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Title: Ru(II)-Catalyzed Sequential One-Pot Double Annulation of N-Methoxybenzamides with Symmetrical/Unsymmetrical Alkynes and Alkenes: Regioselective Construction of Isoindolo[2,1-b]isoquinolin-5(7H)-one Framework

Authors: Praveen Kumar Naikawadi, Lingaswamy Mucherla, Rambabu Dandela, Madhavi Sambari, and Shiva Kumar Kota

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One-Pot Two-Step Double Annulation of *N*-Methoxybenzamides with Alkynes and Alkenes: Regioselective Construction of Isoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones

Praveen Kumar Naikawadi, [a] Lingaswamy Mucherla,[a] Rambabu Dandela,[b] Madhavi Sambari,[a] K. Shiva Kumar[a]*

[a]Department of Chemistry, Osmania University, Hyderabad-500 007, India
E-mail: shivakumarkota@yahoo.co.in; shivakumarkota@osmania.ac.in
[b]Department of Industrial and Engineering Chemistry, Institute of Chemical Technology, IOC-Odisha Campus, Samantpuri, Bhubaneswar-751013, India

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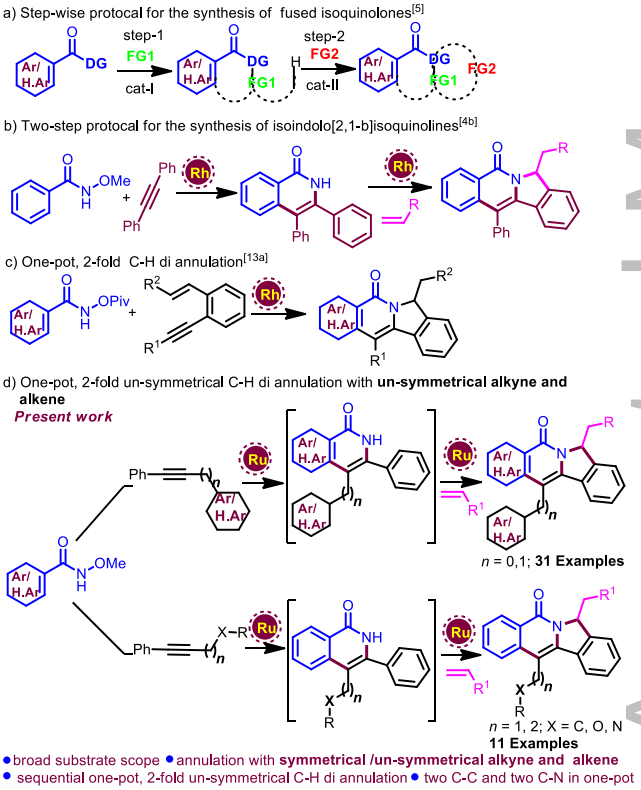
Abstract. A one-pot two-step double annulation strategy to produce isoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones *via* the reaction of *N*-methoxybenzamides with symmetrical/unsymmetrical alkynes and alkenes has been developed, which proceeds through Ru-catalysed unsymmetrical double annulations using a single DG under single catalytic conditions. Furthermore, we have developed amide-alkyne regioselective annulations using unsymmetrical internal alkynes having oxygen/nitrogen substituents leading to a single isomer. The developed procedure offers broad substrate scope, tolerates a wide range of functional groups and affords good product yields.

Keywords: isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one; regioselective; ruthenium; annulations; amides

Introduction

The one-pot annulation strategy has emerged as an ideal one-step powerful platform to furnish various structurally novel complex molecules, particularly polycyclic heteroaromatic systems with extended conjugation.[1] In this regard, tandem cyclization *via* transition metal (TM)-catalysed and directing group (DG)-supported activation/functionalization, and annulation of inert C−H bonds with high regio- and chemoselectivity are invaluable[2] and has found good applications in the synthesis of complex natural products with promising bioactivities.[3-7]

Generally, two synthetic steps are required to realize a cascade 2-fold annulation of arenes/heteroarenes with different coupling partners. Consequently, reactions involving diverse functional groups require different catalytic conditions (Scheme-1a).[5] In particular, construction of various fused isoquinolones in the presence of transition metal catalysts *via* the two steps synthetic process, in which the first step involves construction of isoquinolone ring followed by the oxidative annulation of *NH*-isoquinolone with different coupling partners such as α-diazo-1,3-diketones,[8] sulfoxonium ylides,[9] alkynes,[10] carbon monoxide,[5b] benzoquinone[11] and carbon dioxide[12] in the second step has been achieved.



Scheme 1. 2-Fold symmetrical/unsymmetrical annulations of arenes/hetero arenes

Du and Li *et al*[4b] reported Rh(III)-catalysed synthesis of isoindolo[2,1-*b*]isoquinolines in two steps involving oxidative coupling reaction between methyl benzohydroxamate and alkyne to give isoquinolone in the first step, followed by olefin insertion in the second step (Scheme-1b). Only three compounds were prepared using this one pot method

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without isolation of isoquinolone intermediate. Very recently Reddy *et al*[13a] demonstrated Rh(III)-catalysed synthesis of aromathecins *via* domino [4+2] annulation/aza-Michael addition of *N*-(pivaloyloxy)benzamides with 1,5-enynes involving a C-H activation process(Scheme-1c). Volla *et al*[13b] reported synthesis of isoindolo[2,1-b]isoquinolin-5(7*H*)-ones *via* Rh(III)-catalysed redox-neutral cascade annulation of benzamides with *p*-quinone.

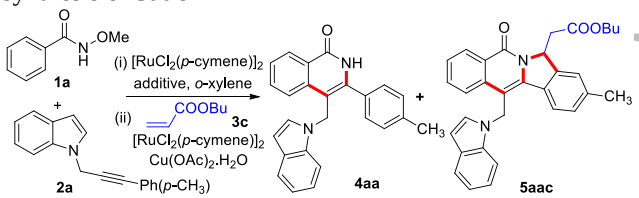
The isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one framework has been found to be an integral part of several natural products, bioactive molecules and drugs. Among them rosettacin, camptothecin and 22-hydroxyacuminatine etc.[14] are notable examples. However, limited efforts have been devoted towards the development of one-pot two-fold C-H functionalization method for the synthesis of this class of fused heterocycles. While their synthesis have attracted attention[15] in recent time but most of the reported methods are limited to the use of i) two step process, ii) 2-fold symmetrical C−H diannulation, iii) symmetrical alkynes only and iv) expensive Rh catalyst. Additionally, most of the reported procedures involving metal catalysed amide-alkyne annulations use symmetrical or unsymmetrical internal alkynes having carbon/nitrogen/oxygen/sulphur substituents. However, the use of unsymmetrical internal alkynes with uncontrollable regioselectivity afforded a mixture of products in several cases.[16] Yao *et al*[17] demonstrated that the annulation of unsymmetrical internal alkynes having sulphur based substituted phenyl(phenylethynyl)sulfane and *N*-methoxybenzamides through Ru- catalysed *C−H/N−O* activation resulted in a mixture of regioisomers.

Thus, the sequential one-pot, 2-fold unsymmetrical C−H di annulation of arenes/heteroarenes with different coupling partners (symmetrical/unsymmetrical alkyne having oxygen/nitrogen substituents and alkene) in the presence of a single directing group under single catalytic conditions is attractive for the construction of isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one ring. In continuation of our study on the development of construction of various heterocycles *via* C-H activation/functionalizations,[18] we disclose herein a Ru-catalysed regioselective controlled annulation of *N*-methoxybenzamide with symmetrical/unsymmetrical alkyne followed by olefin insertion *via* C-H activation. This process afforded isoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones *via* the formation of four (two C-C and two C-N) bonds (**Scheme-1d**).

Results and Discussion

Our initial attempts to achieve the one-pot two-step sequential double annulation process focused on the reaction between *N*-methoxybenzamides (**1a**) with alkyne (**2a**) and alkene (**3c**) (Table 1). $[RuCl_2(p\text{-cymene})]_2$ in combination with $Cu(OAc)_2.H_2O$ as the catalyst (known for annulation reactions under mild reaction condition)[15,19] provided the mono annulated product **4aa** in 85% yield. The reaction was performed using *o*-xylene as a solvent at room temperature for 8 h (entry 1). The second annulation product (expected after participation of alkene) was not obtained even with the increase in the reaction time (16 h) (entry 2). To obtain the unsymmetrical double annulation product **5aac**, the annulation between the **1a**, **2a**, and **3c** was conducted at room temperature for 8 h (where alkyne undergoes cyclization) and followed by 110 °C (olefin insertion *via* C-H activation) for 4 h to deliver the desired product **5aac** with complete regiocontrol in a single pot under one catalytic condition (Table 1, entry 3). When we used $Cu(OAc)_2$ and $Cu(OTf)_2$ as oxidants, the product yield was decreased to 25% and 20%, respectively (entries 4 and 5). During the screening of various additives, NaOPiv KOAc and AgOAc gave moderate yields compared to NaOAc (entries 6–8). Changing the additive to CsOAc, affected the reaction productivity and gave the product in 80% yield (entry 9). A lower yield of **5aac** was achieved when the reaction was performed at a lower temperature i.e 80 °C and or at a higher temperature i.e 130 °C (entries 10 and 11). Finally, the reaction of **1a** and **2a** under the catalyst system $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), NaOAc (40 mol%) in *o*-xylene at room temperature for 8 h followed by the addition of **3c** (1.5 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv) at 110 °C for 4 h afforded **5aac** (entry 3). The reaction was further optimized for reaction stoichiometry, solvent, and other reaction parameters (for more details, please see Table S1 in the SI).[20]

Table 1. Optimization of reaction conditions for the synthesis of **5aac** [a]



Entry	Additive	Temperature (°C)	Yield (%)[b]	
			4aa	5aac
1	NaOAc	RT	85[c]	-
2	NaOAc	110	73[c]	-
3	NaOAc	RT/110	-	84
4[d]	NaOAc	RT/110	-	25
5[e]	NaOAc	RT/110	-	20
6	NaOPiv	RT/110	-	32
7	KOAc	RT/110	-	22
8	AgOAc	RT/110	-	18
9	CsOAc	RT/110	-	80
10	NaOAc	RT/80	20	52
11	NaOAc	RT/130	-	80

[a]Conditions: **1a** (0.331 mmol, 1.0 equiv), **2a** (0.331 mmol, 1.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), additive (40 mol%), *o*-xylene (1.5 mL) at rt for 8 h; then $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $Cu(OAc)_2.H_2O$ (0.662 mmol, 2.0

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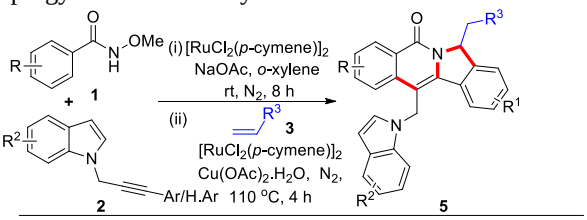
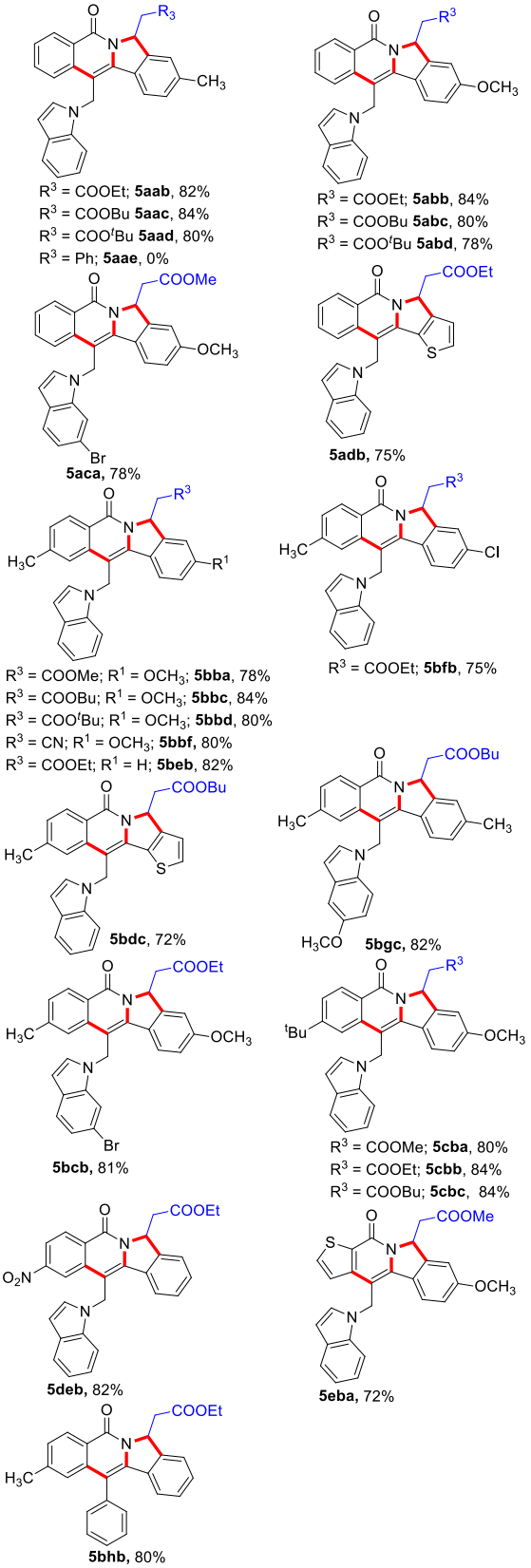
equiv), alkene (0.496 mmol, 1.5 equiv) at 110 °C for 4 h. [b]Isolated yields. [c]All of the reactants and catalyst added in one time. [d]$Cu(OAc)_2$ was used instead of $Cu(OAc)_2.H_2O$. [e]$Cu(OTf)_2$ was used instead of $Cu(OAc)_2.H_2O$

With the optimal reaction conditions in hand, the cascade cyclization scope of various *N*-methoxy amides (**1**) with unsymmetrical alkyne (**2**) and alkene (**3**) were investigated. As shown in Table 2, a variety of *N*-propargylindoles (**2a−h**), which had different substituted indole moieties, were investigated. The indoles containing electron donating substitute such as methoxy reacted smoothly to give the corresponding double annulated product **5bgc** in 82% yield. The presence of halogens on indole ring did not change the reaction pathway and afforded the desired products in good yields (entry **5aca** and **5bcb**). Different substituents on phenyl groups at the terminal position of the triple bonds, were investigated. The reaction was compatible with substituents present at the *para*-position of the benzene rings of internal alkynes, such as Me− (entries **5aab**, **5aac, 5aad** and **5bgc**), MeO− (entries **5abb**, **5abc**, **5abd**, **5aca**, **5bba**, **5bbc**, **5bbd**, **5bbf, 5bcb**, **5cba, 5cbb**, **5cbc** and **5eba**) and Cl− group (entry **5bfb**), providing the corresponding isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one products in good yields (72%−84%). Furthermore, a heterocyclic thiophene motif could also give the corresponding product in 72-75% yield (entries **5adb** and **5bdc)**. Next, we surveyed the scope of the reaction with various substituted benzamides **1**. Pleasingly, *N*-methoxybenzamides having *para*-substituents on the arene moiety, electron-donating $-CH_3$ (entries **5bba**, **5bbc**, **5bbd**, **5bbf, 5beb**, **5bfb**, **5bdc**, **5bgc, 5bcb** and **5bhb**), $-^tBu$ (**5cba**, **5cbb** and **5cbc**) and strong electron-withdrawing groups $-NO_2$ (**5deb)** smoothly reacted with **2** and **3** under the optimized procedure to afford corresponding double annulated isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one. Moreover, methyl acrylate (**5aca**, **5bba, 5cba** and **5eba**), ethyl acrylate (**5aab**, **5abb, 5adb, 5beb, 5bfb, 5bcb, 5cbb, 5deb** and **5bhb),** butyl acrylate (**5aac, 5abc, 5bbc, 5bdc, 5bgc** and **5cbc)** *tert*-butyl acrylate (**5aad, 5abd** and **5bbd)** and acrylonitrile **(5bbf)** found to be effective for the synthesis of isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one. Unfortunately, styrene failed to provide the desired product (**5aae**). In addition, the product **5bhb** is formed in good yields (80%) when symmetrical alkyne [diphenylacetylene (**2h**)] is used in the place of unsymmetrical alkyne.

We further extended the scope of unsymmetrical alkyne *N*-propargyl-7-azaindoles for the synthesis of important class of azaindoles substituted isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one derivatives (Table-3). The reaction worked well in the presence of different functional groups [(neutral (H), rich

Table 2. Substrate scope of hetero(arene) amides, *N*-propargylindoles and acrylate[a][b]





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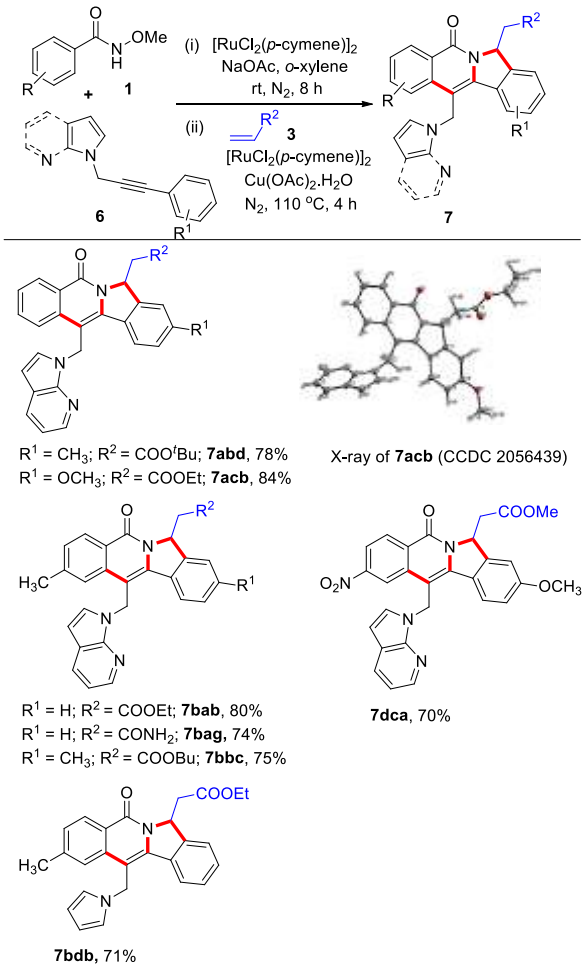
[a]Reaction conditions: **1** (0.331 mmol), **2** (0.331 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), NaOAc (40 mol %), *o*-xylene (2.0 mL) at rt for 8 h; then $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), acrylates **3 (** 0.496 mmol), $Cu(OAc)_2.H_2O$ (0.662 mmol) at 110 °C for 4 h, [b]isolated yield.

(methyl) and poor (nitro)] at the C4 position of the amide ring,furnishing azaindoles substituted isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one (**7**) in good yields. Similarly, *N*-propargyl-7-azaindoles **6** with methyl (**3a**), ethyl (**3b**), *n*-butyl (**3c**), *tert*-butyl (**3d**) acrylates and acrylamide **(3g)** were compatible and afforded the corresponding products (**7bab, 7abd, 7acb, 7bbc, 7dca, 7bdb** and **7bag**). Likewise, the use of a *N*-propargyl pyrrole substrate turned out to be viable that gave the desired product in good yields (**7bdb**, 71%). The regioselectivity of annulation was further confirmed by the X-ray crystallographic analysis of product **7acb** (Please see SI).[21]

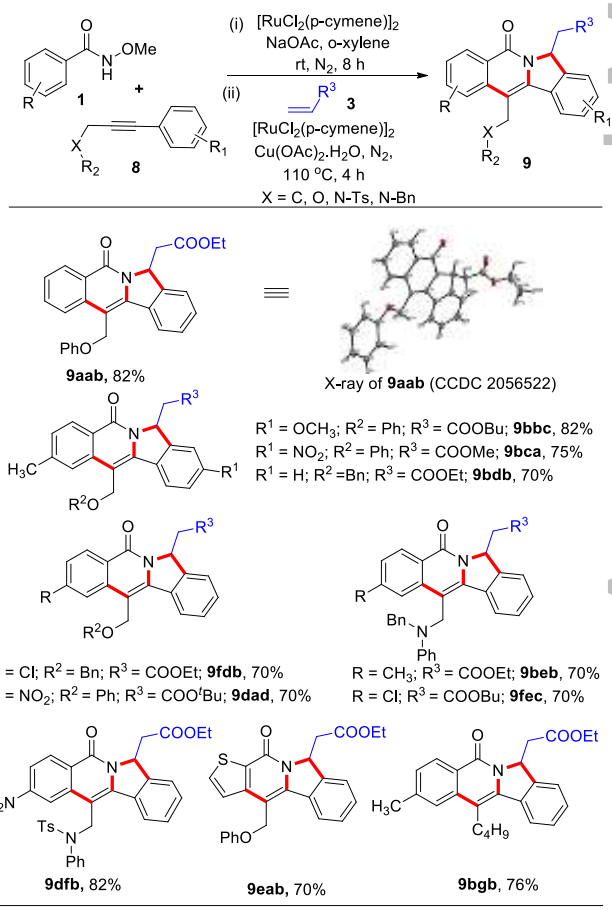
Table 3. Substrate scope of *N*-propargyl-7-azaindoles[a] [b]



[a]Reaction conditions: **1** (0.331 mmol), **6** (0.331 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), NaOAc (40 mol %), *o*-xylene (2.0 mL) at rt for 8 h; then $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), acrylates **3 (**0.496 mmol), $Cu(OAc)_2.H_2O$ (0.662 mmol) at 110 °C for 4 h, [b]isolated yield.

The versatility of the optimised Ru-catalysed regioselective double annulation strategy for isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one analogues was not limited to *N*-propargyl indoles/azaindoles. Indeed, this protocol could be successfully extended to unsymmetrical internal alkynes having oxygen/nitrogen substituents like propargyl aryl ethers (**8a-d**) and propargyl aryl amines (**8e-f**). These moieties were well tolerated under the standard reaction conditions to afford corresponding double annulated products. Propargyl aryl ethers (**8**) having the substituents at the *para*-position on the benzene rings of alkynes, such as electron donating -OMe (**8b**) and strong electron withdrawing group $-NO_2$ (**8c**) provided the corresponding regioselective isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one products **9bbc** and **9bca** in 82% and 75% yields, respectively. The structure of **9aab** was unambiguously confirmed by X-ray single crystal analysis. (Please see SI).[21] The propargyl aryl amines having *N*-benzylaniline (**8e**) and *N*-phenylbenzene sulfonamide (**8f**) were well tolerated under the standard conditions, and furnished the corresponding products (**9beb, 9fec** and **9dfb**) in good yields (70-82%). Additionally, the reaction employing the non-functionalized internal alkynes (**8g**) also proceeded smoothly to furnish the corresponding isoquinolones **9bgb** in good yields.

Table 4. Substrate scope of propargyl aryl ethers/ propargyl aryl amines[a][b]



[a]Reaction conditions: **1** (0.331 mmol), **8** (0.331 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), NaOAc (40 mol %), *o*-

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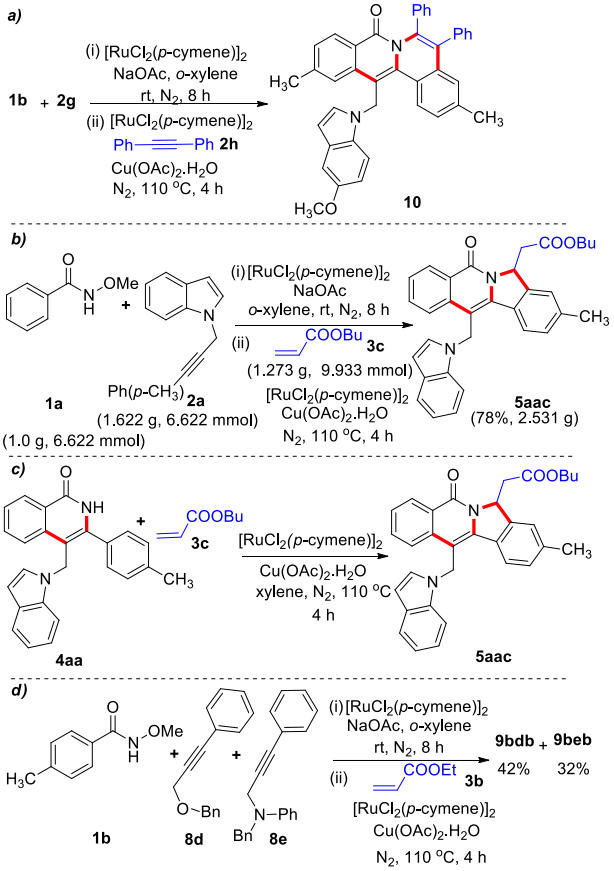
xylene (2.0 mL) at rt for 8 h; then $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), acrylates **3** (0.496 mmol), $Cu(OAc)_2.H_2O$ (0.662 mmol) at 110 °C for 4 h, [b]isolated yield.

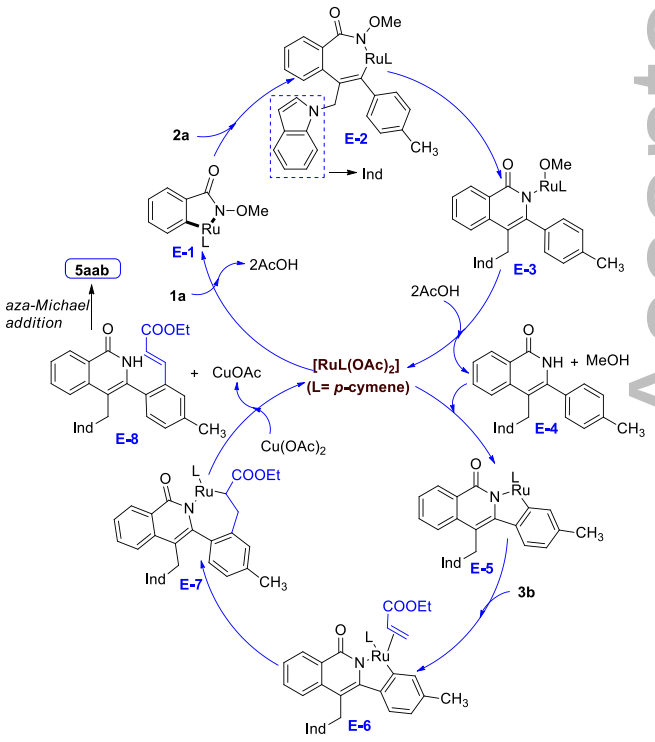
Encouraged by the above results, we explored the one-pot two-step sequential double annulation of N-methoxy-4-methylbenzamide (**1b**) with *N*-propargyl-substituted indole (**2g**) and diphenylacetylene (**2h**) using Ru(II) catalyst and produced the corresponding isoquinolino[3,2-*a*]isoquinolineone derivative **10** (75%) as shown in **Scheme-2a.** In order to demonstrate the utility of this chemistry, the Ru-catalysed regioselective double annulation strategy for isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one were conducted on a gram scale. The reaction of **1a**, **2a** and **3c** was completed within 12 h under standard conditions, generating the desired product (**5aac**) in 78% (2.53 g) yield (Scheme 2b). As discussed above, the formation of isoindolo[2,1-*b*]isoquinoline was assumed to take place *via* the generation of isoquinolin-1(2*H*)-one (**4aa**) *in situ*. To confirm this, we performed a reaction using isoquinolin-1(2*H*)-one intermediate (**4aa**) (0.331 mmol) $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), **3c** (0.496 mmol) and $Cu(OAc)_2.H_2O$ (0.662 mmol) in *o*-xylene (2 mL) at 110 °C for 4 h. As expected, this reaction resulted in the formation of desired isoindolo[2,1-*b*]isoquinoline **5aac** with 85% yield (Scheme 2c). Moreover, we conducted an experiment to assess the intermolecular competition between propargyl aryl ether (**8d**) and propargyl aryl amine (**8e**). The reaction of substrate **1b** (1.0 equiv),



Scheme 2. Synthetic elaboration, gram-scale and control experiments

propargyl aryl ether **8d** (0.5 equiv) and propargyl aryl amine **8e** (0.5 equiv) with ethyl acrylate (**3b**) (1.0 equiv) was performed under the optimized conditions (Scheme 2d) when **9bdb** was obtained in 42% yield and **9beb** in 32% yield. This result indicated that the propargyl aryl ether is more reactive then propargyl aryl amines for the synthesis of isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one under present experimental conditions.

Based on the previous reports, a proposed mechanism for the one-pot two-step sequential double annulation of *N*-methoxybenzamides with *N*-propargyl-substituted indoles and activated olefins is shown in **Scheme-3**. First, the active complex Ru catalyst coordinates with the *N*-moiety of *N*-methoxybenzamides (**1a**), affording a five-membered ruthenacyclic intermediate (**E-1**) *via* *o*-C(sp^2)-H activation of arene/heteroarene. Then, regioselective coordination and insertion of alkyne into the compound (**E-1**) occurs to generated the seven-membered ruthenacycle intermediate (**E-2**). Then on reductive elimination and N−O cleavage **E-2** affords the mono annulations intermediate isoquinolone (**E-4**) *via* **E-3**. Subsequently, **E-4** undergoes proximal C−H metalation to deliver 5-membered Ru metallacycle (**E-5**). The alkene **3b** on coordination with the Ru species in **E-5** affords **E-6**, in which it is inserted in to the Ru−C bond to give a seven-membered ruthenacycle intermediate (**E-7**). The *β*-H elimination[22] of **E-7** affords the acrylic ester intermediate (**E-8**) and a ruthenium complex that regenerates the active Ru(II)-catalyst in the presence of $Cu(OAc)_2.H_2O$.[15b,23] Finally, an intramolecular aza-Michael addition would give the double annulated product **5aab**.[22,24]



Scheme 3. The proposed reaction pathway

Conclusion

In summary, we have successfully developed sequential one-pot two-step method for the synthesis of isoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones *via* the 2-fold unsymmetrical double annulation of *N*-methoxybenzamide derivatives with symmetrical/unsymmetrical alkynes and activated olefins *via* Ru-catalysed C-H activation. The different unsymmetrical alkynes (*N*-propargyl-substituted indole/azaindoles/pyrrole, propargyl aryl ether and propargyl aryl amines) were successfully coupled with *N*-methoxybenzamide and acrylate in a regioselective manner to afford the isoindolo[2,1-*b*]isoquinolin-5(7*H*)-one derivatives in good yields. Overall, this transformation involved the formation of four (two C-C and two C-N) bonds.

Experimental Section

General Procedure for the Preparation of Isoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones (5/7/9/10)
To an oven-dried 50 mL Schlenk tube under an nitrogen atmosphere were added *N*-methoxybenzamide (**1**) (0.331 mmol), alkyne (**2**/**6**/**8**) (0.331 mmol), [e.g. Ru(*p*-cymene)$Cl_2]_2$ (5 mol%), NaOAc (40 mol %). The solvent *o*-xylene (2.0 mL) was added to the reaction mixture and the resulting mixture was stirred at room temperature for 8 h. Then to this reaction mixture was added Ru(*p*-cymene)$Cl_2]_2$ (5 mol%), $Cu(OAc)_2.H_2O$ (0.662 mmol) and acrylate **(3)**/diphenyl acetylene (**2h**) (0.496 mmol) were added. The resulting mixture was stirred at 110 ^oC for 4 h. The reaction mixture was cooled to ambient temperature, filtered through a celite and then washed with dichloromethane (3×15 mL). The solvents were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel using ethyl acetate-hexane to give the desired product **5**/**7**/**9**/**10**.

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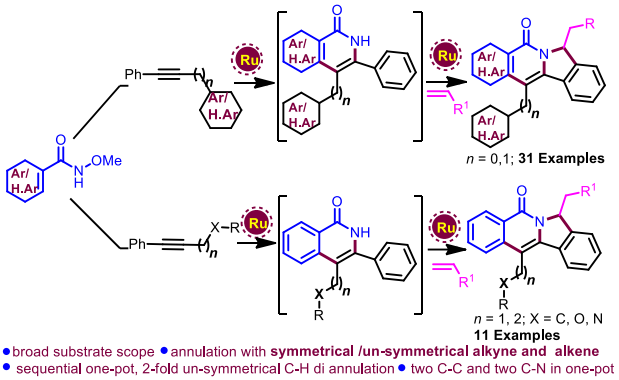
FULL PAPER

One-Pot Two-Step Double Annulation of *N*-Methoxybenzamides with Alkynes and Alkenes: Regioselective Construction of Isoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones



● broad substrate scope ● annulation with **symmetrical /un-symmetrical alkyne and alkene**
● sequential one-pot, 2-fold un-symmetrical C-H di annulation ● two C-C and two C-N in one-pot

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