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Rhodium(III)-Catalyzed Intramolecular Annulation through C-H Activation: Concise Synthesis of Rosettacin and Oxypalmatime†

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A flexible and efficient rhodium(III)-catalyzed intramolecular annulation of bearing alkyne-tethered benzamides for the synthesis of indolizinones and quinolizinones is reported. This reaction shows a broad substrate scope and excellent functional-group tolerance, including different kinds of heterocyclic substrates, such as furan, thiophene, pyrrole, benzofuran, benzothiophene, indole and isonicotinamide substrates. This method also provides a practical and efficient approach for the synthesis of rosettacin and oxypalmatime.

The indolizinone and quinolizinone frameworks form the core of lots of nature products with pharmacological relevance, such as rosettacin,[1] oxypalmatime,[1a,2] camptothecin[1a,3] and norketoyobyrine[1a,4] (Figure 1). Although several methods for synthesizing these scaffolds have been reported, most of them need harsh conditions or many steps.[1-4] Thus developing easy synthetic approaches still has significant value.

In recent years, transition-metal catalyzed C-H bond activation and functionalization plays an important role in synthetic organic chemistry.[5] One of the challenges is the control of position selectivity. When a weakly coordinating directing group is used for medicinally important heterocyclic substrates, the heteroatoms can strongly coordinate with the transition-metal catalyst, leading to either poisoning of the catalyst or undesired selectivity.[6] Therefore, new methods should be explored to overcome these problems.

During the last decade, rhodium(III)-catalyzed C-H activation has received great attention because of its high efficiency, selectivity and functional-group tolerance.[7] Many reports show that rhodium(III)-catalyzed C-H activation is a powerful strategy to achieve intermolecular annulation of alkynes with aryl or

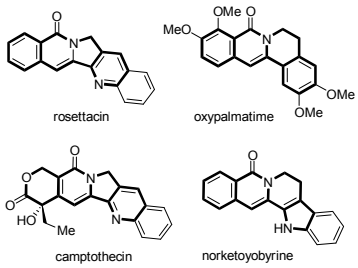

Figure 1 Representative examples of natural products with indolizinone or quinolizinone scaffold.

alkenyl amides with different directing groups (Scheme 1a and 1b). However, most of the intermolecular annulations result in the formation of a single ring and few cascade reactions to build multiple ring are reported.[8] When unsymmetrical alkynes are utilized, the regioselectivity depends on the difference between both substituents on the alkynes, often leading to poor regioselectivity.[7c,7d] Obviously, intramolecular annulation of alkynes with aryl or alkenyl amides can overcome these limitations and can also allow the construction of multiple rings existing in more complex scaffolds (Scheme 1c and 1d).[9] Considering the advantages, we designed an intramolecular annulation of alkyne-tethered benzamides, providing a flexible synthesis of indolizinone and quinolizinone scaffolds (Scheme 1). Herein we report the construction of indolizinone and quinolizinone scaffolds based on a rhodium(III)-catalyzed intramolecular annulation. The generality of this approach is demonstrated by accomplishing the synthesis of diverse heterocyclic products including rosettacin and oxypalmatime.

We selected *N*-alkynylbenzamide **1a** as our model substrate. As revealed by the results in Table 1, $[RhCp^*Cl_2]_2$ could easily perform the construction of indolizinone **2a**. We found that treatment of **1a** with $[RhCp^*Cl_2]_2$ (5 mol%) and $Cu(OAc)_2$ (2 equiv.) in *t*-AmOH at 110 °C gave **2a** in 98% yield in 12 h (Table 1, entry 1). Screening of various solvents, such as 1,4-dioxane, DMF and toluene, assured that *t*-AmOH was the most efficient

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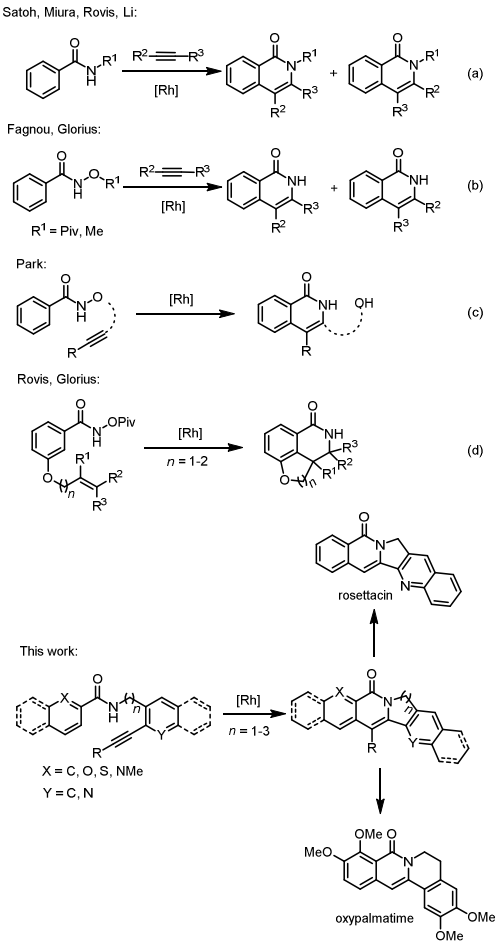
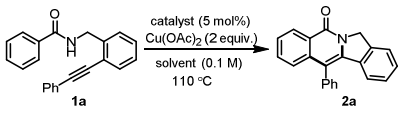


Scheme 1 Towards the synthesis of rosettacin and oxypalmatime.

one (Table 1, entries 2-4). We also evaluated the performance of other metals, confirming $[RhCp^*Cl_2]_2$ as the best choice. $Pd(OAc)_2$ and $Ni(OAc)_2{\cdot}4H_2O$ did not work, while with [Ru(*p*-cymene)$Cl_2]_2$ 83% yield was obtained (Table 1, entries 5-7). Further investigation showed that a lower temperature was deleterious for the reaction, leading to a very poor conversion (Table 1, entry 8). We also tested $[RhCp^*Cl_2]_2$ in combination with CsOAc, resulting in an acceleration of the reaction, yielding **2a** in 99% yield in 8 h when 50 mol% CsOAc was added (Table 1, entry 9).

With the optimized reaction conditions in hand, we next examined various substrates to evaluate the scope of the protocol. The annulation reactions proceeded smoothly to afford indolizinones and quinolizinones in good to excellent yields (Table 2). Substrates with electron-donating or electron-withdrawing groups at the *para* position of the aryl moiety of benzamide performed well under the reaction conditions (**2b-2e**). The *meta*-methyl benzamide was totally selective to give the corresponding indolizinone **2f** in good yield. We also tested the reactions with substrates containing a methyl or fluoro group in the *ortho* position of the benzamide. Both gave the corresponding products **2g** and **2h** in excellent yields. Naphthylbenzamide was an

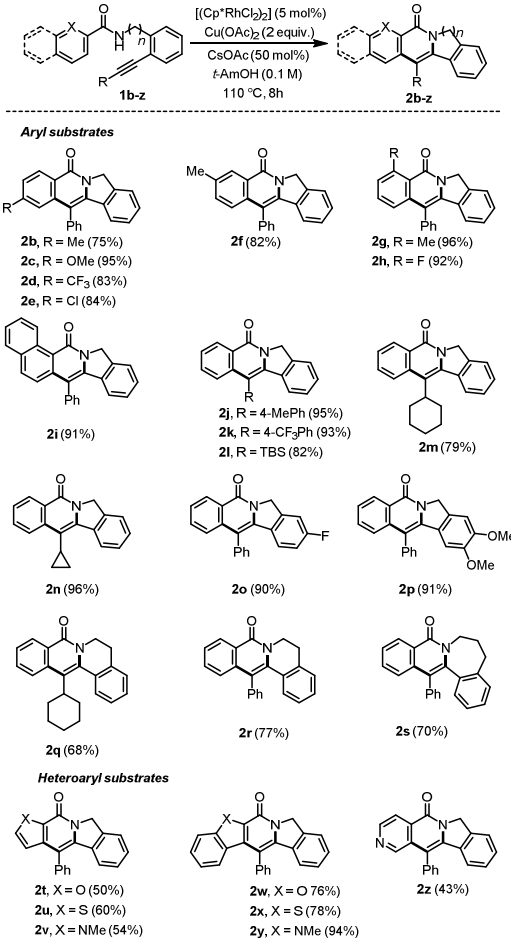
Table 1 Optimization of the reaction conditions.[a]



Entry	Solvent	Catalyst	*t* (h)	Yield (%)[b]
1	*t*-AmOH	$[RhCp^*Cl_2]_2$	12	98
2	1,4-Dioxane	$[RhCp^*Cl_2]_2$	12	87
3	DMF	$[RhCp^*Cl_2]_2$	12	<5
4	Toluene	$[RhCp^*Cl_2]_2$	12	<5
5	*t*-AmOH	$Pd(OAc)_2$	12	0
6	*t*-AmOH	[Ru(*p*-cymene)$Cl_2]_2$	12	83
7	*t*-AmOH	$Ni(OAc)_2{\cdot}4H_2O$	12	0
8[c]	*t*-AmOH	$[RhCp^*Cl_2]_2$	12	<5
9[d]	***t*-AmOH**	**$[RhCp^*Cl_2]_2$**	**8**	**99(93)[e]**

[a] Condition: **1a** (0.3 mmol), catalyst (0.015 mmol), $Cu(OAc)_2$ (0.6 mmol), solvent (3.0 mL). [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. [c] 90 °C. [d] CsOAc (50 mol%) were added. [e] Isolated yield. *t*-AmOH = *tert*-Amyl alcohol. Cp* = pentamethylcyclopentadienyl. *p*-cymene = 4-isopropyltoluene.

Table 2 Scope for aryl and heteroaryl substrates.[a,b]



[a] Condition: **1** (0.3 mmol), $[RhCp^*Cl_2]_2$ (0.015 mmol), $Cu(OAc)_2$ (0.6 mmol), *t*-AmOH (3.0 mL), CsOAc (0.15 mmol). [b] Isolated yield.

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acceptable substrate, leading to the cycloadduct **2i** in excellent yield. The annulation reaction also tolerated electron-donating and electron-withdrawing groups in the phenyl substituent of the alkyne like methyl and trifluoromethyl groups (**2j** and **2k**). When we replaced the aryl groups of the alkyne by a cyclohexyl, cyclopropyl or a *tert*-butyldimethylsiyl (TBS) group, the reaction smoothly proceeded to give the cycloadducts **2m**, **2n** and **2l**. Finally we tested substrates containing electron-donating or electron-withdrawing groups in the phenyl substituent of the benzylamine. Both gave the corresponding products **2o** and **2p** in excellent yields.

Interestingly, we found that the cycloaddition worked with substrates bearing a longer carbon chain between the benzamide and the alkyne, leading to interesting products containing either a six- (**2q-2r**) or seven-membered ring (**2s**) in good yields. Considering that heterocycles are widely present in many drug candidates,[6] we extended the cycloaddition to heteroaryl carboxamides, such as furan, thiophene, pyrrole, benzofuran, benzothiophene and indole. They all smoothly afforded the corresponding cycloadducts in moderate to excellent yields (**2t-2y**). Even an isonicotinamide substrate delivered the cycloadduct in moderate yield (**2z**).

To further demonstrate the synthetic utility, we used this intramolecular annulation as a key ring-forming step for the concise synthesis of rosettacin (**5a**) and oxypalmatime (**5b**) (Scheme 2). Cycloadduct **4a** could be obtained from benzamide **3a** using the optimized conditions in 71% yield. Removal of the TBS-group afforded rosettacin (**5a**) in good overall yield. To our surprise, oxypalmatime (**5b**) could be directly obtained in 66% yield from benzamide **3b** in one step employing the standard condition.

Based on the above results, we proposed a possible mechanism (Scheme 3).[9,10] First, an irreversible C-H bond cleavage occurs to afford a five-membered rhodacycle intermediate **A** with simultaneous loss of acetic acid. Next, coordination of the alkyne furnishes intermediate **B**, which undergoes insertion into the Rh-C bond to produce seven-membered rhodacycle **C**. Subsequent reductive elimination gives the desired product, followed by reoxidation of Rh(I) by $Cu(OAc)_2$ to regenerate the catalyst.

In summary, we have developed an efficient rhodium(III)-catalyzed intramolecular annulation of benzamides bearing *N*-tethered alkynes for the synthesis of indolizinones and quinolizinones. This reaction features a broad substrate scope and excellent functional-group tolerance, including annulation of different heterocyclic substrates, such as furan, thiophene, pyrrole, benzofuran, benzothiophene, indole and isonicotinamide substrates. This method also provides a reliable and highly efficient approach for the synthesis of rosettacin and oxypalmatime.

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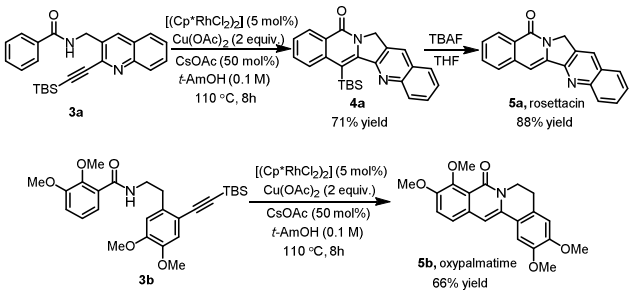
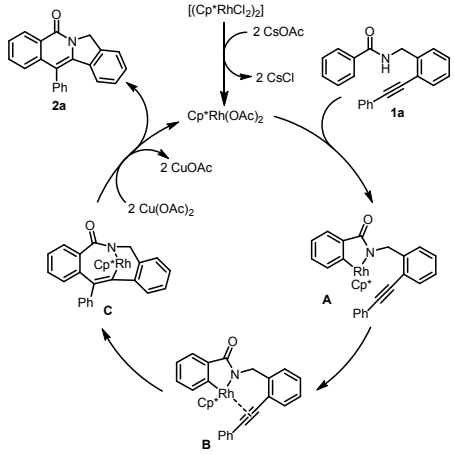


Scheme 2 Synthesis of rosettacin (**5a**) and oxypalmatime (**5b**).



Scheme 3 Plausible mechanism.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 For representative rosettacin syntheses, see: (*a*) K. Li, J. Ou and S. Gao, *Angew. Chem. Int. Ed.,* 2016, **55**, 14778-14783; (*b*) K. Cheng, N. J. Rahier, B. M. Eisenhauer, R. Gao, S. J. Thomas and S. M. Hecht, *J. Am. Chem. Soc.,* 2005, **127**, 838-839; (*c*) L. El Blidi, A. Namoune, A. Bridoux, V. D. Nimbarte, A. M. Lawson, S. Comesse and A. Daïch, *Synthesis,* 2015, **47**, 3583-3592; (*d*) J. C. Godfrey, *J. Org. Chem.,* 1959, **24**, 581; (*e*) W.-K. Luo, X. Shi, W. Zhou and L. Yang, *Org. Lett.,* 2016, **18**, 2036-2039; (*f*) H. T. M. Van and W.-J. Cho, *Bioorg. Med. Chem. Lett.,* 2009, **19**, 2551-2554.

2 For representative oxypalmatime syntheses, see: (*a*) S.-Q. Zhou and R.-B. Tong, *Chem. Eur. J.* , 2016, **22**, 7084-7089; (*b*) S. Gadhiya, S. Ponnala and W. W. Harding, *Tetrahedron,* 2015, **71**, 1227-1231.

3 For representative camptothecin syntheses, see: (*a*) S. Yu, Q. Q. Huang, Y. Luo and W. Lu, *J. Org. Chem.,* 2012, **77**, 713-717; (*b*) C.-Q. Wei, Z.-H. Jiang, S.-J. Tian and D.-Z. Zhang, *Tetrahedron Lett.,* 2013, **54**, 4515-4517; (*c*) P. Xu, D. S. Chen, J. Xi and Z. J. Yao, *Chem. Asian. J.,* 2015, **10**, 976-981; (*d*) Y.-H. Hsiang, R. Hertzberg, S. Hecht and L. F. Liu, *J. Bio. Chem.,* 1985, **260**, 14873-14878; (*e*) B. M. Fox, X.-S. Xiao, S. Antony, G. Kohlhagen, Y. Pommier, B. L. Staker, L. Stewart and M. Cushman, *J. Med. Chem.,* 2003 **46**, 3275-3282.

View Article Online
DOI: 10.1039/C7CC06860C

4 For representative norketoyobyrine syntheses, see: (*a*) X. Pan and T. D. Bannister, *Org. Lett.,* 2014, **16**, 6124-6127; (*b*) M. Yar, M. Arshad, M. N. Akhtar, S. A. Shahzad, I. U. Khan, Z. A. Khan, N. Ullah and I. Ninomiya, *Eur. J. Chem.,* 2012, **3**, 26-31.

5 For representative recent reviews on transition metal-catalyzed C–H bond functionalizations, see: (*a*) L. Ackermann, *J. Org. Chem.,* 2014, **79**, 8948-8954; (*b*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.,* 2007, **107**, 174-238; (*c*) R. G. Bergman, *Nature,* 2007, **446**, 391-393; (*d*) Z.-K. Chen, B.-J. Wang, J.-T. Zhang, W.-L. Yu, Z.-X. Liu and Y.-H. Zhang, *Org. Chem. Front.,* 2015, **2**, 1107-1295; (*e*) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev.,* 2016, **45**, 2900-2936; (*f*) S. A. Girard, T. Knauber and C.-J. Li, *Angew. Chem. Int. Ed.,* 2014, **53**, 74-100; (*g*) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.,* 2011, **40**, 1885-1898; (*h*) G. Rouquet and N. Chatani, *Angew. Chem. Int. Ed.,* 2013, **52**, 11726-11743; (*i*) T. Satoh and M. Miura, *Chem. Eur. J.,* 2010, **16**, 11212-11222; (*j*) D. J. Schipper and K. Fagnou, *Chem. Mater.,* 2011, **23**, 1594-1600; (*k*) S. Tani, T. N. Uehara, J. Yamaguchi and K. Itami, *Chem. Sci.,* 2014, **5**, 123-135; (*l*) X.-S. Zhang, K. Chen and Z.-J. Shi, *Chem. Sci.,* 2014, **5**, 2146-2159; (*m*) R.-Y. Zhu, M. E. Farmer, Y.-Q. Chen and J.-Q. Yu, *Angew. Chem. Int. Ed.,* 2016, **55**, 10578-10599.

6 (*a*) M. Shang, M.-M. Wang, T. G. Saint-Denis, M.-H. Li, H.-X. Dai and J.-Q. Yu, *Angew. Chem. Int. Ed.,* 2017, **56**, 5317-5321; (*b*) L. Ackermann and A. V. Lygin, *Org. Lett.,* 2011, **13**, 3332-3335; (*c*) Y. Fujiwara, J. A. Dixon, F. O'Hara, E. D. Funder, D. D. Dixon, R. A. Rodriguez, R. D. Baxter, B. Herle, N. Sach, M. R. Collins, Y. Ishihara and P. S. Baran, *Nature,* 2012, **492**, 95-99; (*d*) Y.-J. Liu, H. Xu, W.-J. Kong, M. Shang, H.-X. Dai and J.-Q. Yu, *Nature,* 2014, **515**, 389-393; (*e*) H. A. Malik, B. L. Taylor, J. R. Kerrigan, J. E. Grob, K. N. Houk, J. Du Bois, L. G. Hamann and A. W. Patterson, *Chem. Sci.,* 2014, **5**, 2352-2361; (*f*) H. Wang, M. M. Lorion and L. Ackermann, *Angew. Chem. Int. Ed.,* 2016, **55**, 10386-10390; (*g*) X.-C. Wang, Y. Hu, S. Bonacorsi, Y. Hong, R. Burrell and J.-Q. Yu, *J. Am. Chem. Soc.,* 2013, **135**, 10326-10329; (*h*) M. Wasa, B. T. Worrell and J.-Q. Yu, *Angew. Chem. Int. Ed. ,* 2010, **49**, 1275-1277; (*i*) Z. Zhang, K. Tanaka and J.-Q. Yu, *Nature,* 2017, **543**, 538-542.

7 For Rh-catalyzed annulations, see: (*a*) N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.,* 2011, **133**, 6449-6457; (*b*) N. Guimond, C. Gouliaras and K. Fagnou, *J. Am. Chem. Soc.,* 2010, **132**, 6908-6909; (*c*) J. R. Huckins, E. A. Bercot, O. R. Thiel, T. L. Hwang and M. M. Bio, *J. Am. Chem. Soc.,* 2013, **135**, 14492-14495; (*d*) T. K. Hyster and T. Rovis, *J. Am. Chem. Soc.,* 2010, **132**, 10565-10569; (*e*) S. Mochida, N. Umeda, K. Hirano, T. Satoh and M. Miura, *Chem. Lett.,* 2010, **39**, 744-746; (*f*) F. W. Patureau and F. Glorius, *Angew. Chem. Int. Ed.,* 2011, **50**, 1977-1979; (*g*) H.-G. Wang, C. Grohmann, C. Nimphius and F. Glorius, *J. Am. Chem. Soc.,* 2012, **134**, 19592-19595; (*h*) D.-G. Yu, F. de Azambuja and F. Glorius, *Angew. Chem. Int. Ed.,* 2014, **53**, 2754-2758.

8 (*a*) K. K. Gollapelli, S. Kallepu, N. Govindappa, J. B. Nanubolu and R. Chegondi, *Chem. Sci.,* 2016, **7**, 4748-4753; (*b*) Y. Fukui, P. Liu, Q. Liu, Z.-T. He, N.-Y. Wu, P. Tian and G.-Q. Lin, *J. Am. Chem. Soc.,* 2014, **136**, 15607-15614; (*c*) G. Song, D. Chen, C.-L. Pan, R. H. Crabtree and X.-W. Li, *J. Org. Chem.,* 2010, **75**, 7487-7490.

9 (*a*) N. Quiñones, A. Seoane, R. García-Fandiño, J. L. Mascareñas and M. Gulías, *Chem. Sci.,* 2013, **4**, 2874-2879; (*b*) X.-X. Xu, Y. Liu and C.-M. Park, *Angew. Chem. Int. Ed.,* 2012, **51**, 9372-9376; (*c*) T. A. Davis, T. K. Hyster and T. Rovis, *Angew. Chem. Int. Ed,* 2013, **52**, 14181-14185; (*d*) Z.-Z. Shi, M. Boultadakis-Arapinis, D. C. Koester and F. Glorius, *Chem. Commun.,* 2014, **50**, 2650-2652; (*e*) D. Y. Li, L. L. Jiang, S. Chen, Z. L. Huang, L. Dang, X. Y. Wu and P. N. Liu, *Org. Lett.,* 2016, **18**, 5134-5137; (*f*) P. Tao and Y. Jia, *Chem. Commun.,* 2014, **50**, 7367-7370; (*g*) B. Zhou, J. Du, Y. Yang and Y. Li, *Chem. Eur. J.,* 2014, **20**, 12768-12772; (*h*) B. Zhou, Y. Yang, H. Tang, J. Du, H. Feng and Y. Li, *Org. Lett.,* 2014, **16**, 3900-3903.

10 T. Swamy, B. Maheshwar Rao, J. S. Yadav, V. Ravinder, B. Sridhar and B. V. Subba Reddy, *RSC Adv.,* 2015, **5**, 68510-68514.