

CrossMark
click for updatesCite this: *Chem. Sci.*, 2016, 7, 4748

Carbonyl-assisted reverse regioselective cascade annulation of 2-acetylenic ketones triggered by Ru-catalyzed C–H activation†

Krishna Kumar Gollapelli,‡^a Shivakrishna Kallepu,‡^a Nagendra Govindappa,^a Jagadeesh Babu Nanubolu^b and Rambabu Chegondi*^a

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

Received 1st April 2016
Accepted 12th April 2016

DOI: 10.1039/c6sc01456a

www.rsc.org/chemicalscience

Introduction

Transition metal-catalyzed oxidative annulations of alkynes *via* C–H bond activation have attracted significant interest in recent years, as this atom-economic strategy allows access to 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, the research groups of Guimond/Fagnou,^{3a} Rovis,^{3b} and Miura^{3c} independently developed the Cp*Rh-catalyzed annulation of alkynes with various types of benzamides. In subsequent reports, the research groups of Ackermann^{4a} and Li/Wang^{4b} 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 of the benzamides used in the above synthetic transformations, *O*-substituted *N*-hydroxy benzamides have been paid great attention since they act as an internal oxidant

and also increase reactivity under mild conditions.^{8,9} Based on previous approaches, the annulation of alkynes with *O*-substituted *N*-hydroxy benzamides proceeds *via* the C–N bond reductive elimination of a 7-membered metallocycle intermediate and a 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 a Rh-catalyzed tunable arylation cascade annulation/Michael addition of cyclohexadienone-containing 1,6-enynes with *O*-substituted *N*-hydroxy benzamides.^{10a} In their report, the substrate scope was limited to terminal or alkyl substituted alkynes due to the regioselectivity of the annulation products. In general, the oxidative annulation of benzamides with unsymmetrical alkynes substituted with alkyl and aryl groups allows the installation of aryl groups at the 3-position of isoquinolones with high regioselectivity (Scheme 1a). In 2012, Park and co-workers reported for the first time a 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 *via* 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 a less expensive ruthenium-catalyzed annulation of acetylenic 1,3-diketones with *N*-methoxybenzamides. We envisioned that

^aDivision of Natural Product Chemistry, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India. E-mail: rchegondi@iict.res.in

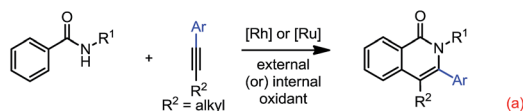
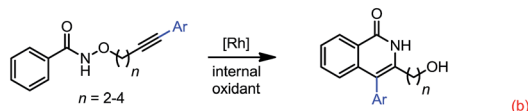
^bCentre for X-ray Crystallography, CSIR-Indian Institute of Chemical Technology, Hyderabad 500007, India

† Electronic supplementary information (ESI) available. CCDC 1449113. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6sc01456a

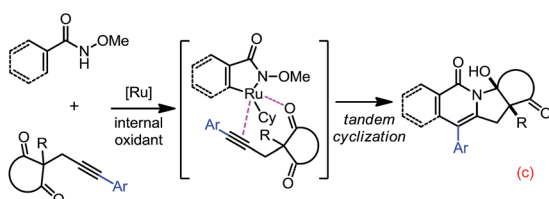
‡ Authors contributed equally to this work.



Fagnou; Miura; Rovis; Li; Ackermann: Standardized methods

Park: Reverse regioselectivity via tether-mediated intramolecular cyclization^{3e}

This work: Reverse regioselectivity with intermolecular weak coordination



Scheme 1 Previous and present approaches.

the ketone functionality would initially form an intermolecular chelation with the five-membered ruthenacycle of benzamide and subsequently undergo insertion with the alkyne (Scheme 1c). We commenced our study with the reaction of benzamide **1a** and 1,3-diketone **2a** by employing $[(\text{RuCl}_2\{p\text{-cymene}\})_2]$ (10 mol%) and NaOAc (2 equiv.) in MeOH (0.2 M) at 80 °C for 24 hours. To our delight, the desired tetracyclic product (\pm)-**3a** was obtained *via* isoquinolone formation with reverse regioselectivity followed by the cascade cyclization of a neutral NH group with the ketone in a 75% yield (Table 1, entry 1). The structure of **3a** was fully characterized using NMR spectroscopy, IR, and HRMS. Single-crystal X-ray analysis of compound **3a** also unambiguously established its indolizidine structure (Fig. 1).¹² Many biologically active natural products such as solanidine, septicine and rosettacin contain the core indolizidine structural motif (Fig. 2).¹³

When the reaction was performed at room temperature using the 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 and CsOAc gave moderate yields when compared to NaOAc. However, the use of $\text{Cu}(\text{OAc})_2$ and AgOAc as additives resulted in a decreased catalytic efficiency (Table 1, entries 3–6). Among all of the solvents tested, the protic solvents (^tBuOH and ⁱPrOH) provided **3a** in moderate to good yields and the polar solvents (DMF and 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 a 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, $[\text{RhCp}^*\text{Cl}_2]_2$ was evaluated, and it afforded **3a** in a 31% yield (Table 1, entry 15).

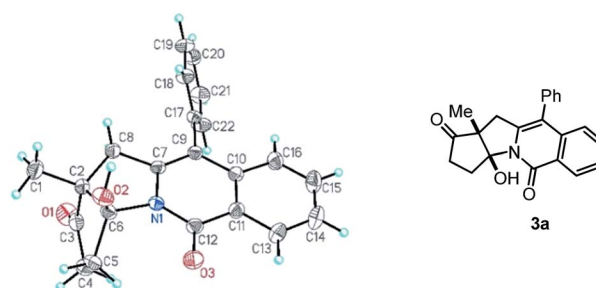
With the optimal reaction conditions in hand, the cascade cyclization scope of various 2-acetylenic ketones **2** were

Table 1 Optimization of reaction conditions^{a,b}

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

^a Reactions were carried out with **1a** (0.6 mmol), **2a** (0.4 mmol), and an additive (0.8 mmol) in 0.2 M solvent. ^b Yields determined using ¹H NMR analysis with an internal standard 1,1,2,2-tetrachloroethane.

investigated with *N*-methoxy benzamide **1a**. As shown in Table 2, electron-rich aryl groups 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 and CN groups failed to give the products. Different substituents such as ethyl and benzyl groups at the C2 position of cyclopentadienone 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 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 the case of *ortho*-substituted aryl groups on the acetylenic 1,3-diketones, an inseparable mixture of atropdiastereomers **3o**

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

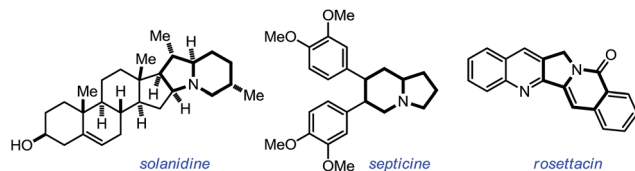
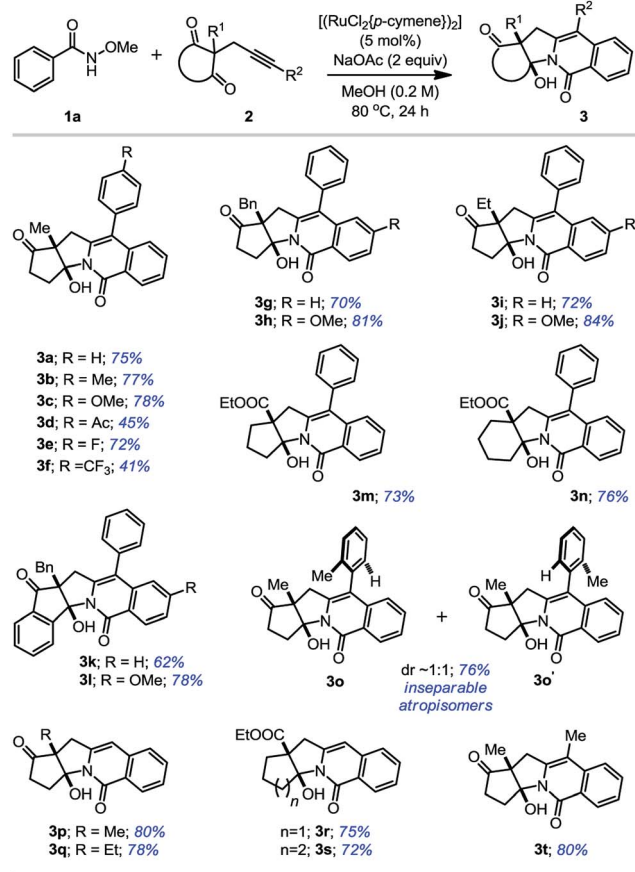


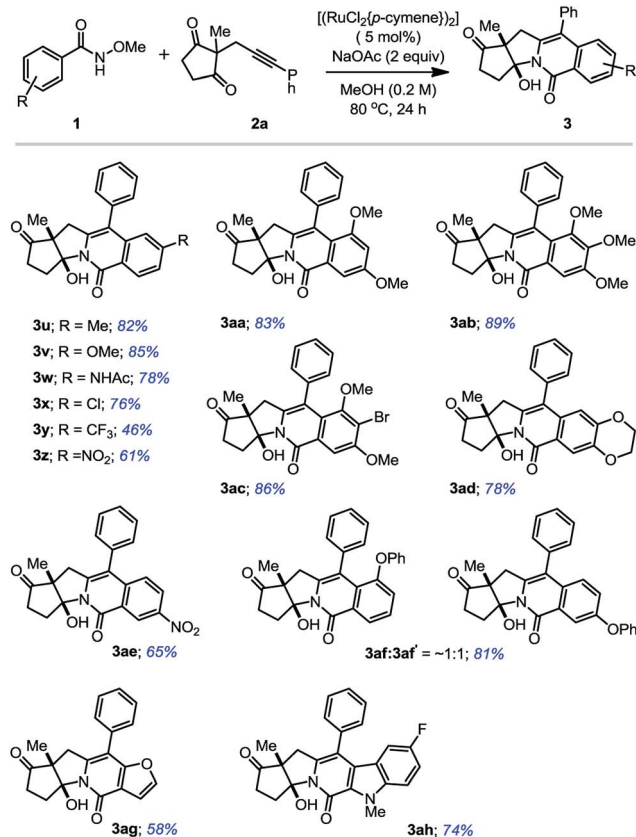
Fig. 2 Representative natural products bearing an indolizidine core.

Table 2 Substrate scope for ketones^{a,b}

^a Reaction conditions: **1a** (0.6 mmol), **2** (0.4 mmol), [(RuCl₂(*p*-cymene))₂] (5 mol%), and NaOAc (0.8 mmol) in MeOH (2 mL) at 80 °C for 24 h. ^b Yields of products isolated after column chromatography.

and **3o'** (dr ~ 1 : 1) were obtained in a 76% yield. This cascade cyclization is not limited to aryl substituted alkynes, substrates containing a terminal alkyne as well as alkyl substituted alkynes 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 an

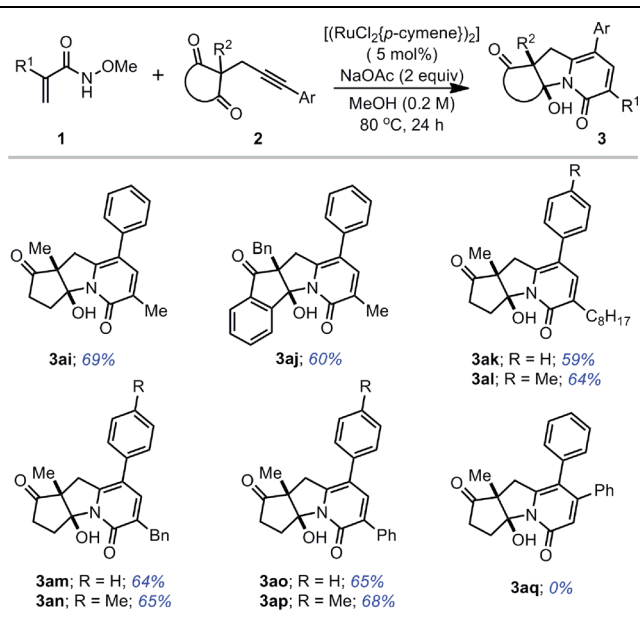
Table 3 Substrate scope for benzamides^{a,b}

^a Reaction conditions: **1** (0.6 mmol), **2a** (0.4 mmol), [(RuCl₂(*p*-cymene))₂] (5 mol%), and NaOAc (0.8 mmol) in MeOH (2 mL). ^b Yields of products isolated after column chromatography.

annulation reaction with considerably higher yields than electron-deficient benzamides. In the 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 an 81% yield with almost 1 : 1 regioselectivity probably due to the planar 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 the annulation reaction is in full agreement with previous reports by Ackermann.¹⁴ In addition, the extension of this cascade reaction to heteroaromatic carboxamides, such as furan and indole gave isoquinolone derivatives **3ag** (58%) and **3ah** (74%), respectively, with the expected regioselectivity (Table 3).

Enticed by these results, we examined the reactivity of different acrylamides in the annulation/cascade reaction (Table 4).¹⁵ Alkyl substitutions, such as with methyl, octyl and benzyl groups, on the acrylamide at the 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 the



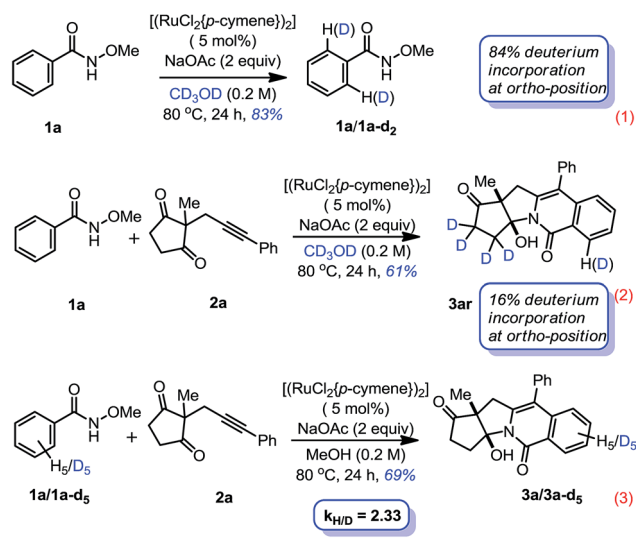
Table 4 Substrate scope for acrylamides^{a,b}

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

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

Disappointingly, phenyl substituted acrylamide at the 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** using

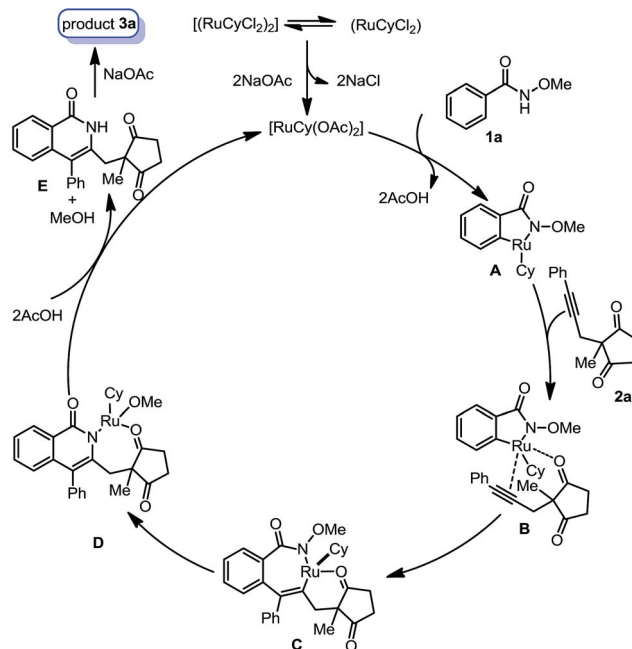


Scheme 2 Deuteriation experiments.

standard conditions, which furnished **1a/1a-d₂** 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 the *ortho*-position and almost complete deuteration on the cyclopentanone ring due to the enolization of both ketones in **2a** in the presence of NaOAc. In addition, a kinetic isotope effect (KIE) of $k_{\text{H}}/k_{\text{D}} = 2.33$ was observed using a 1 : 1 ratio of **1a/1a-d₅** 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}

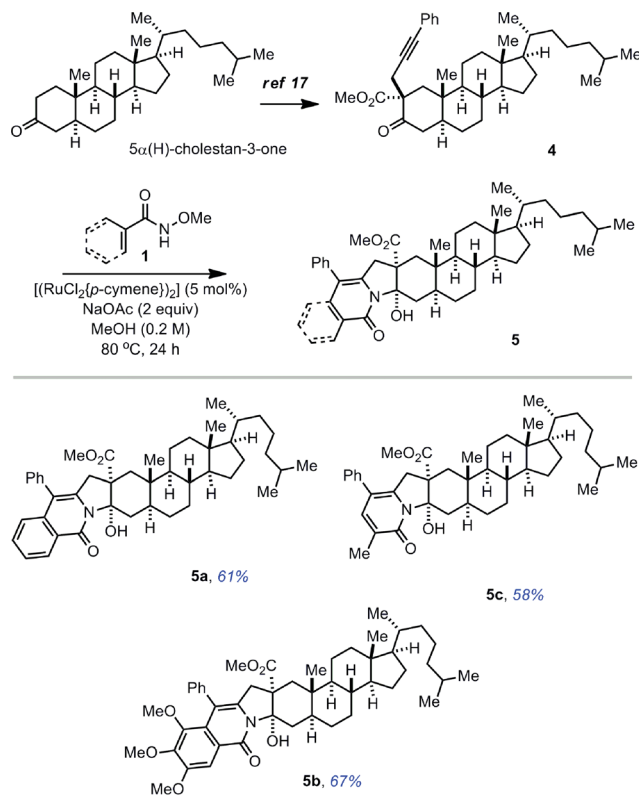
A plausible mechanism is proposed, based on the above experimental outcome, in Scheme 3. The ruthenium-catalyzed oxidative annulation starts from C–H bond activation to afford a five-membered ruthenacycle **A** with the simultaneous loss of acetic acid. The formation of intermediate **A** is the turnover-limiting 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 affords tetracyclic intermediate **C**. It is believed that the chelation of the carbonyl group with ruthenacycle **A** is responsible for the reverse regioselectivity.^{3a,16} The following intramolecular oxidative C–N bond formation provides intermediate **D**, which is readily protonated by acetic acid to furnish isoquinolone intermediate **E** and regenerates the active $[\text{RuCy}(\text{OAc})_2]$ catalyst.⁴ Finally, the intramolecular cyclization of **E** under basic conditions allows the formation of tandem product **3a**.

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 the procedure from the literature in 3 steps,¹⁷



Scheme 3 Plausible mechanism for the cascade arylation cyclization reaction.





Scheme 4 Synthetic utility^{a,b}. ^aReaction conditions: **1** (0.6 mmol), **4** (0.4 mmol), [(RuCl₂(*p*-cymene))₂] (5 mol%), and NaOAc (0.8 mmol) in MeOH (2 mL); ^byields of products isolated after column chromatography.

which was further subjected to the annulation reaction with **1a**, **1b** and **1i** under standard reaction conditions to afford the desired polycyclic products **5a**, **5b** and **5c**, respectively, in 58–67% yields.

Conclusions

In summary, we have 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 the alkyne insertion was induced by the 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 an 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 a broad range of substrate scope. The regioselective tandem process would give access to complex heterocyclic structural motifs, which have several synthetic and pharmaceutical applications.

Experimental

General procedure

A screw-cap vial equipped with a stirrer bar was charged with *N*-methoxybenzamide/*N*-methoxy acrylamide **1** (0.6 mmol, 1.5 equiv.), 2-acetylenic ketone **2** (0.4 mmol), [RuCl₂(*p*-cymene)]₂ (18.4 mg, 0.03 mmol, 5.0 mol%), NaOAc (98.4 mg, 1.2 mmol, 2 equiv.) and dry MeOH (2 mL) under nitrogen atmosphere. The reaction mixture was stirred at 80 °C for 24 h. Afterwards, it was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue was purified using flash column chromatography on silica gel (20 to 30% EtOAc in hexane) to give the desired product **3**.

Acknowledgements

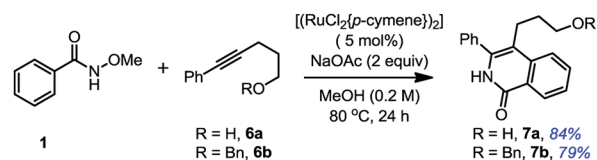
The Department of Science and Technology (DST), New Delhi, India, is acknowledged for the award of a Start-up Research Grant (young scientists) to RC. SK, NG, and RC thank the Council of Scientific and Industrial Research (CSIR), New Delhi, and KKG thanks DST, New Delhi, for a research fellowship. The authors thank Dr S. Chandrasekhar for valuable discussions and Dr Kiran Singarapu for 2D NMR analysis.

Notes and references

- Recent reviews on transition metal-catalyzed C–H bond functionalizations, see: (a) S. Tani, T. N. Uehara, J. Yamaguchi and K. Itami, *Chem. Sci.*, 2014, **5**, 123; (b) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem., Int. Ed.*, 2014, **53**, 74; *Angew. Chem.*, 2014, **126**, 76; (c) L. Ackermann, *J. Org. Chem.*, 2014, **79**, 8948; (d) X.-S. Zhang, K. Chen and Z.-J. Shi, *Chem. Sci.*, 2014, **5**, 2146; (e) J. Wencel-Delord and F. Glorius, *Nat. Chem.*, 2013, **5**, 369; (f) G. Rouquet and N. Chatani, *Angew. Chem., Int. Ed.*, 2013, **52**, 11726; *Angew. Chem.*, 2013, **125**, 11942; (g) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788; (h) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885; (i) D. J. Schipper and K. Fagnou, *Chem. Mater.*, 2011, **23**, 1594; (j) T. Satoh and M. Miura, *Chem.–Eur. J.*, 2010, **16**, 11212; (k) O. Daugulis, *Top. Curr. Chem.*, 2010, **292**, 57; (l) L. Ackermann, R. Vicente and A. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792; *Angew. Chem.*, 2009, **121**, 9976; (m) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (n) R. G. Bergman, *Nature*, 2007, **446**, 391.
- (a) P. Giri and G. S. Kumar, *Mini-Rev. Med. Chem.*, 2010, **10**, 568; (b) K. Bhadra and G. S. Kumar, *Mini-Rev. Med. Chem.*, 2010, **10**, 1235; (c) A. Capasso, S. Piacente, N. De Tommasi, L. Rastrelli and C. Pizza, *Curr. Med. Chem.*, 2006, **13**, 807; (d) K. W. Bentley, *Nat. Prod. Rep.*, 2006, **23**, 444; (e) K. W. Bentley, *Nat. Prod. Rep.*, 2005, **22**, 249; (f) V. A. Glushkov and Y. V. Shklyaev, *Chem. Heterocycl. Compd.*, 2001, 723; (g) T. Nagatsu, *Neurosci. Res.*, 1997, **29**, 99.
- For Rh-catalyzed isoquinolone syntheses see: (a) N. Guimond, C. Gouliaras and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 6908; (b) T. K. Hyster and T. Rovis, *J. Am.*



- Chem. Soc.*, 2010, **132**, 10565; (c) S. Mochida, N. Umeda, K. Hirano, T. Satoh and M. Miura, *Chem. Lett.*, 2010, **39**, 744; (d) N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2011, **133**, 6449; (e) X. Xu, Y. Liu and C.-M. Park, *Angew. Chem., Int. Ed.*, 2012, **51**, 9372; (f) H. Wang, C. Grohmann, C. Nimphius and F. Glorius, *J. Am. Chem. Soc.*, 2012, **134**, 19592; (g) J. R. Huckins, E. A. Bercot, O. R. Thiel, T.-L. Hwang and M. M. Bio, *J. Am. Chem. Soc.*, 2013, **135**, 14492; (h) D.-G. Yu, F. de Azambuja and F. Glorius, *Angew. Chem., Int. Ed.*, 2014, **53**, 2754.
- 4 For Ru-catalyzed isoquinolone syntheses, see: (a) L. Ackermann, A. V. Lygin and N. Hofmann, *Angew. Chem., Int. Ed.*, 2011, **50**, 6379; (b) B. Li, H. Feng, S. Xu and B. Wang, *Chem.-Eur. J.*, 2011, **17**, 12573; (c) L. Ackermann and S. Fenner, *Org. Lett.*, 2011, **13**, 6548; (d) J. Ghesquire, N. Gauthie, J. D. Winter, P. Gerbaux, C. Moucheron, E. Defrancq and A. K.-D. Mesmaeker, *Chem.-Eur. J.*, 2012, **18**, 355; (e) B. Li, H. Feng, N. Wang, J. Ma, H. Song, S. Xu and B. Wang, *Chem.-Eur. J.*, 2012, **18**, 12873; (f) M. Deponti, S. I. Kozhushkov, D. S. Yufit and L. Ackermann, *Org. Biomol. Chem.*, 2013, **11**, 142; (g) C. Kornhaa, C. Kuper and L. Ackermann, *Adv. Synth. Catal.*, 2014, **356**, 1619.
- 5 For Ni- & Pd-catalyzed isoquinolone syntheses, see: (a) B. Ye and N. Cramer, *Angew. Chem., Int. Ed.*, 2014, **53**, 7896; (b) H. Zhong, D. Yang, S. Wang and J. Huang, *Chem. Commun.*, 2012, **48**, 3236; (c) Y. Kajita, S. Matsubara and T. Kurahashi, *J. Am. Chem. Soc.*, 2008, **130**, 6058; (d) H. Shiota, Y. Ano, Y. Aihara, Y. Fukumoto and N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 14952; (e) T. Miura, M. Yamauchi and M. Murakami, *Org. Lett.*, 2008, **10**, 3085.
- 6 D.-G. Yu, F. de Azambuja, T. Gensch, C. G. Daniliuc and F. Glorius, *Angew. Chem., Int. Ed.*, 2014, **53**, 9650.
- 7 S. Manna and A. P. Antonchick, *Angew. Chem., Int. Ed.*, 2014, **53**, 7324.
- 8 For recent C-H bond functionalizations of *N*-(pivaloyloxy) benzamides, see: (a) S. Wu, R. Zeng, C. Fu, Y. Yu, X. Zhang and S. Ma, *Chem. Sci.*, 2015, **6**, 2275; (b) J. R. Huckins, E. A. Bercot, O. R. Thiel, T.-L. Hwang and M. M. Bio, *J. Am. Chem. Soc.*, 2013, **135**, 14492; (c) B. Ye and N. Cramer, *Science*, 2012, **338**, 504; (d) T. K. Hyster, L. Knörr, T. R. Ward and T. Rovis, *Science*, 2012, **338**, 500; (e) H. Wang and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 7318.
- 9 For recent C-H bond functionalizations of *N*-(methoxy) benzamides, see: (a) J. Shi, J. Zhou, Y. Yan, J. Jia, X. Liu, H. Song, H. E. Xu and W. Yi, *Chem. Commun.*, 2015, **51**, 668; (b) J.-Q. Wu, Z.-P. Qiu, S.-S. Zhang, J.-G. Liu, Y.-X. Lao, L.-Q. Gu, Z.-S. Huang, J. Li and H. Wang, *Chem. Commun.*, 2015, **51**, 77; (c) B. Ye, P. A. Donets and N. Cramer, *Angew. Chem., Int. Ed.*, 2014, **53**, 507; (d) S. Pimparkar and M. Jeganmohan, *Chem. Commun.*, 2014, **50**, 12116; (e) G. Liu, Y. Shen, Z. Zhou and X. Lu, *Angew. Chem., Int. Ed.*, 2013, **52**, 6033; (f) Z. Shi, C. Grohmann and F. Glorius, *Angew. Chem., Int. Ed.*, 2013, **52**, 5393; (g) B. Ye and N. Cramer, *J. Am. Chem. Soc.*, 2013, **135**, 636; (h) J. Karthikeyan, R. Haridharan and C.-H. Cheng, *Angew. Chem., Int. Ed.*, 2012, **51**, 12343; (i) R. Zeng, C. Fu and S. Ma, *J. Am. Chem. Soc.*, 2012, **134**, 9597; (j) S. Rakshit, C. Grohmann, T. Besset and F. Glorius, *J. Am. Chem. Soc.*, 2011, **133**, 2350.
- 10 (a) Y. Fukui, P. Liu, Q. Liu, Z.-T. He, N.-Y. Wu, P. Tian and G.-Q. Lin, *J. Am. Chem. Soc.*, 2014, **136**, 15607; (b) G. Song, D. Chen, C.-L. Pan, R. H. Crabtree and X. Li, *J. Org. Chem.*, 2010, **75**, 7487.
- 11 (a) S. Kallepu, K. K. Gollapelli, J. B. Nanubolu and R. Chegondi, *Chem. Commun.*, 2015, **51**, 16840; (b) A. S. Murthy, S. Donikela, C. S. Reddy and R. Chegondi, *J. Org. Chem.*, 2015, **80**, 5566.
- 12 CCDC - 1449113 (compound **3a**) contains the supplementary crystallographic data for this paper.†
- 13 For selected reviews, see: (a) J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 139; (b) W. Du, *Tetrahedron*, 2003, **59**, 8649; (c) Z. G. Li, Z. Jin and R. Q. Huang, *Synthesis*, 2001, 2365; (d) E. Höhne, K. Schreiber, H. Ripperger and H.-H. Worch, *Tetrahedron*, 1966, **22**, 673.
- 14 (a) L. Ackermann, *Chem. Rev.*, 2011, **111**, 1315; (b) L. Ackermann, A. V. Lygin and N. Hofmann, *Angew. Chem., Int. Ed.*, 2011, **50**, 6379 and also see ref. 4.
- 15 For 2-pyridone syntheses with alkynes see: (a) L. Ackermann, A. V. Lygin and N. Hofmann, *Org. Lett.*, 2011, **13**, 3278; (b) T. K. Hyster and T. Rovis, *Chem. Sci.*, 2011, **2**, 1606; (c) Y. Su, M. Zhao, K. Han, G. Song and X. Li, *Org. Lett.*, 2010, **12**, 5462.
- 16 Protected and free alcohols containing alkynes afforded corresponding 3-phenylsubstituted isoquinolones with opposite regioselectivity.



- 17 S. Zhu, Q. Zhang, K. Chen and H. Jiang, *Angew. Chem., Int. Ed.*, 2015, **54**, 9414.

