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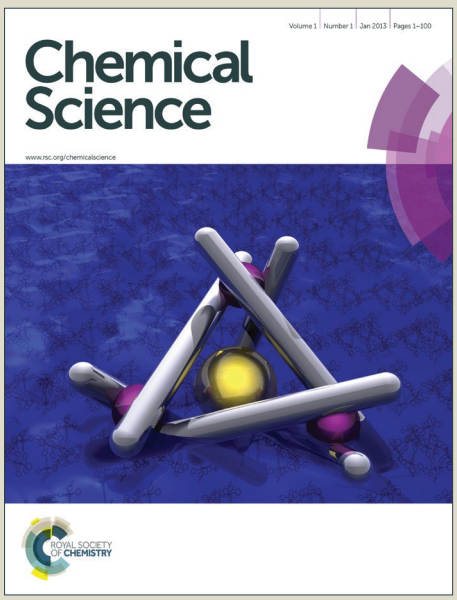

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ARTICLE

Carbonyl-Assisted Reverse Regioselective Cascade Annulation of 2-Acetylenic Ketones Triggered by Ru-Catalyzed C–H Activation

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The first reverse regioselective intermolecular annulation of aryl substituted 2-acetylenic ketones with *O*-substituted *N*-hydroxybenzamides or acrylamides followed by tandem cyclization is reported via ruthenium-catalyzed C–H activation. Excellent reverse selectivity of alkyne insertion was induced by the weak coordination between carbonyl group and ruthenium complex. This highly efficient and practical reaction has broad range of substrate scope with excellent functional-group tolerance. The tandem reaction provides a wide range of polycyclic products having indozilidine structural motif, which found to be synthetically and pharmaceutically valuable potential.

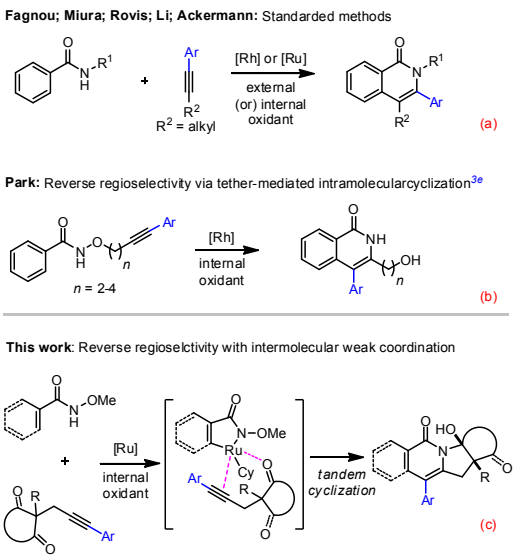
Introduction

Transition-metal-catalyzed oxidative annulations of alkynes by C–H bond activation have attracted significant interest in recent years, as this atom-economic strategy allows to access a wide range of heterocyclic scaffolds.[1] Among them, isoquinolone is one of the key structural motifs present in numerous bioactive natural products.[2] Consequently, several efficient synthetic routes have been developed for the construction of isoquinolones using metal-catalyzed C–H bond activation.[3-5]

Recently, Guimond/Fagnou,[3a] Rovis,[3b] and Miura[3c] research groups independently developed Cp*Rh-catalyzed annulation of alkynes with various types of benzamides. In subsequent reports, Ackermann[4a] and Li/Wang[4b] research groups demonstrated an efficient ruthenium-catalyzed oxidative annulation reaction. Later, Glorius et al. described the formation of 2-isoquinolinylboronates and bis-isoquinolones using rhodium catalyzed C–H activation,[6] while Antonchick and co-workers reported an organocatalytic annulation of *N*-alkoxybenzamide derivatives with alkynes through a nitrenium ion process[7].

Among all benzamides used in above synthetic transformations, *O*-substituted *N*-hydroxy benzamides have been paid great attention since it acts as an internal oxidant and also increases the reactivity under mild conditions.[8,9] Based on previous approaches, annulation of alkynes with *O*-substituted *N*-hydroxy benzamides proceeds through C–N bond reductive elimination of 7-membered metallocycle intermediate and subsequent N–O bond oxidative addition followed by protonolysis to afford isoquinolones with free NH functionality.[3-5] This functional handle can undergo cascade reactions to provide *N*-substituted isoquinolones that are less explored in literature.[10]

Most recently, Lin and co-workers elegantly demonstrated the Rh-catalyzed tunable arylative cascade annulation/Michael addition of cyclohexadienone-containing 1,6-enynes with *O*-substituted *N*-hydroxy benzamides.[10a] In their report, substrate scope was limited to terminal or alkyl substituted alkynes due to regioselectivity of the annulation products. In general,



Scheme 1 Previous and present approaches

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oxidative annulation of benzamides with unsymmetrical akynes substituted with alkyl and aryl groups allows installation of an aryl groups at the 3-position of isoquinolones with high regioselectivity (Scheme 1a). In 2012, Park and co-workers first time reported highly efficient and practical reverse regioselective tether-mediated intramolecular annulation reaction with excellent synthetic potential (Scheme 1b).[3e] Based on these observations, we intended to develop a straightforward metal-catalyzed reverse regioselective intermolecular chelation controlled annulation through C–H activation using aryl substituted alkynes.

Results and discussion

As part of our program aimed at the desymmetrization of *C*2-symmetric molecules,[11] we became interested in executing less expensive ruthenium-catalyzed annulation of acetylenic 1,3-diketones with *N*-methoxybenzamides. We envisioned that the ketone functionality would initially form an intermolecular chelation with five-membered ruthenacycle of benzamide and subsequently undergo the insertion with alkyne (Scheme 1c). We commenced our study with the reaction of benzamide **1a** and 1,3-diketone **2a** by employing [($RuCl_2${*p*-cymene})$_2$] (10 mol%) and NaOAc (2 equiv) in MeOH (0.2 M) at 80 °C for 24 hours. To our delight, the desired tetracyclic product (±)-**3a** was obtained via isoquinolone formation with reverse regioselectivity followed by cascade cyclization of neutral NH group with ketone in 75% yield (Table 1, entry 1). The structure of **3a** was fully characterized by NMR spectroscopy, IR, and HRMS. Single-crystal X-ray analysis of compound **3a** also unambiguously established its indolizidine structure (Figure 1).[12] Many biologically active natural products such as solanidine, septicine and rosettacin contains the core indolizidine structural motif (Figure 2).[13]

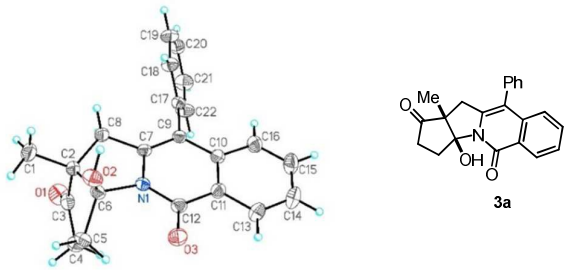


Fig. 1 ORTEP diagram of compound **3a** at the 30% probability level.

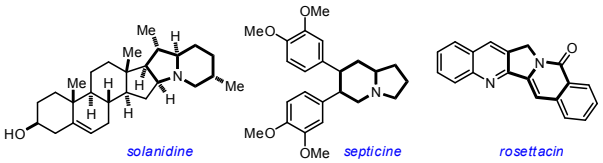
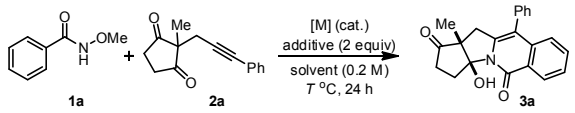


Fig. 2 Representative natural products bearing indolizidine core.

Table 1 Optimization of reaction conditions[a,b]



1a 2a 3a

Entry	[M], amount (mol%)	Solvent	Additive (2 equiv)	*T* (°C)	Yield[b] (%)
1	**[($RuCl_2${*p*-cymene})$_2$], 10**	**MeOH**	**NaOAc**	**80**	**75**
2	[($RuCl_2${*p*-cymene})$_2$],10	MeOH	NaOAc	rt	17
3	[($RuCl_2${*p*-cymene})$_2$],10	MeOH	KOAc	80	54
4	[($RuCl_2${*p*-cymene})$_2$],10	MeOH	CsOAc	80	57
5	[($RuCl_2${*p*-cymene})$_2$],10	MeOH	$Cu(OAc)_2$	80	19
6	[($RuCl_2${*p*-cymene})$_2$],10	MeOH	AgOAc	80	14
7	[($RuCl_2${*p*-cymene})$_2$],10	^{t}BuOH	NaOAc	80	64
8	[($RuCl_2${*p*-cymene})$_2$],10	^{i}PrOH	NaOAc	80	58
9	[($RuCl_2${*p*-cymene})$_2$],10	DMF	NaOAc	80	<5
10	[($RuCl_2${*p*-cymene})$_2$],10	CH_3CN	NaOAc	80	<5
11	**[($RuCl_2${*p*-cymene})$_2$], 5**	**MeOH**	**NaOAc**	**80**	**73**
12	[($RuCl_2${*p*-cymene})$_2$], 3	MeOH	NaOAc	80	38
13	-	MeOH	NaOAc	80	0
14	[($RuCl_2${*p*-cymene})$_2$], 5	MeOH	-	80	0
15	[Cp*$RhCl_2]_2$, 5	MeOH	NaOAc	80	31

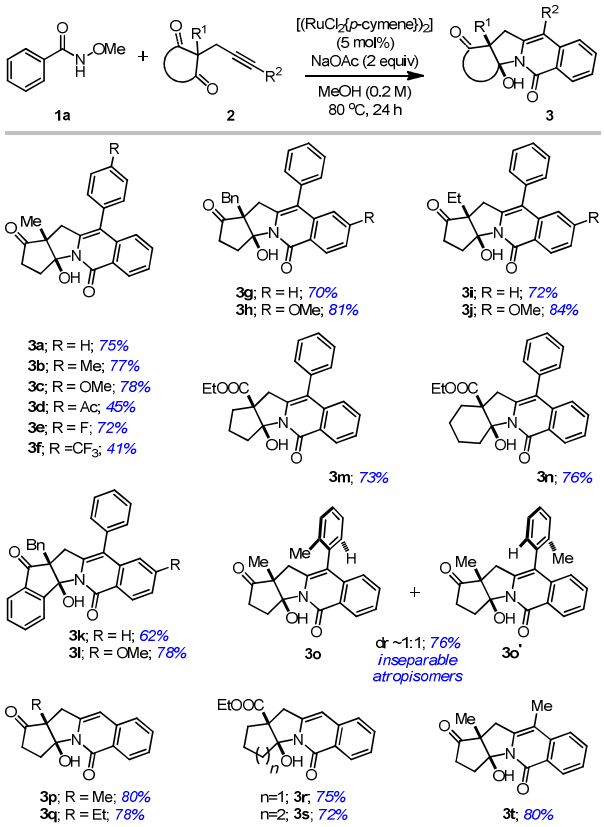
[a]Reactions were carried out with **1a** (0.6 mmol), **2a** (0.4 mmol), additive (0.8 mmol) in 0.2 M solvent; [b]Yields determined by ^{1}H NMR analysis with an internal standard 1,1,2,2-tetrachloroethane

When the reaction performed at room temperature using same conditions; only 17% of **3a** was obtained and most of the starting materials were recovered (Table 1, entry 2). In the screening of various metal acetates, KOAc, CsOAc gave moderate yields when compared to NaOAc. However, the use of $Cu(OAc)_2$ and AgOAc as an additive resulted in decreased catalytic efficiency (Table 1, entries 3-6). Among all solvents tested, protic solvents (^{t}BuOH, ^{i}PrOH) provided **3a** in moderate to good yields and polar solvents (DMF, CH_3CN) afforded very low yields (Table 1, entries 7-10). It was found that running the reaction with reduced catalyst loading (5 mol%) could also provide similar yield. However, lowering the catalyst loading to 3 mol% considerably decreased the yield (Table 1, entries 11 and 12). The control reactions indicated that the catalyst or additive alone did not produce any required product (Table 1, entries 13 & 14). Finally, [RhCp*$Cl_2]_2$ was evaluated, and it resulted **3a** in 31% yield (table 1, entry 15).

With the optimal reaction conditions in hand, the cascade cyclization scope of various 2-acetylenic ketones **2** were investigated with *N*-methoxy benzamide **1a**. As shown in table 2, electron-rich aryl group on the acetylenic 1,3-diketones led to higher yields of the tetracyclic products rather than electron poor arynes (**3a**-**f**). However, strong electron-withdrawing substituents such as NO_2, CN groups failed to give the products. Different substituents such as ethyl, benzyl groups at C2 position of cyclopentadienone were smoothly participated in the reaction to give the cyclized products in good yields (**3g**-**j**). Similarly, alkynes substituted with indane-

1,3-dione also afforded the corresponding annulation products **3k** and **3l** in

Table 2 Substrate scope for ketones[a,b]

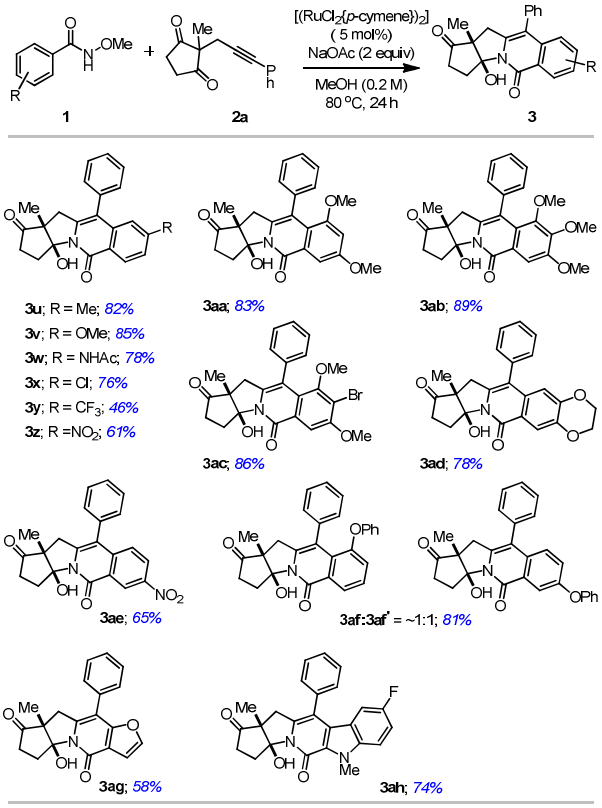


[a]Reaction conditions: **1a** (0.6 mmol), **2** (0.4 mmol), [($RuCl_2${*p*-cymene})$_2$] (5 mol %), NaOAc (0.8 mmol) in MeOH (2 mL) at 80 °C for 24 h; [b]Yields of products isolated after column chromatography

62% and 78% yields, respectively. Furthermore, five and six-membered 2-acetylenic *β*-ketoesters in which one carbonyl group is not part of the ring were well tolerated to furnish the cyclization products **3m** and **3n** in good yields. In case of ortho-substituted aryl group on the acetylenic 1,3-diketones, inseparable mixture of atropdiastereomers **3o** and **3o'** (dr~1:1) were obtained in 76% yield. This cascade cyclization is not limited to aryl substituted alkynes, substrates containing a terminal alkyne as well as alkyl substituted alkynes were also underwent the annulation reaction to provide the corresponding products **3p**-**t** in good to excellent yields (Table 2).

Next, we surveyed the scope of the reaction with various substituted benzamides **1** (Table 3). Both electron-poor and electron-rich *para*-substituted *N*-methoxybenzamides smoothly proceeded to furnish the corresponding isoquinolones **3u**-**3z** in moderate to excellent yields. Other symmetrical benzamides also provided cascade products **3aa**-**3ac** in higher yields. It was observed that the electron-rich benzamides reacted faster in annulation reaction with

Table 3 Substrate scope for benzamides[a,b]



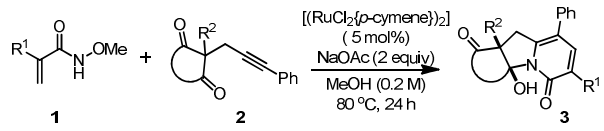
[a]Reaction conditions: **1** (0.6 mmol), **2a** (0.4 mmol), [($RuCl_2${*p*-cymene})$_2$] (5 mol%), NaOAc (0.8 mmol) in MeOH (2 mL); [b]Yields of products isolated after column chromatography

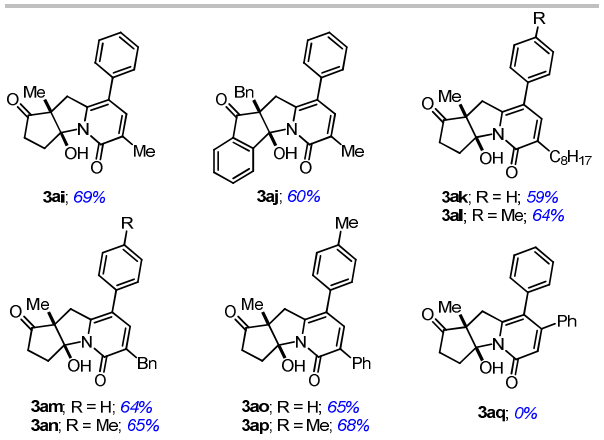
considerably higher yields than electron-deficient benzamides. In case of unsymmetrical *meta*-substituted benzamides, single regioisomers **3ad** and **3ae** were observed exclusively and the product formation was mainly controlled by steric interactions. In contrast, phenoxy substituted benzamide afforded **3af** and **3af'** in 81% yield with almost 1:1 regioselectivity probably due to planer structure and π-electron density of the phenoxy group which might coordinate with ruthenium. Both isomers **3af** and **3af'** were separated by careful column chromatography. The site selectivity of annulation reaction is in full agreement with previous reports by Ackermann.[14] In addition, extension of this cascade reaction to heteroaromatic caboxamides, such as furan and indole gave isoquinolone derivatives **3ag** (58%) and **3ah** (74%) respectively with expected regioselectivity (Table 3).

Enticed by these results, we examined the reactivity of different acrylamides in annulation/cascade reaction (Table 4).[15] Alkyl substitutions such as methyl, octyl and benzyl groups on the acrylamide at *α*-position were well tolerated to give tricyclic 2-pyridones **3ai**-**3an** in good yields (59-69%). At the same time, aryl substituted acrylamide also afforded

corresponding products **3ao** and **3ap** in 65% and 68% yields, respectively.

Table 4 Substrate scope for acrylamides [a,b]

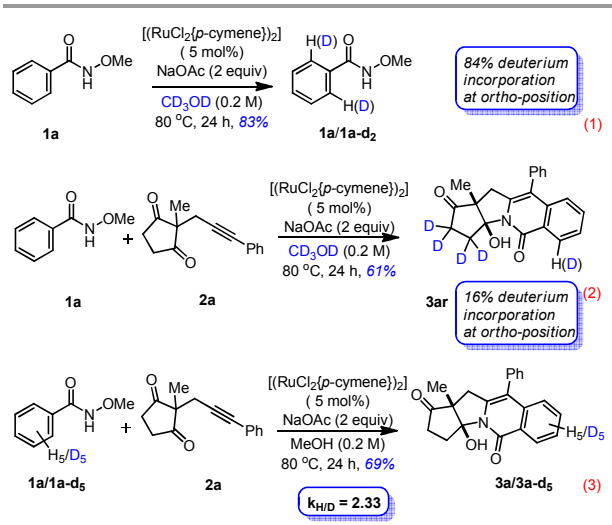




[a]Reaction conditions: 1 (0.6 mmol), 2 (0.4 mmol), [(RuCl$_2${*p*-cymene}$)_2$] (5 mol%), NaOAc (0.8 mmol) in MeOH (2 mL); [b]Yields of products isolated after column chromatography.

Disappointingly, phenyl substituted acrylamide at *β*-position failed to provide the required product **3aq** and the starting material was recovered.

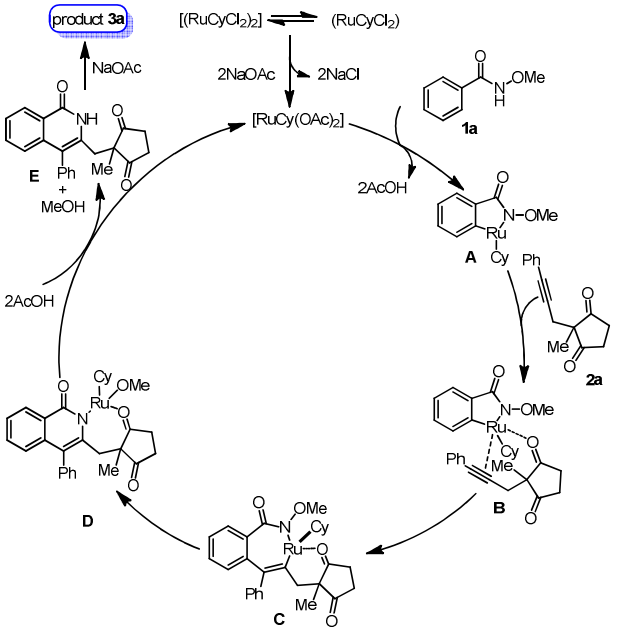
To probe the mechanism of this tandem reaction, a set of experiments were conducted with isotopically labelled solvents and substrates (Scheme 2). Initially, the reaction was carried out with amide **1a** in deuterated MeOH in the absence of **2a**



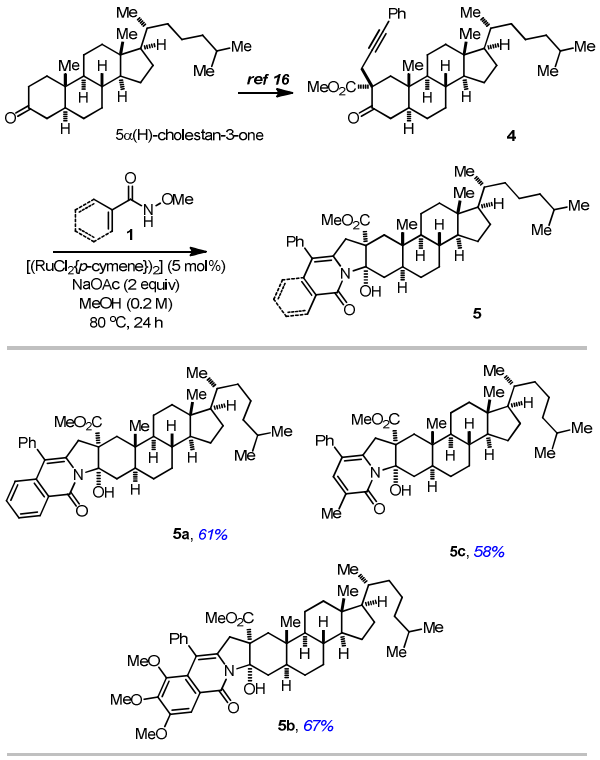
Scheme 2 Deuteration experiments

using standard conditions which furnished **1a/1a-d$_2$** with 84% deuterium incorporation at both *ortho*-positions without N-O bond cleavage. The same reaction in the presence of alkyne **2a** delivered compound **3ar** with 16% deuterium incorporation at *ortho*-position and almost complete deuteration on the cyclopentanone ring due to enolization of both ketones in **2a** in the presence of NaOAc. In addition, a kinetic isotope effect (KIE) of k_H/k_D = 2.33 was observed using 1:1 ratio of **1a**/**1a-d$_5$** in the intermolecular isotopic study. These experiments suggest that, the C-H bond ruthenation step is probably reversible and most likely involved in the rate-limiting step (Scheme 2).[3a,b; 4a,b]

A plausible mechanism is proposed based on the above experimental outcome in scheme 3. The ruthenium-catalyzed oxidative annulation starts from C–H bond activation to afford a five-membered ruthenacycle **A** with simultaneous loss of acetic acid. The formation of intermediate **A** is the turnover-limiting step in the whole cascade process. Subsequent intermolecular weak coordination of the carbonyl group oxygen lone pair with the ruthenium (**B**) followed by alkyne insertion afforded tetracyclic intermediate **C**. It is believed that the chelation of carbonyl group with ruthenacycle **A** is responsible for reverse regioselectivity.[3a, 16] The following intramolecular oxidative C–N bond formation provided intermediate **D**, which is readily protonated by acetic acid to furnish isoquinolone intermediate **E** and regenerates the active [Rucy(OAc)$_2$] catalyst.[4] Finally, intramolecular cyclization of **E** under basic conditions allows the formation of tandem product **3a**.



Scheme 3 Plausible mechanism for cascade arylative cyclization reaction



[a]Reaction conditions: **1** (0.6 mmol), **4** (0.4 mmol), [(RuCl$_2${*p*-cymene}$)_2$] (5 mol%), NaOAc (0.8 mmol) in MeOH (2 mL); [b]Yields of products isolated after column chromatography.

Scheme 4 Synthetic utility [a,b]

To further demonstrate the synthetic utility of this methodology, the cascade annulation reaction was then employed on the 2-acetylenic ketone **4** derived from the steroid 5α-cholestan-3-one (Scheme 4). Initially, 5α-cholestan-3-one was converted to alkyne **4** using literature procedure in 3 steps,[17] which was further subjected to annulation reaction with **1a**, **1ab** and **1ai** under standard reaction conditions to afford the desired polycyclic products **5a**, **5b** and **5c**, respectively in 58-67% yields.

Conclusions

In summary, we developed the first highly efficient and practical reverse regioselective intermolecular annulation of aryl substituted 2-acetylenic ketones with *O*-substituted *N*-hydroxybenzamides/acrylamides followed by tandem cyclization via Ru-catalyzed C–H activation. Excellent reverse selectivity of alkyne insertion was induced by weak coordination of the carbonyl group with the five-membered ruthenacycle. Apart from assisting the excellent regioselectivity, the carbonyl functionality yields polycyclic products which contain indozilidine structural motif by undergoing a cascade reaction. Additionally, mechanistic insights of the reaction revealed that C–H bond activation is the turnover-limiting step. The described methodology showed excellent functional-group tolerance and broad range of substrate scope. The regioselective tandem process would give access to complex heterocyclic structural motifs, which has several synthetic and pharmaceutical applications.

Experimental

Genereal Procedure: A screw-cap vial equipped with stirred bar was charged with *N*-methoxybenzamide/*N*-methoxy acrylamide **1** (0.6 mmol, 1.5 equiv), 2-acetylenic ketone **2** (0.4 mmol), [RuCl$_2$(*p*-cymene)]$_2$ (18.4 mg, 0.03 mmol, 5.0 mol%) and NaOAc (98.4 mg, 1.2 mmol, 2 equiv) and dry MeOH (2 mL) under nitrogen atmosphere. The reaction mixture was stirred at 80 ^{o}C for 24 h. Afterwards, it was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silical gel (20 to 30% EtOAc in hexane) to give the desired product **3**.

Acknowledgements

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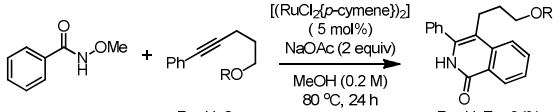

1 R = H, **6a** R = Bn, **6b** R = H, **7a**, *84%* R = Bn, **7b**, *79%*

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