ChemComm

COMMUNICATION

Rh(III)-Catalyzed intramolecular redox-neutral cyclization of alkenes *via* C–H activation†

Cite this: DOI: 10.1039/c4cc00029c

Zhuangzhi Shi, Mélissa Boultadakis-Arapinis, Dennis C. Koester and Frank Glorius*

Received 2nd January 2014,
Accepted 14th January 2014

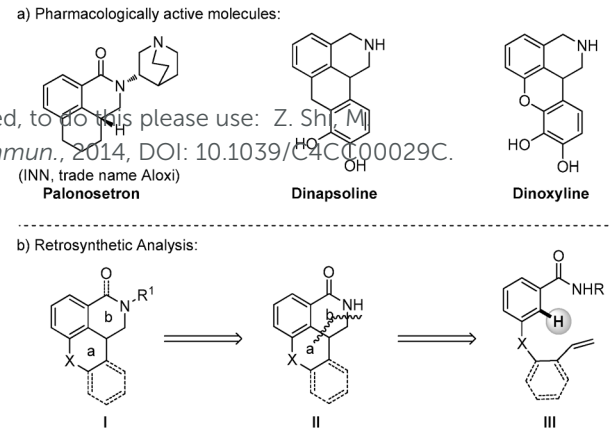
DOI: 10.1039/c4cc00029c

www.rsc.org/chemcomm

Biologically interesting fused oligocyclic lactams have been prepared *via* an intramolecular redox-neutral cyclization process. By the proper choice of the substrates with a wide variety of tethered olefins, the less favored C–H bond can be activated and functionalized. This C–H activation proceeds under mild conditions, obviates the need for external oxidants, and displays a broad scope with respect to the substituents.

Fused oligocyclic lactams and their reduced derivatives are widespread in drugs and natural products with pharmacological relevance.[1] Prominent examples are palonosetron, a 5-HT3 antagonist used in the prevention and treatment of chemotherapy-induced nausea and vomiting (CINV);[2a] dinapsoline, a drug for the treatment of Parkinson's disease;[2b] and dinoxyline, a potent agonist of all five dopamine receptor subtypes (Scheme 1a).[2c] Many traditional methods have been developed to synthesize these important structural motifs.[3] During the past decade, transition-metal-catalyzed C–H activation made a significant impact on how chemists make molecules.[4] The most vital advantage of C–H activations over traditional strategies is the obviation of prefunctionalization.[5] Scheme 1b illustrates the assembly of the simplified structure **I** from lactam **II**, which would emanate from the intramolecular cyclization of an appropriate benzamide with a tethered alkene **III** *via* C–H activation. Consequently, the development of C–H activation methods allowing the construction of such fused oligocyclic systems could be synthetically applicable.

Because of the diversity of C–H bonds with different reactivities in complex molecules, the intramolecular C–H activation and cyclization for accessing some unfavored C–H bonds *via* regioselective insertion is a particularly useful strategy.[6] In 2001, Bergman and Ellman *et al.* elegantly demonstrated Rh(I)-catalyzed intramolecular olefin hydroarylations utilizing an aldimine as a directing group (eqn (1), Scheme 2).[7] Moreover, they developed an enantioselective version



Scheme 1 Fused oligocyclic lactam skeleton of pharmacologically active molecules and its retrosynthetic analysis.

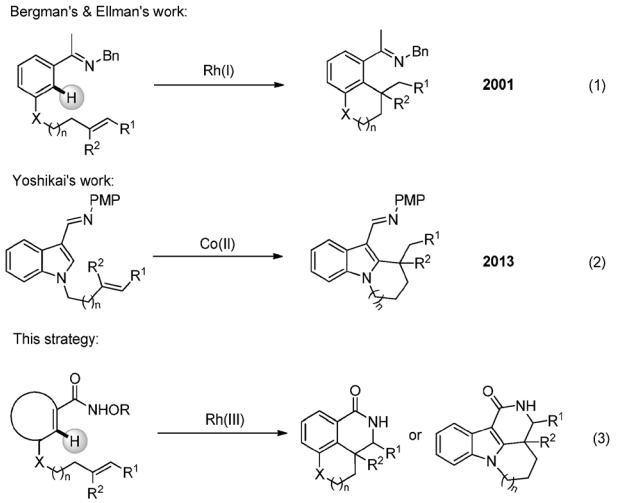
and applied it to rapidly synthesize indole alkaloids.[8] Very recently, Yoshikai *et al.* also uncovered a cobalt–NHC-catalyzed intramolecular cyclization on an indole platform to generate dihydropyrroloindole and tetrahydropyridoindole derivatives under mild conditions (eqn (2), Scheme 2).[9] Different from the above hydroarylation process, herein, we demonstrate the viability of the approach to construct fused oligocyclic lactams,[10] including indole derivatives, in one step (eqn (3), Scheme 2).

Rh(III)-catalyzed direct C–H activation has received significant interest in recent years because of its high efficiency, selectivity, and functional-group tolerance.[11] We[12] and others[13] have reported Rh(III)-catalyzed intermolecular cyclizations of alkenes using amides as the directing group and internal oxidants. We selected 3-(allyloxy)-*N*-(pivaloyloxy)-benzamide **1a** as starting material and subjected it to 2.5 mol% $[(Cp^*RhCl_2)_2]$ and 2.0 equiv. CsOPiv as an additive, at room temperature under an Ar atmosphere in CH_3CN. This set of conditions afforded the desired product **2a** in 72% yield after 12 hours (Table 1, entry 1). The diallyloxy-substituted benzamide **1b** bearing two equally reactive C–H bonds was converted to the desired product **2b** in good yield as expected (Table 1, entry 2). Interestingly, the 2,2-disubstituted alkene **1c** successfully underwent

Westfälische Wilhelms-Universität Münster, Organisch-Chemisches Institut, Corrensstrasse 40, 48149 Münster, Germany. E-mail: glorius@uni-muenster.de; Web: http://www.uni-muenster.de/Chemie.oc/glorius/index.html; Fax: +49 251-83-33202

† Electronic supplementary information (ESI) available: Detailed synthetic procedures and characterization of new compounds. See DOI: 10.1039/c4cc00029c

View Article Online
DOI: 10.1039/C4CC00029C
ChemComm



Scheme 2 The development of intramolecular cyclization of alkenes *via* C–H activation.

the cyclization affording product **2c** bearing an all-carbon quaternary stereocenter in 81% yield (Table 1, entry 3). Starting from an (*E*)-configured double bond the cinnamyl substrate **1d** gave product **2d** as a single isomer (Table 1, entry 4). The substrates **1e** and **1f** with a homoallyl group smoothly underwent six-membered ring formation to afford tri- and tetracyclic lactams **2e** and **2f** (Table 1, entries 5 and 6). To our delight, substrate **1g** in which the oxygen atom in the tether was replaced by a methylene unit smoothly yielded the corresponding lactam **2g**, albeit in moderate yield. This intermediate might be utilized to assemble the drug palonosetron in a very short route (Table 1, entry 7). Furthermore, a model substrate providing quick access to dinoxyline was prepared. Styrene derivative **1h** produced the desired tetracyclic lactam **2h** in a decent yield of 56% (Table 1, entry 8). We next explored the cyclization of indole substrates bearing substituted allyl tethers on an oxygen atom in the benzene ring or on the nitrogen atom of the pyrrole substructure, respectively. The substrates **1i** and **1j** can afford fused tetracyclic indoles in good yields (Table 1, entries 9 and 10) and **1k–1l** can generate dihydropyrroloindole and tetrahydropyridoindole core skeletons, which are present in numerous pharmaceuticals and biologically active compounds (Table 1, entries 11 and 12).

Inspired by previous work on Heck-type redox-neutral olefination, the intramolecular variant was also explored. When changing the directing group from *N*-OPiv to *N*-OMe on the amide, the substrate 3-(allyloxy)-*N*-methoxybenzamide **3a** selectively generated a 2,3-dihydrobenzofuran product **4a** in good yield with a minor benzofuran isomer **4a′** (eqn (4)). Notably, **3b** produced benzofuran product **4b** as the only detectable product in 62% yield (eqn (5)). Homoallyl substituted amide such as **3e** was converted to **4e** as the sole product in good yield (eqn (6)).

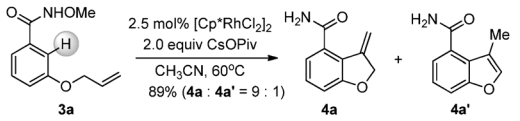
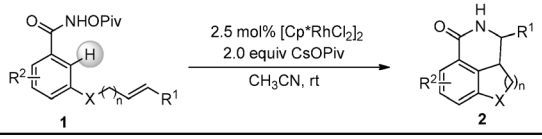
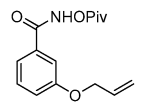
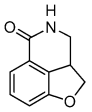
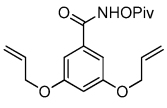
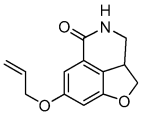
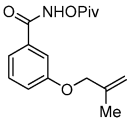
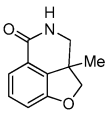
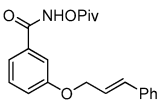
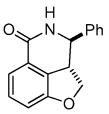
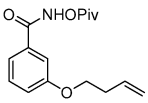
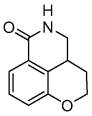
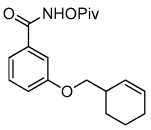
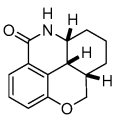
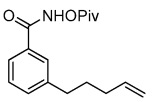
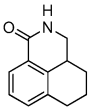
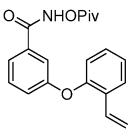
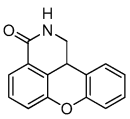
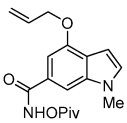
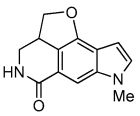
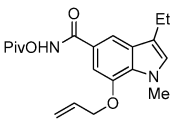
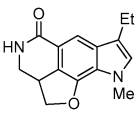
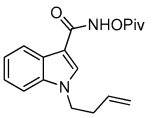
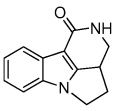
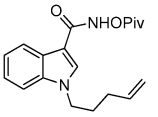
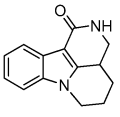
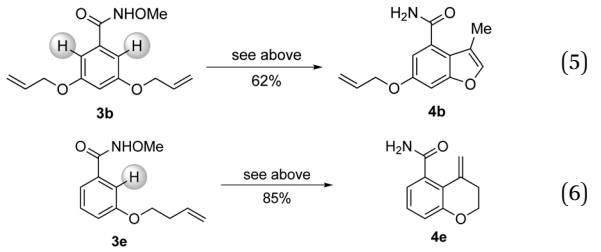


Table 1 Rh(III)-Catalyzed intramolecular cyclization to fused multicyclic lactams[a]



Entry	Substrates		Products		Yield[b] (%)
1		**1a**		**2a**	72
2		**1b**		**2b**	87
3		**1c**		**2c**	81[c]
4		**1d**		**2d**	88
5		**1e**		**2e**	77
6		**1f**		**2f**	50[c]
7		**1g**		**2g**	40
8		**1h**		**2h**	56
9		**1i**		**2i**	88
10		**1j**		**2j**	90
11		**1k**		**2k**	63
12		**1l**		**2l**	60

[a] Reaction conditions: **1** (0.2 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol%), CsOPiv (0.4 mmol), CH_3CN (4.0 mL), room temperature, 12 h, under Ar. [b] Yield of isolated products. [c] Using 5.0 mol% $[Cp^*RhCl_2]_2$.



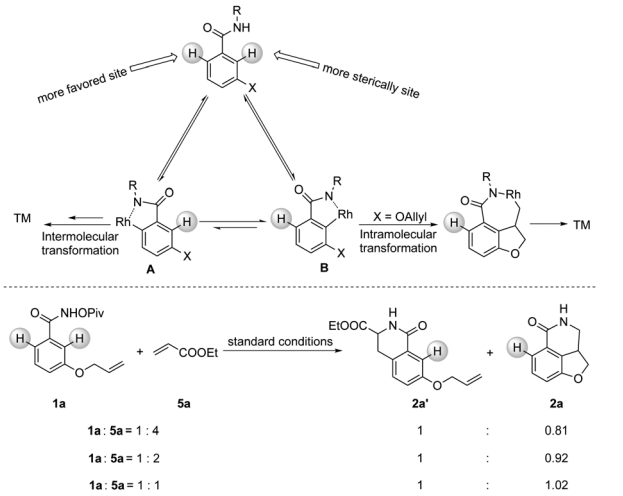


Fig. 1 Plausible mechanistic pathways.

In intermolecular Rh(III)-catalyzed C–H activations of benzamides bearing a *meta*-substituent, a regioselective *ortho*-rhodation was noted in favor of the less sterically hindered position to form intermediate **A** which reacts with external alkenes to give rise to the corresponding products (Fig. 1). In the intramolecular version, which we pursued in the present study, the alkenes were tethered at the *meta*-position leading to the activation of the more sterically hindered site to afford the desired products, presumably *via* intermediate **B.** To test the reactivities of these two C–H bonds in molecule **1a**, we selected ethyl acrylate (**5a**) as a coupling partner. Treatment of **1a** with 4 equiv. of ethyl acrylate (**5a**) applying standard conditions led to full conversion of **1a** and afforded the intermolecular and intramolecular cyclization products **2a′** and **2a** in a 55 : 45 ratio as determined by ^{1}H NMR. When the amount of ethyl acrylate (**5a**) was decreased, the amount of **2a** increased. However, employing an equimolar ratio of **1a** and **5a** under the same conditions resulted in a 49.5 : 50.5 mixture of **2a′** and **2a.**

In summary, we have developed a mild and efficient method for the synthesis of fused oligocyclic lactam skeletons *via* intramolecular C–H activation and cyclization utilizing the directing group as an internal oxidant.[10] This reaction generates oligocyclic systems with high selectivity, displays a broad scope with respect to the substituents and the lactam products and provides additional synthetic opportunities to convert the generated products into important natural products. Furthermore, dehydrogenative Heck-type products can also be generated under suitable reaction conditions.

This work was supported by the Alexander von Humboldt Foundation (Z. S.). Generous financial support from the European Research Council under the European Community's Seventh Framework Program (FP7 2007–2013)/ERC Grant agreement no 25936 is gratefully acknowledged.

Notes and references

1 For reviews, see: (*a*) J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 139; (*b*) J. P. Michael, *Nat. Prod. Rep.*, 2007, **24**, 191; (*c*) J. P. Michael, *Nat. Prod. Rep.*, 2005, **22**, 603.

2 (*a*) A. D. Leon, "*Palonosetron (Aloxi): a second-generation 5-HT(3) receptor antagonist for chemotherapy-induced nausea and vomiting*", Proceedings (Baylor University, Medical Center), 2006, 19, 413; (*b*) A. G. Gulwadi, C. D. Korpinen, R. B. Mailman, D. E. Nichols, S. Y. Sit and M. T. Taber, *J. Pharmacol. Exp. Ther.*, 2001, **296**, 338; (*c*) R. A. Grubbsa, M. M. Lewisb, C. Owens-Vancea, E. A. Gayb, A. K. Jassenb, R. B. Mailmanb and D. E. Nicholsa, *Bioorg. Med. Chem.*, 2002, **14**, 1403.

3 (*a*) D. Ghosh, S. E. Snyder, V. J. Watts, R. B. Mailman and D. E. Nichols, *J. Med. Chem.*, 1996, **39**, 549; (*b*) S.-Y. Sit, K. Xie, S. Jacutin-Porte, M. T. Taber, A. G. Gulwadi, C. D. Korpinen, K. D. Burris, T. F. Molski, E. Ryan, C. Xu, H. Wong, J. Zhu, S. Krishnananthan, Q. Gao, T. Verdoorn and G. Johnson, *J. Med. Chem.*, 2002, **45**, 3660.

4 For recent reviews on using a C–H bond strategy in natural product synthesis, see: (*a*) L. McMurray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev.*, 2011, **40**, 1885; (*b*) H. M. L. Davies, B. J. Du and J.-Q. Yu, *Chem. Soc. Rev.*, 2011, **40**, 1855; (*c*) J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem., Int. Ed.*, 2012, **51**, 8960.

5 For recent reviews on C–H activation, see: (*a*) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (*b*) M. C. White, *Science*, 2012, **335**, 807; (*c*) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, *Acc. Chem. Res.*, 2012, **45**, 788; (*d*) S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res.*, 2012, **45**, 936; (*e*) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 10236; (*f*) J. Wencel-Delord and F. Glorius, *Nat. Chem.*, 2013, **5**, 369; (*g*) L. Ackermann, *Acc. Chem. Res.*, 2013, DOI: 10.1021/ar3002798.

6 (*a*) P. S. Baran and E. J. Corey, *J. Am. Chem. Soc.*, 2002, **124**, 7904; (*b*) P. S. Baran, C. A. Guerrero and E. J. Corey, *J. Am. Chem. Soc.*, 2003, **125**, 5628; (*c*) E. M. Beck, R. Hatley and M. J. Gaunt, *Angew. Chem., Int. Ed.*, 2008, **48**, 3046; (*d*) E. M. Stang and M. C. White, *Nat. Chem.*, 2009, **1**, 547; (*e*) X. Xu, Y. Liu and C.-M. Park, *Angew. Chem., Int. Ed.*, 2012, **51**, 9372; (*f*) N. Quiñones, A. Seoane, R. García-Fandiño, J. L. Mascareñas and M. Gulías, *Chem. Sci.*, 2013, **4**, 2874.

7 R. K. Thalji, K. A. Ahrendt, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2001, **123**, 9692.

8 (*a*) R. M. Wilson, R. K. Thalji, R. G. Bergman and J. A. Ellman, *Org. Lett.*, 2006, **8**, 1745; (*b*) S. J. O'Malley, K. L. Tan, A. Watzke, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2005, **127**, 13496; (*c*) R. K. Thalji, K. A. Ahrendt, R. G. Bergman and J. A. Ellman, *J. Org. Chem.*, 2005, **70**, 6775; (*d*) R. K. Thalji, J. A. Ellman and R. G. Bergman, *J. Am. Chem. Soc.*, 2004, **126**, 7192; (*e*) K. L. Tan, A. Vasudevan, R. G. Bergman, J. A. Ellman and A. J. Souers, *Org. Lett.*, 2003, **5**, 2131; (*f*) K. A. Ahrendt, R. G. Bergman and J. A. Ellman, *Org. Lett.*, 2003, **5**, 1301.

9 Z. Ding and N. Yoshikai, *Angew. Chem., Int. Ed.*, 2013, **52**, 8574.

10 During the preparation of this manuscript, Rovis *et al.* and Cramer *et al.* published closely related papers, respectively. See: (*a*) T. A. Davis, T. K. Hyster and T. Rovis, *Angew. Chem., Int. Ed.*, 2013, **52**, 14181; (*b*) B. Ye, P. A. Donets and N. Cramer, *Angew. Chem., Int. Ed.*, 2014, **53**, 507.

11 For reviews on Rh(III)-catalyzed C–H activations, see: (*a*) T. Satoh and M. Miura, *Chem.–Eur. J.*, 2010, **16**, 11212; (*b*) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651; (*c*) F. W. Patureau, J. Wencel-Delord and F. Glorius, *Aldrichimica Acta*, 2012, **45**, 31.

12 (*a*) S. Rakshit, C. Grohmann, T. Besset and F. Glorius, *J. Am. Chem. Soc.*, 2011, **133**, 2350; (*b*) H. Wang and F. Glorius, *Angew. Chem., Int. Ed.*, 2012, **51**, 7318; (*c*) H. Wang, C. Grohmann, C. Nimphius and F. Glorius, *J. Am. Chem. Soc.*, 2012, **134**, 19592.

13 (*a*) N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2011, **133**, 6449; (*b*) T. L. Hyster, L. Knörr, T. R. Ward and T. Rovis, *Science*, 2012, **338**, 500; (*c*) B. Ye and N. Cramer, *Science*, 2012, **338**, 504; (*d*) J. R. Huckins, E. A. Bercot, O. R. Thiel, T.-L. Hwang and M. M. Bio, *J. Am. Chem. Soc.*, 2013, **135**, 14492; (*e*) S. Cui, Y. Zhang and Q. Wu, *Chem. Sci.*, 2013, **4**, 3421.