on ruthenium-catalyzed heterocyclic synthesis, herein, we investigated the ruthenium(II)-catalysed synthesis of pyrazolo[1,5-*a*]isoquinolenes by the annulation of substituted pyrazoles and alkynes in the presence of Cu(OAc)₂.H₂O and AgSbF₆ in water. It is noteworthy that in the recent past, C-H bond functionalization with ruthenium-catalyst has been paid considerable attention to the use of molecular oxygen as an oxidant [35-37]. Because of this growing interest, the annulation of (1) and (2) with alkynes have also been attempted under silver salt and Cu(OAc)₂.H₂O free condition in methanol at a lower temperature say 60 °C under oxygen (Figure 2).

Results and Discussion

The ruthenium(II)-catalysed annulation of substituted pyrazoles (1 or 2) and alkynes (3) involving a C-H/N-H bond cleavage reaction has been investigated in the presence of an oxidant and an additive leading to a series of pyrazolo[5,1-*a*]isoquinolenes (4 or 5) (Scheme 1).

Scheme 1. Reaction pathway for the synthesis of pyrazolo[5,1-*a*]isoquinolenes in water.



To obtain an optimized reaction condition, several reactions were carried out under various reaction parameters. Initially, the reaction was performed using 3-methyl-5-phenyl-1H-pyrazole (1) (0.5 mmol), diphenylacetylene (1.1 equiv.), [(*p*-cymene)RuCl₂]₂ (10 mol%), Cu(OAc)₂.H₂O (1.2 equiv.) and KPF₆ (40 mol%) in water which gave the desired product, 2-methyl-5,6-diphenylpyrazolo[5,1-*a*]isoquinoline (4a) in 61% (Table S1, entry 1).

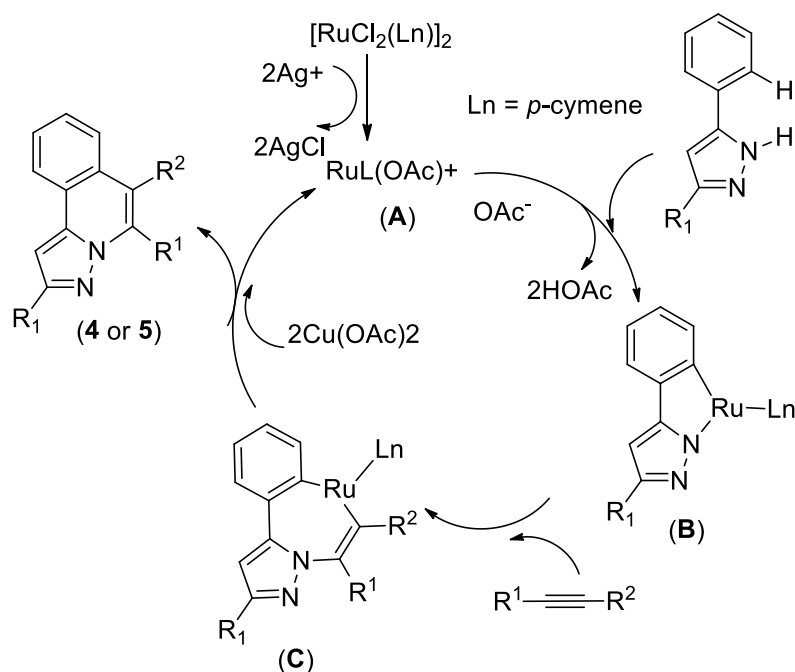
The annulation reaction was performed at 100 °C, a temperature normally employed in most of the catalytic reaction performed in water [31, 33]. The reaction efficacy was increased dramatically when AgSbF₆ was used as an additive instead of KPF₆, affording the product, pyrazolo[5,1-*a*]isoquinoline (4a) in 81% yield (Table S1, entry 2). The reaction conducted

employing other additives such as KOAc and AgOTf gave 53% and 63% of (**4a**), respectively (Table S1 entries 3 & 4). This indicates that the annulation undergoes favorably by the participation of a silver salt under the specified condition. However, a decreased in the catalyst loading from 10 to 5 mol% resulted in a lower yield of **4a** (Table S1 entries 5 & 6). When the reaction was performed without an additive resulted in a very low yield of (**4a**) (Table S1, entries 7-9). Notably, the reaction performed with 0.5 equiv. of Cu(OAc)₂.H₂O or a shorter reaction time say 7 h, gave only 28% and 25% of **4a**, respectively (Table S1 entries 10 and 11). Further, the efficacy of the reaction was evaluated in other solvents such as dimethylformamide (DMF) and 1,2-dichloroethane (DCE) which gave 41% and 25% of (**4a**), respectively (Table S1, entries 12 & 13).

The annulation reaction of pyrazole (**1**) and diphenyl acetylene (**3a**) performed with other ruthenium catalysts such as [(*p*-cymene)Ru(*quinto*)Cl] and [(*p*-cymene)Ru(PySO₃)Cl] gave the desired product (**4a**) in 25 and 21%, respectively (Table S1 entries 14 & 15). It is noteworthy that most of the C-H/N-H annulation reactions normally employed electron rich alkynes, to understand the scope of the alkynes in this reaction, we have screened this C-H/N-H annulation reaction with terminal alkyne *viz.* phenylacetylene but unfortunately, no reaction occurred. On the other hand reaction using electron deficient alkynes such as dimethylacetylene dicarboxylate and diethylacetylene dicarboxylate produced no desired C-H/N-H annulation product, pyrazolo[5,1-*a*]isoquinoline. It is notable that the transition metal-catalyzed C-H/N-H or C-H/O-H annulation reaction exclusively employed electron rich alkynes [21-22, 34]. Earlier Zhou et al. reported the synthesis of pyrazolo[5,1-*a*]isoquinoline employing dimethylacetylene dicarboxylate via silver triflate-catalyzed reaction involving [3+2] cycloaddition [38]. Further, it is notable that annulation of pyrazoles with terminal alkyne such as phenyl acetylene proceeds only with a pre-functionalized brominated pyrazole such as 3-(2-bromophenyl)pyrazoles [19].

The annulation reaction in the presence of silver salt in water might proceeded via the formation of cationic ruthenium species [Ru(OAc)(*p*-cymene)]⁺ (intermediate A) [39]. It is expected that the deprotonation of the substrate by acetate results in the formation of a five-membered organoruthenacyclic intermediate (intermediate B) which undergoes addition of an alkyne to give intermediate C followed by reductive elimination gave the product (**4** or **5**) and regenerate the cationic ruthenium species (Scheme 2). The oxidant, Cu(OAc)₂.H₂O played a dual role, it not only oxidize the ruthenium(0) species formed to the active ruthenium(II) catalyst but also provides acetate in the catalytic process [34].

Scheme 2. The proposed reaction mechanism for the annulation of **1** or **2** with alkynes in water.



The annulation reaction has been attempted at room temperature in methanol in the presence of an additive such as AgSbF_6 , BTA, AgOTf at room temperature which gave 45%, 49% and 70% of **4a**, respectively (Table S1, entries 16-19). Interestingly, reaction performed with 5 mol% of catalyst and 20 mol% of AgOTf in MeOH gave a fairly good yield, 53% of **4a** (Table S1, entry 19). To understand the effect of additive, we have performed the reaction without AgSbF_6 in methanol and ethanol affording a good yield of the desired product (**4a**) (Table S1, entries 20 & 21). We then evaluated the reaction without chemical oxidant, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and additive, AgSbF_6 but in the presence of a carboxylate ligand, DMB (2,4-dimethylbenzoic acid) under an oxygen atmosphere at 60°C for 24h which gave the desired product (**4a**) in 72 % yield (Table S1, entry 22). However, the reaction was un-reactive in the absence $[(p\text{-cymene})\text{RuCl}_2]_2$ (Table S1 entry 23), indicating the presence of ruthenium-catalyst is essential in this reaction.

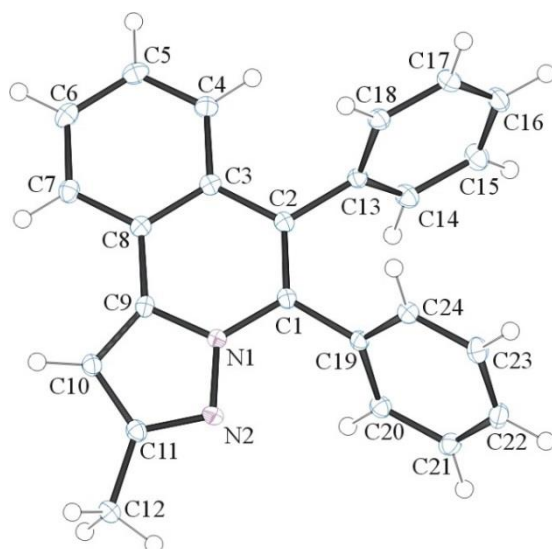
The optimization study clearly showed that, the presence of silver salt boosts the reaction only when performed in water but not essential for the reaction conducted in methanol. For instances, annulation reaction of **1** with diphenylacetylene with or without AgOTf gave comparable yields, indicating AgOTf is not essential for the reaction efficacy (Table S1, entries 18-20). In the case of reaction performed in methanol in the absence of silver salt, the reaction might proceed slightly different pathway from that of in water i.e. probably without the formation of cationic

ruthenium species rather than through a neutral ruthenium species, say $[(p\text{-cymene})\text{Ru}(\text{OAc})_2]$ as proposed for carboxylate assisted pathway [36]. Since the reaction is free of silver salt and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ the active catalyst could be the ruthenium-carboxylate intermediate formed with DMB, $[(p\text{-cymene})\text{Ru}(\text{DMB})_2]$. However, in both the cases whether in water or MeOH, the reaction is expected to proceed through carboxylate assisted pathways either *via* cationic $[(p\text{-cymene})\text{Ru}(\text{OAc})]^+$ or $[(p\text{-cymene})\text{Ru}(\text{DMB})_2]$ intermediates, respectively.

From the above reaction screening under various parameters, we found that the best result was obtained when 3-methyl-5-phenyl-1H-pyrazole, (**1**) (0.5 mmol), diphenylacetylene (1 mmol), ruthenium-catalyst (10 mol%), AgSbF_6 (40 mol%) and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (2 equiv.) were reacted in water under nitrogen at 100 °C for 24 h. On the other hand, the optimized condition for the annulation of pyrazole and alkyne conducted in methanol in the presence of carboxylic acid ligand was obtained when the reaction was performed using 3-methyl-5-phenyl-1H-pyrazole (0.5 mmol), diphenylacetylene (1 mmol), catalyst (10 mol%), and DMB (1.1 equiv.) in methanol stirring at 60 °C for 24h.

The compound **4a** was characterized by FTIR, ^1H , ^{13}C -NMR, and ESI-MS mass spectral data and the crystal structure of compound **4a** has been determined by a single-crystal X-ray diffraction (Figure 3). The compound crystallizes in triclinic crystal system and P-1 space group with final R = 0.041 (see supporting information for details crystallography and data collection parameters).

Figure 3. Crystal structure of **4a** with thermal ellipsoid at 50% probability.



During the course of our work, Ackerman and Algarra reported related chemistry using Ru [21] and Rh/Ru catalysts [40]. Ackermann's research group performed the annulation of a pyrazole derivative namely, 5-(4-nitrophenyl)-1H-pyrazole and diphenylacetylene with a ruthenium(II)-catalyst in the

presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and AgSbF_6 in 1,2-dichloroethane (DCE) which gave the desired products in 77%. However, the reaction was not productive when performed in water, affording only 13% of the desired product [21]. Whereas, Algarra *et al.* [40] performed the reaction of pyrazole ring substituted derivatives and alkynes with both Rh(III) or Ru(II) in the presence of AgPF_6 either in DCE or *t*-AmOH to give the desired products. They found that $[\text{Rh}(\text{MeCN})_3\text{Cp}^*]\text{PF}_6$ to be much better catalyst than that of $[\text{RhCl}_2\text{Cp}^*]_2$ as the former catalyst and can complete the reaction in just 1h at 83 °C. Further, the reaction proceeded with $[\text{RuCl}_2(p\text{-cymene})]_2$ under harsher condition than rhodium-catalysts. The reaction was performed much higher temperature say at 120 °C in *t*-AmOH giving 65% of the desired product with octyne but produced only 14% of the product when used diphenylacetylene even in the presence of AgPF_6 [40].

In this study, we observed that pyrazole ring substituted derivative, namely, 3-methyl-5-phenyl-1H-pyrazole (**1**) undergo annulation efficiently with diphenylacetylene in water to give excellent yield (81%) of desired product **4a**, in contrast, only 41% and 25% of **4a** were obtained when the reaction was performed in DMF and DCE, respectively (Table S1 entries 2, 12 & 13). This result showed that water is the solvent of choice and could be used for the annulation of pyrazole ring-substituted derivative, namely, 3-methyl-5-phenyl-1H-pyrazole (**1**) with diphenyl acetylene (**3a**) and it was more productive than in DCE or DMF (Table S1, entries 2, 12 & 13). It is notable that the annulation reaction of pyrazole (**1**) and diphenyl acetylene (**3a**) in organic solvent is less productive than in water under the specified condition. For instances, Algarra *et al.* [40] obtained only 14% of (**4a**) in the reaction of (**1**) with diphenyl acetylene with ruthenium catalyst, $[\text{RuCl}_2(p\text{-cymene})]_2$ in *t*-AmOH. Further, they found that the reaction proceeded less efficiently with the formation of side product in the absence of silver salt.

We have performed annulation of (**1**) with several alkynes in water under the optimized reaction condition to give various pyrazolo[5,1-*a*]isoquinolenes (Scheme 1, Table 1). The annulation of (**1**) with 4-octyne and 3-hexyne in water gave pyrazolo[5,1-*a*]isoquinolenes (**4c**) and (**4d**) in excellent yields of 82 and 85%, respectively (Table 2 entries 4 and 5). Analogously, annulation of (**2**) with diphenylacetylene, 4-octyne, and 3-hexyne afforded the products (**5a**), (**5c**), and (**5d**) in 70, 72, and 82% yields, respectively (Table 1 entries 5, 7, 8). The reaction proceeded in a regioselective manner when either **1** or **2** reacted with unsymmetrical alkyne such as 1-phenyl-1-propyne. Thus, the annulation of 1-phenyl-1-propyne and 3-methyl-5-phenyl-1H-pyrazole (**1**) gave (**4ba**) and (**4bb**) in 12 and 73% isolated yields, respectively (Table 1, entry 2). Whereas, the reaction of 1-phenyl-1-propyne and (**2**) afforded (**5ba**) and (**5bb**) in 10 and 57% yields, respectively (Table 1 entry 6).

The annulation reaction of pyrazole and alkynes have been attempted in MeOH without $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and silver salts but in the presence of DMB ligand under air or oxygen affording moderate to excellent yields of the desired products (Scheme 3, Table 1).

Scheme 3. Reaction pathway for the synthesis of pyrazolo[5,1-*a*]isoquinolenes in MeOH.

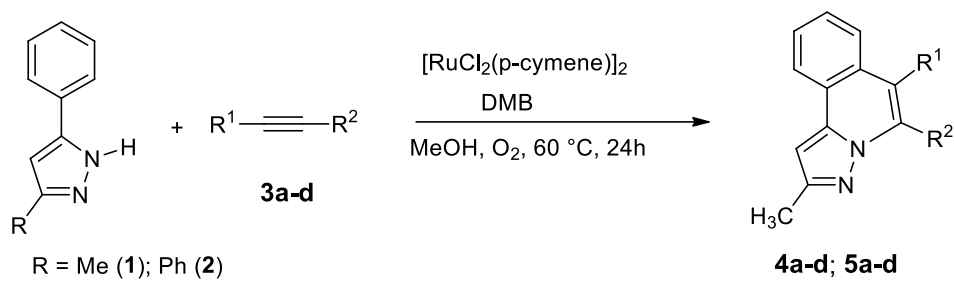
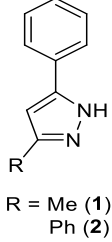
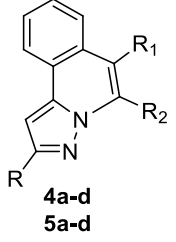


Table 1: Ruthenium(II)-catalyzed synthesis of pyrazolo[5,1-*a*]isoquinolenes in H₂O^[a] and MeOH^[b]

Entry	Substrates	Alkynes	Products	Yield ^[c]	
				H ₂ O	MeOH
	 R = Me (1) Ph (2)	$R_1\text{---}\equiv\text{---}R_2$ 3a-d	 4a-d 5a-d		
[1]	1	Ph $\text{---}\equiv\text{---}$ Ph	R ₁ = R ₂ = Ph (4a)	81	72
[2]	1	Ph $\text{---}\equiv\text{---}$ Me	R ₁ = Ph, R ₂ = Me (4ba) R ₁ = Me, R ₂ = Ph (4bb)	12 73	5 80
[3]	1	Pr $\text{---}\equiv\text{---}$ Pr	R ₁ = R ₂ = Pr (4c)	82	43
[4]	1	Et $\text{---}\equiv\text{---}$ Et	R ₁ = R ₂ = Et (4d)	85	62
[5]	2	Ph $\text{---}\equiv\text{---}$ Ph	R ₁ = R ₂ = Ph (5a)	70	43
[6]	2	Ph $\text{---}\equiv\text{---}$ Me	R ₁ = Ph, R ₂ = Me (5ba) R ₁ = Me, R ₂ = Ph (5bb)	10 57	Traces 57
[7]	2	Pr $\text{---}\equiv\text{---}$ Pr	R ₁ = R ₂ = Pr (5c)	72	40
[8]	2	Et $\text{---}\equiv\text{---}$ Et	R ₁ = R ₂ = Et (5d)	82	36

^[a]Reaction conditions: Pyrazole derivatives **1** or **2** (0.5 mmol), Ru-catalyst (0.05 mmol), alkyne (0.6 mmol), Cu(OAc)₂·H₂O (1 mmol, 2 equiv.), AgSbF₆ (0.2 mmol, 40 mol%), water (2 mL), Temp 100 °C, 24h, under N₂; ^[b]Reaction conditions: Substrate (**1**) or (**2**) (0.5 mmol), Ru-catalyst (0.05 mmol), alkyne (0.6 mmol), DMB (0.3 mmol), MeOH (3 mL), 60 °C, 24 h under air; ^[c] Isolated yields after column chromatography.

The pyrazole derivative (**1**) reacted with diphenylacetylene (**3a**), 4-octyne (**3c**), and 3-hexyne (**3d**) gave 72, 43 and 62%, of the corresponding pyrazolo[5,1-*a*]isoquinolenes (**4a**), (**4b**), and (**4c**), respectively (Table 1, entries 1, 3, 4). Similarly, annulation of pyrazole derivative (**2**) with diphenylacetylene (**3a**), 4-octyne (**3c**) and 3-hexyne (**3d**) resulted in modest yield of the corresponding pyrazolo[1,5-*a*]isoquinolenes (**5a**), (**5c**), and (**5d**) (Table 1, entries 5, 7, 8). Regioselectivity was observed for the reaction performed in methanol as well when the

unsymmetrical alkyne, namely, 1-phenyl-1-propyne (**3b**) reacted with (**1**) affording excellent yield of **4bb** (80%) and **4ba** (5%), similarly, (**2**) reacted with (**3b**) gave the regioisomer product (**5bb**) in 57% along with the traces of isomer (**5ba**) (Table 1, entries 2 and 6). The reaction conducted in methanol is attractive as it is free from the use of silver salt and chemical oxidant and moreover, it could be performed at a lower temperature.

Conclusion

This manuscript describes a ruthenium(II)-catalyzed synthesis of pyrazolo[5,1-*a*]isoquinolene derivatives in high to excellent yield via the annulation of pyrazole derivatives with alkynes under two reaction conditions in water as green solvent and methanol. The annulation proceeded through a C-H/N-H bond cleavage reaction with [(*p*-cymene)RuCl₂]₂ (10 mol%), AgSbF₆ (40 mol%) in the presence of an oxidant, Cu(OAc)₂.H₂O. The reaction undergoes in a regioselective manner when reacted pyrazole derivative (**1**) or (**2**) with unsymmetrical alkyne namely, 1-phenyl-1-propyne. The present study demonstrated that pyrazole annulation with alkyne can be profitably performed in water and even more efficiently than organic solvents. Our result showed that water is ideal solvent of choice for annulation reaction with ruthenium(II)-catalysts and it is an alternative to toxic organic solvents. We also demonstrated that the annulation of substituted pyrazoles and alkynes could also be performed under the silver salt and Cu(OAc)₂.H₂O free condition in the presence of a carboxylic acid ligand in methanol under air to give comparable yields or in some cases lower yields of the desired products than those performed in water.

EXPERIMENTAL

Material and Methods

Reactions were performed in Schlenck tubes either under the nitrogen atmosphere in water or oxygen in methanol. The solvent used in the reactions were of analytical grade and used as received, distilled water was degassed before used. RuCl₃.3H₂O was obtained from Arrora Matthey Ltd., India. All the other chemicals *viz.* diphenylacetylene, 1-phenyl-1-propyne, 3-hexyne, 4-octyne, 1-benzoylacetone, dibenzoylmethane, silver hexafluoroantimonate(V), Silver trifluoromethane sulfonate (AgOTf) Cu(OAc)₂.H₂O and KOAc were purchased from Sigma Aldrich, India. ¹H and ¹³C-NMR spectra of all the compounds were recorded on a Bruker Avance 300 MHz spectrometer at 300.13 (1H), 75.47 MHz (¹³C) with SiMe₄ as an internal reference and coupling constants are given in Hertz. ESI-MS analyses were performed using Waters UPLC-MSMS (Xevo TQD) mass spectrometer. The complexes [(*p*-cymene)RuCl₂]₂ [41], [(*p*-cymene)Ru(quinto)Cl] [42] and [(*p*-cymene)Ru(PySO₃)Cl]

[43] (where quinto = 2-quinaldinato; PySO₃ = 2-pyridinesulfonato) were prepared following a reported method.

Crystal structure analysis and refinement

Single crystal of the compound **4a** suitable for X-ray analysis was obtained from the ethyl acetate solution of **4a**. The X-ray diffraction data were collected on a Bruker APEX II single crystal X-ray diffractometer employing MoK α radiation ($\lambda = 0.71073 \text{ \AA}$). The distance of Crystal-to- detector was 40 mm and the exposure time was 10 seconds per frame. The data collection was 99.4% complete to 25° in θ . The direct methods (SHELXS, SIR97) [44] were used for solving the structure and the structure was refined by difference Fourier method using SHELXL97 [45]. The refinement of crystal structure determination was converged to a final R-value of 0.0401 (for observed data F), and the wR₂ value was 0.1064 (for unique data F²). Detail crystal structure data determination and selected bond lengths (Å) & angles (°) of **4a** are presented in Table S2 & Table S3.

Procedure for the synthesis of compounds

Preparation of 3-methyl-5-phenyl-1H-pyrazole and 3,5-diphenyl-1H-pyrazole

A 250 mL round bottom flask was loaded with 1-benzoylacetone or dibenzoylmethane and hydrazine hydrate in the ratio 1:1 and stirred in ethanol at room temperature for 20 h. The white solid obtained was collected by filtration and washed with water (2 x 10 mL) then dried under vacuum.

General procedure for the ruthenium(II)-catalysed annulation of 3-methyl-5-phenyl-1H-pyrazole or 3,5-diphenyl-1H-pyrazole and alkynes in water

An oven-dried Schlenk tube was charged with [(*p*-cymene)RuCl₂]₂ (0.0306g, 0.0499 mmol, 10 mol%), 3-methyl-5-phenyl-1H-pyrazole (**1**) or 3,5-diphenyl-1H-pyrazole (**2**) (0.5mmol), alkyne (0.675 mmol), Cu(OAc)₂.H₂O (0.2 g, 1.0 mmol) and AgSbF₆ (0.068g, 0.2 mmol). To this reaction mixture, 2 mL of degassed water was added and stirred at 100°C for 24 h under nitrogen atmosphere. The Schlenk tube was then cooled to room temperature and ethyl acetate (5 mL) was added. The reaction mixture was transferred to a separating flask and extracted using EtOAc (3 x 10 mL). The ethyl acetate fractions obtained were combined and treated with magnesium sulfate then dried in a rotary evaporator. The desired products were obtained in good yield after purification of the residue by column chromatography on silica gel column using petroleum ether and ethyl acetate solvent gradient. Spectroscopic data of the compounds were well matched with the reported values [40] (see Supplementary information).

General procedure for ruthenium(II) catalyzed annulation of 3-methyl-5-phenyl-1H-pyrazole or 3,5-diphenyl-1H-pyrazole and alkyne in methanol

An oven-dried Schlenk tube was charged with 3-methyl-5-phenyl-1H-pyrazole (**1**) or 3,5-diphenyl-1H-pyrazole (**2**) (0.5 mmol), alkyne (0.60 mmol), [(*p*-cymene)RuCl₂]₂ (10 mol%), and DMB (0.3 mmol). Then methanol or ethanol (2 mL) was added to the reaction mixture and stirred at 60 °C under the O₂ atmosphere for 24h. The solution was rotary evaporated to dryness and the residue was dissolved in dichloromethane. The product was purified by column chromatography on the silica gel column with petroleum ether and ethyl acetate solvent gradient, in some cases, the product precipitated out from the reaction mixture which was directly filtered and dried.

Yields and spectroscopic data:

2-methyl-5,6-diphenylpyrazolo[5,1-*a*]isoquinoline (**4a**)

White solid; Yield: 135 mg (81%); FTIR (KBr, cm⁻¹): 3053, 2929, 1620, 1539, 1487, 1317; ¹H-NMR (300 MHz, CDCl₃): δ 8.14 (d, 1H, *J* = 7.8), 7.54 (t, 1H, *J* = 7.2), 7.41 (m, 2H, *J* = 6.3), 7.34 (d, 2H, *J* = 4.8), 7.26 (s, 7H), 7.19 (d, 1H, *J* = 5.7), 6.92 (s, 1H), 2.49 (s, 1H); ¹³C-NMR (75 MHz, CDCl₃): 150.66, 139.39, 136.47, 136.22, 133.24, 131.73, 131.06, 129.97, 128.14, 127.92, 127.71, 127.44, 127.02, 126.99, 126.55, 123.70, 123.45, 122.88, 97.32, 14.38; ESI-MS: *m/z* 335.2 (M+H)⁺.

2, 5-dimethyl-6-phenylpyrazolo[5,1-*a*]isoquinoline (**4ba**)

Light brown solid; Yield: 16 mg (12%); FTIR (KBr, cm⁻¹): 3026, 2932, 1612, 1486; ¹H NMR (300 MHz, CDCl₃, δ): 8.10 (d, 1H, *J* = 7.8), 7.55-7.47 (m, 4H), 7.41-7.33 (m, 3H), 7.25 (d, 1H, *J* = 3.9), 6.89 (s, 1H), 2.60 (s, 3H), 2.57 (s, 3H); ¹³C-NMR (75 MHz, CDCl₃, δ): 150.29, 138.98, 137.12, 131.03, 129.89, 128.59, 127.60, 127.35, 126.22, 125.97, 123.37, 122.85, 121.60, 97.34, 29.67, 15.85, 14.17; ESI-MS: *m/z* 273.2 (M+H)⁺

2,6-dimethyl-5-phenylpyrazolo[5,1-*a*]isoquinoline (**4bb**)

Light brown solid; Yield: 99 mg (73%); FTIR (KBr, cm⁻¹): 3055, 2924, 1625, 1546, 1471, 1386; ¹H NMR (300 MHz, CDCl₃, δ): 8.12 – 8.09 (m, 1H), 7.90 – 7.87 (m, 1H), 7.61 – 7.48 (m, 7H), 6.83 (s, 1H), 2.44 (s, 3H), 2.32 (s, 3H); ¹³C NMR (75 MHz, CDCl₃, δ): 149.94, 138.85, 135.80, 134.01, 130.59, 129.89, 128.64, 128.47, 127.56, 126.90, 124.29, 123.84, 123.73, 114.96, 96.98, 14.92, 14.28; ESI-MS: *m/z* 273.2 (M+H)⁺.

2-methyl-5, 6-dipropylpyrazolo[5,1-*a*]isoquinoline (**4c**)

Pale yellow solid; Yield: 108 mg (82%); FTIR (KBr, cm^{-1}): 3107, 3074, 2958, 2870, 1625, 1541, 1469, 1394, 1091; $^1\text{H-NMR}$ (300 MHz, CDCl_3 , δ): 8.04 (d, 1H, $J = 7.2$), 7.82 (d, 1H, $J = 8.1$), 7.56 – 7.47 (m, 2H), 6.77 (s, 1H), 3.25 (t, 2H, $J = 7.5$), 2.93 (t, 2H, $J = 8.1$), 2.54 (s, 3H), 1.88-1.80 (m, 2H), 1.74-1.66 (m, 2H), 1.13-1.08 (m, 6H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3 , δ) 149.42, 138.56, 136.66, 129.01, 127.33, 125.92, 123.85, 123.79, 123.49, 117.83, 96.69, 29.89, 29.64, 23.79, 21.26, 14.44, 14.29, 14.21, 1.01; ESI-MS: m/z 267.2 (M+H) $^+$.

5,6-diethyl-2-methylpyrazolo[5,1-*a*]isoquinoline (**4d**, $\text{C}_{16}\text{H}_{18}\text{N}_2$)

Light orange solid; Yield: 101 mg (85%); FTIR (KBr, cm^{-1}): 3118, 2972, 2933, 1624, 1541, 1467, 1338, 1271; $^1\text{H NMR}$ (300 MHz, CDCl_3 , δ): 8.06 (d, 1H, $J = 7.5$), 7.86 (d, 1H, $J = 7.8$), 7.57 – 7.46 (m, 2H), 6.78 (s, 1H), 3.32 (q, 2H, $J = 7.2$), 3.0 (q, 2H, $J = 7.5$), 2.56 (s, 3H), 1.40 (t, 3H, $J = 7.2$), 1.31 (t, 3H, $J = 7.5$); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3 , δ): 149.51, 138.54, 137.54, 128.74, 127.43, 125.96, 123.92, 123.61, 123.54, 118.79, 96.78, 21.25, 20.49, 15.04, 14.19, 12.64; ESI-MS: m/z 239.2 (M+H) $^+$.

2,5,6-triphenylpyrazolo[5,1-*a*]isoquinoline (**5a**)

Off white solid; Yield: 139 mg (70%); FTIR (KBr, cm^{-1}): 3059, 3030, 1737, 1622, 1535, 1456, 1388, 1342, 1273, 1180; $^1\text{H NMR}$ (300 MHz, CDCl_3 , δ): 8.25 (d, 1H, $J = 7.8$), 7.95 (d, 2H, $J = 7.2$), 7.61 – 7.58 (m, 1H), 7.46 – 7.44 (m, 7H), 7.41 – 7.30 (m, 8H), 7.25 – 7.23 (m, 1H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3 , δ) 159.26, 139.91, 136.46, 136.38, 133.46, 133.01, 131.72, 131.37, 130.03, 128.53, 128.06, 128.02, 127.68, 127.51, 127.27, 127.13, 126.76, 126.41, 123.99, 123.82, 123.53, 94.57, ESI-MS: m/z 397.2 (M+H) $^+$.

5-methyl-2,6-diphenylpyrazolo[5,1-*a*]isoquinoline (**5ba**)

Light pink solid; Yield: 17 mg (10%); FTIR (KBr, cm^{-1}): 3059, 2922, 2852, 1625, 1541, 1458, 1371, 1024; $^1\text{H NMR}$ (300 MHz, CDCl_3 , δ): 8.20 (d, 1H, $J = 7.8$), 8.09 (d, 2H, $J = 7.5$), 7.55 – 7.36 (m, 11H), 7.29 (s, 1H), 2.66 (s, 3H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3 , δ): 152.20, 139.44, 137.04, 133.68, 133.54, 130.98, 129.94, 128.71, 128.13, 127.68, 127.55, 126.41, 126.13, 123.43, 123.16, 122.52, 94.73, 15.78; ESI-MS: m/z 335.2 (M+H) $^+$.

6-methyl-2,5-diphenylpyrazolo[5,1-*a*]isoquinoline (**5bb**)

Light brown solid; Yield: 98 mg (57%); FTIR (KBr, cm^{-1}): 3032, 2918, 2862, 1625, 1543, 1456, 1388, 1332, 1265, 1078; $^1\text{H NMR}$ (300 MHz, CDCl_3 , δ): 8.21 – 8.20 (m, 1H), 7.94 – 7.88 (m, 3H), 7.64 – 7.52 (m, 7H), 7.40 – 7.27 (m, 4H), 2.40 (s, 3H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3 , δ): 151.62,

139.35, 136.07, 133.69, 133.58, 130.91, 129.97, 128.56, 128.47, 128.22, 127.88, 127.78, 127.13, 126.28, 124.48, 124.09, 123.79, 116.03, 94.24, 30.86; ESI-MS: m/z 335.2 (M+H)⁺.

2-phenyl-5,6-dipropylpyrazolo[5,1-*a*]isoquinoline (**5c**)

Pale yellow solid; Yield: 119 mg (72%) ; FTIR (KBr, cm⁻¹): 3059, 2956, 2870, 1627, 1535, 1456, 1392, 1282, 1085; ¹H NMR (300 MHz, CDCl₃, δ): 8.17 – 8.06 (m, 3H), 7.86 (d, 1H, *J* = 7.2), 7.58 – 7.46 (m, 4H), 7.38 (d, 1H, *J* = 7.5), 7.30 (s, 1H), 3.36 (t, 2H, *J* = 7.8), 2.98 (t, 2H, *J* = 7.8), 1.96 – 1.88 (m, 2H), 1.75 – 1.57 (m, 2H), 1.18 – 1.12 (m, 6H); ¹³C-NMR (75 MHz, CDCl₃, δ): 151.29, 139.02, 136.97, 133.93, 129.07, 128.62, 127.91, 126.26, 126.17, 123.97, 123.92, 123.79, 118.93, 94.04, 29.99, 29.74, 23.81, 21.23, 14.42; ESI-MS: m/z 329.3 (M+H)⁺.

5,6-diethyl-2-phenylpyrazolo[5,1-*a*]isoquinoline (**5d**, C₂₁H₂₀N₂)

Light orange solid; Yield: 123 mg (82%); FTIR (KBr, cm⁻¹): 3070, 2970, 2870, 1745, 1625, 1537, 1456, 1392, 1338, 1199, 1062; ¹H-NMR (300 MHz, CDCl₃, δ): 8.16 (d, 1H, *J* = 7.2), 8.07 (d, 2H, *J* = 7.2), 7.89 (d, 1H, *J* = 7.8), 7.60 – 7.46 (m, 4H), 7.40 – 7.31 (m, 1H), 7.27 (s, 1H), 3.42 (q, 2H, *J* = 7.5), 3.04 (q, 2H, *J* = 7.5), 1.46 (t, 3H, *J* = 7.5), 1.35 (t, 3H, *J* = 7.5); ¹³C NMR (75 MHz, CDCl₃, δ): 151.43, 138.99, 137.89, 133.94, 128.80, 128.64, 127.92, 127.64, 126.31, 126.19, 123.98, 123.79, 119.88, 94.15, 21.30, 20.62, 15.02, 12.53; ESI-MS: m/z 301.2 (M+H)⁺.

SUPPLEMENTARY INFORMATION

Crystal structure data determination for compound 4a has been deposited with the CCDC No. 1949920. This information may be access via www.ccdc.cam.ac.uk/data_request/cif. Further, the detailed characterization of all the compounds (¹H, ¹³C-NMR, and ESI-MS data), selected bond lengths and angles of 4a as well as copies of the ¹H and ¹³C-NMR spectra of all the compounds are provided as supplementary information.

Statements and Declarations

The authors have no competing interest to declare.

Acknowledgements. KSS thanks the Council of Scientific and Industrial Research (CSIR) India for financial support and the Director, CSIR-NIO for providing necessary facilities.

References

1. Hunt HJ, Belanoff JK, Gourdet B, Phillips T, Swift D, Thomas J, Unitt JF, Walters I (2015) *Bioorg Med Chem Lett* 25: 5720
2. Kees KL, Fitzgerald JJ, Steiner KE, Mattes JF, Mihan B, Tosi T, Mondoro D, McCaleb ML (1996) *J Med Chem* 39: 3920

3. Ochi T, Magari K. J, Yonezawa A, Matsumori K, Fujii T (1999) *Eur. J. Pharma*, 365:259-266
4. Souza FR, Souza VT, Ratzlaff V, Borges LP, Oliveira MR, Bonacorso HG, Zanatta N, Martins MA, Mello CF (2002) *Eur J Pharm* 451:141
5. Nicolai E, Cure G, Goyard J, Kirchner M, Teulon JM, Versigny A, Cazes M, Virone-Oddos A, Caussade F, Cloarec A (1994) *Chem Pharm Bull* 42: 1617
6. Demirayak S, Karaburum AS, Beis R (2004) *Eur J Med Chem* 39: 1089
7. Chen ZY, Wu J (2010) *Org Lett* 12: 4856
8. Johns BA, Gudmundsson KS, Turner EM, Allen SH, Samano VA, Ray JA, Freeman GA, Boyd Jr. FL, Sexton CJ, Sellese DW, Creech KL Moniri KR (2005) *Bioorg Med Chem* 13: 2397
9. Cheung M, Harris PA, Badiang JG, Peckham GE, Chamberlain SD, Alberti MJ, Jung DK, Harris SS, Bramson NH, Epperly AH, Stimpson SA, Peel MR (2008) *Bioorg Med Chem Lett* 18: 5428
10. Johns BA, Gudmundsson KS, Turner EM, Allen SH, Jung DK, Sexton CJ, Boyd JFL, Peel MR (2003) *Tetrahedron* 59: 9001
11. Koike T, Takai T, Hoashi Y, Nakayama M, Kosugi Y, Nakashima M, Yoshikubo S, Hirai K, Uchikawa O (2011) *J Med Chem* 54: 4207
12. Chauhan M, Kumar R (2013) *Bioorg Med Chem* 21: 5657
13. Hays DS, Danielson M, Gerster J, Niwas S, Prince R, Kshirsagar T, Heppner P, Moser W, Moseman J, Radmer M, Kavanagh M, Strong S, Bonk J (2006) *Pyrazolopyridines and analogs thereof US patent US 20060100229A1* May 11, 2006
14. Garofalo AW, Jagodinski JJ, AW Konradi, CM Semko, JL. Smith, YZ Xu, XM Ye (2010) 5-(Arylsulfonyl)-pyrazolopiperidines, in: patent *WO 2007/064914* June 7, 2007
15. Custodi C, Nuti R, Oprea TI, Macchiarulo A (2012) *J Mol Graph Model* 38: 70
16. Dore A, Asproni B, Scampuddu A, Pinna GA, Christoffersen CT, Langgård M and Kehler J (2014) *Eur J Med Chem* 84: 181
17. Begely WJ, Grimshaw J, Trocha-Grimshaw J (1974) *J Chem Soc Perkin Trans* 1: 2633
18. Garg M, Chauhan M, Singh PK, Alex JM, Kumar R (2015) *Eur J Med Chem* 97: 444
19. Yang Y, Ren H, Wang D, Shi F, Wu C (2013) *RSC Advances* 3: 10434
20. Wen LR, Jin XJ, Niu XD, Li M (2015) *J Org Chem* 80: 90
21. Ma W, Graczyk K, Ackermann L (2012) *Org Lett* 14: 6318
22. Li X, Zhao M (2011) *Org Lett* 13: 8530
23. Li B, Dixneuf PH (2013) *Chem Soc Rev* 42: 5744

24. Ackermann L (2014) *Acc Chem Res* 47: 281
25. Manikandan R, Jaganmohan M (2017) *Chem Commun* 53: 8931
26. Gramage-Doria R, Bruneau C (2021) *Coord Chem Rev* 428: 213602
27. Singh KS (2019) *Catalysts* 9:173
28. Singh P, Chouhan KK, Mukherjee A (2021) *Chem Asian J* 16: 2392
29. Jin XY, Xie LJ, Cheng HP, Liu AD, Li XD, Wang D, Cheng L, Liu LJ (2018) *J Org Chem* 83:751
30. Li G, Liu Q, Vasamsetty L, Guo W, Wang J (2020) *Angew Chem Int Ed* 59: 3475
31. Arockiam PB, Fischmeister C, Bruneau C, Dixneuf PH (2010) *Angew Chem Int Ed* 49: 6629
32. Ackermann L, Fenner S (2011) *Org Lett* 13: 6548
33. Singh KS, Dixneuf PH (2013) *ChemCatChem* 5: 1313
34. Singh KS, Sawant SG, Dixneuf PH (2016) *ChemCatChem* 8: 1046
35. Ackermann L, Wang L, Lygin AV (2012) *Chem Sci* 3:177
36. Warratz S, Kornhaaß C, Cajaraville A, Niepötter B, Stalke D, Ackermann L (2015) *Angew Chem Int Ed* 54: 5513
37. Bechtoldt A, Tirler C, Raghuvanshi K, Warratz S, Kornhaaß C, Ackermann L (2016) *Angew Chem Int Ed* 55: 264
38. Zhou X, Liu M, Luo P, Lai Y, Yang T, Ding Q (2014) *Beilstein J. Org. Chem* 10: 2286
39. Chinnagolla RK, Jaganmohan M (2012) *Chem Commun* 48: 2030
40. Algarra AG, Cross WB, Davies DL, Khamker Q, Macgregor SA, McMullin CL, Singh, K (2014) *J Org Chem* 79: 1954
41. Bennett MA, Smith AK (1974) *J Chem Soc Dalton Trans* 233
42. Singh KS, Kaminsky W (2014) *Polyhedron* 68: 279
43. Singh KS, Sawant SG, Kaminsky W (2018) *J Chem Sci* 130: 120
44. Altomare A, Burla C, Camalli M, Cascarano GL, Giacovazzo C, Guagliardi A, Moliterni AGG, Polidori G, Spagna R (1999) SIR97: A new tool for crystal structure determination and refinement. *J Appl Cryst* 32: 115
45. Sheldrick GM (1997) SHELXL-97: Program for the refinement of crystal structures University of Göttingen, Germany

Graphical abstract

Pyrazolo[5,1-*a*]isoquinolines were synthesized via ruthenium(II)-catalysed annulation of pyrazole derivatives with alkynes in the presence of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and AgSbF_6 in water, alternatively in alcohol in the presence of carboxylate ligand under air.

