

View Article Online View Journal

ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: M. Shi, K. Chen, Z. Zhu, X. Tang, Y. Wei and J. Liu, *Chem. Commun.*, 2015, DOI: 10.1039/C5CC07292A.



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard <u>Terms & Conditions</u> and the <u>Ethical guidelines</u> still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.



www.rsc.org/chemcomm

Published on 30 October 2015. Downloaded by UNIVERSITY OF OTAGO on 30/10/2015 20:16:21

Please do not adjust margins ChemComm

View Article Online DOI: 10.1039/C5CC07292A



Journal Name

COMMUNICATION

Substrate-Controlled Rh(II)-Catalyzed Single-Electron-Transfer (SET): Divergent Synthesis of Fused Indoles[†]

Received 00th January 20xx, Accepted 00th January 20xx

Kai Chen,^a Zi-Zhong Zhu,^a Jia-Xin Liu,^a Xiang-Ying Tang,^{*b} Yin Wei^b and Min Shi^{*a,b}

DOI: 10.1039/x0xx00000x

www.rsc.org/

Rh(II)-catalyzed diversified ring expansions controlled by singleelectron-transfer (SET) have been disclosed in this paper, producing a series of indole-fused azetidines and 1*H*-carbazoles or related derivatives in moderate to good yields via Rh₂^{III,II} nitrene radical intermediates. The direction of ring expansion branches according to different ring size of methylenecycloalkanes.

The indole ring system is one of the most ubiquitous heterocycles in nature.¹ Fused indoles, polycyclic indole derivatives, are common cores found in a number of naturally occurring products.² For example, the insecticidal alkaloid Okaramine B carries indole-fused azetidine moiety.³ Valparicine, containing a 1H-carbazole core, shows pronounced cytotoxic effects against KB and Jurkat cells.⁴ another 1H-carbazole derivative. namely. Moreover. akuammiline alkaloid Scholarisine A, is used in traditional Chinese medicine to treat various respiratory diseases (Figure 1).⁵ Their importance in medicinal chemistry has stimulated the development of new synthetic methods to create such structural motifs. Herein, we report a new protocol for facile construction of the above azetidine and 3H-indole akuammiline via ring expansion of methylenecycloalkanes. This method allows two types of ring expansions according to ring size: three-membered ring compounds furnish the azetidine ring; while larger sized substrates deliver 3H-indole fused cycloalkanes.

To rapid generation of molecular complexity from simple starting materials is the permanent pursuit in organic synthesis. To this regard, the ring-expansion (or 1,2-shift) strategy offers an excellent solution because it can facilitate easy formation of polycyclic derivatives, which are otherwise difficult to be

⁺ Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data of new compounds, and CCDC 949600, 1003610. See DOI: 10.1039/b000000x/





Figure 1 Represented important fused indoles



Scheme 1 Rearrangements of cycloalkyl radicals

accessed by traditional methods. Our group has a long interest to investigate the ring expansion of methylenecyclopropanes (MCPs).^{6,7} We then envisaged that a nitrogen radical species could induce the ring expansion of MCPs or methylenecycloalkanes, giving azetidine or 1*H*-carbazole derivatives. Notably, to the best of our knowledge, this is the first example of ring expansion of MCPs to a nitrogen atom to afford azetidines (Scheme 1).⁷

It has been reported that single-electron-transfer (SET) can take place between nitrene and dirodium(II) dimer, resulting in Rh2^{III,II} species which is the catalyst resting state in reactions.⁸ intermolecular amination Furthermore, computational calculations suggested that such reactions were catalyzed by a triplet mixed-valent $Rh_2^{III,II}$ nitrene radical via the SET oxidation of the $Rh_2^{1,11}$ dimer.⁹ On the basis of these results, azide tethered MCPs 1 were treated with a dirhodium complex (Scheme 1). We were glad to find that it underwent a ring expansion to give indole fused azetidines 2. Moreover, we also found that the expansion of larger sized rings 3 under rhodium catalysis would go different direction to give 1Hcarbazoles and related derivatives 4.

^{a.} Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, and 130 MeiLong Road, Shanghai 200237, P. R. China.

^{b.} State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, P. R. China. E-mail: siocxiangying@mail.sioc.ac.cn; mshi@mail.sioc.ac.cn.

COMMUNICATION

Published on 30 October 2015. Downloaded by UNIVERSITY OF OTAGO on 30/10/2015 20:16:21

DOI: 10.1039/C5CC07292A Journal Name



Scheme 2 Rhodium-catalyzed intramolecular reaction of 1a.

We initially investigated the reaction of 1-azido-2-(cyclopropylidene(phenyl)methyl)benzene **1a** catalyzed by $Rh_2(esp)_2$ in toluene under reflux for 8 h. To our delight, the indole fused azetidine **2a** could be furnished in 90% yield (Scheme 2). Its structure has been unambiguously determined by X-ray diffraction (for more details about the optimization of this reaction, please see Table S1 in the Supporting Information).¹⁰

We next examined the substrate scope of this reaction. As for substrates **1b-1e**, in which $R^1 = 2-MeC_6H_4$, $3-MeC_6H_4$, 4- MeC_6H_4 or 4-MeOC_6H_4, R^2 = H, the reactions proceeded smoothly to furnish the desired products 2b-2e in 75-86% vields (Table 1, entries 1-4). In the cases of substrates 1f-1i bearing halogen substituted aryl rings (R¹), the corresponding products 2f-2i were obtained in 79-83% yields (Table 1, entries 5-8). Alternatively, R^2 could be other substituents such as 5-Cl or 4-MeO, and the desired products 2j-2l were formed in 72-83% yields (Table 1, entries 9-11). The electronic property of R¹ and R² did not have significant impact on the reaction outcomes. When substrate **1m**, in which $R^1 = Me$, $R^2 = H$, was treated with Rh₂(esp)₂ under the standard reaction conditions, the corresponding product 2m was afforded in 42% yield (Table 1, entry 12). The reaction of substrate 1n (R¹ = R² = H) did not take place under the standard reaction conditions, suggesting that the derived radical intermediate shown in Scheme 1 is not stable enough when $R^1 = H$ (Table 1, entry 12).



^{*a*} Reaction conditions: **1** (0.2 mmol), catalyst (3 mol %), solvent (1.0 mL). ^{*b*} Isolated yield. esp = a,a,a',a'-tetramethyl-1,3-benzenedipropionic acid.

Next, we turned our interest in constructing 1*H*-carbazoles and related derivatives. Different ring sized methylenecycloalkanes as well as dimethyl substituted alkenes were investigated. These reactions did not occur under the standard reaction conditions (under reflux in toluene), but went on smoothly in chlorobenzene under reflux for 12 h, affording a series of 3*H*-indoles in good yields. When n = 1, the reactions of methylenecyclobutanes **3a-3c** proceeded

smoothly, giving hexahydrocyclopenta[b]indoles 4a-4c in 59-60% yields after reduction by NaBH₃CN, owing to the instability of the corresponding 3H-indole intermediates (Table 2, entries 1-3).¹¹ In the cases of substrates **3d-3h** (n = 2) bearing halogen, methyl and methoxy substituted aromatic ring (R¹), the corresponding tetrahydro-1*H*-carbazoles 4d-4h were obtained in 62-80% yields (Table 2, entries 4-8). Specifically, as for methylenecyclohexanes 3i-3k, the reactions proceeded smoothly and the desired products were easily oxidized by air to afford ketones 4i-4k in 62-75% yields (Table 2, entries 9-11).¹² When substrates **3I-3n** bearing two methyl substituents were treated with Rh₂(esp)₂ under the standard reaction conditions, the products 4I-4n were produced after 1,2-alkyl migration in 81-88% yields (Table 2, entries 12-14). Moreover, 3a, 3d, 3i and 3l could be converted to the corresponding products in less than 10% yield in the absence of Rh(II) complex, indicating that Rh(II) catalyst can promote the reaction efficiently.





 a Reaction conditions: **3** (0.1 mmol), catalyst (5 mol %), solvent (1.0 mL). b Isolated yield. c No catalyst.

To investigate the mechanism, control experiments were conducted (Scheme 3). When radical inhibitors such as TEMPO, 2,6-di-*tert*-butyl-4-methylphenol (BHT) or hydroquinone (2.0 equiv) were added, the reaction outcomes of **1a** were significantly interrupted. To our delight, among them the radical trapping product **2aa** could be isolated in 40% yield. These results indicated that the reaction might indeed start from the Rh₂^{III,II} nitrene radical intermediate and went through a radical pathway. Owing to the instability of azide groups at high temperature, trapping the reaction systems of **3a**, **3d**, **3i** and **3i** with TEMPO only gave complex mixtures along with trace of the desired products. Furthermore, the yields of product **2a** (R¹ = Ph, 90%), **2m** (R¹ = Me, 42%) and **2n** (R¹ = H, 0%) in Table 1 descended in order, clarifying the radical

Published on 30 October 2015. Downloaded by UNIVERSITY OF OTAGO on 30/10/2015 20:16:21

Please do not adjust margins ChemComm

Journal Name



Scheme 3 Radical trapping experiments.

process because the stability of these three radical intermediates decreased in turn.

Based on above experiments and previous reports, a plausible mechanism is outlined in Scheme 4. Coordination of azide to $Rh_2(esp)_2$ complex and extrusion of N_2 give the Rhnitrene **A**.¹³ Next, intramolecular single electron transfer (SET) takes place, resulting in nitrogen centered radical specie **A**^{1,8,9,14} The following radical addition to C=C bond in MCP moiety forms intermediate **B**, which undergoes ring-opening process to furnish homoallylic radical **C**. Subsequent SET from radical to Rh^{III} and ring-closure give rise to **2a** together with the regeneration of the Rh(II) catalyst. When n = 2-4, ring-opening can not take place and intermediate **B** undergoes another SET to afford spirocyclic cationic intermediate **D**. While a 1,2-alkyl shift from **D** can occur to afford the fused indole **E** which produces the corresponding 3*H*-indole product **4** and regenerates the Rh(II) catalyst.



In order to understand why the ring size of substrate can affect the reaction outcome, we did the DFT calculations on the key step in the reaction. All calculations have been performed at BPW91/BS1 level¹⁵ with Gaussian 09 program.¹⁶ The Rh₂-nitrene intermediate A' suggested in Scheme 4 was first investigated theoretically, and its Rh2^{III,II}-nitrene radical character was proved (for details, see Supporting Information). Subsequently, we investigated the ring-opening process of B to generate intermediate C, and another possible reaction pathway starting from **B** which involves to form intermediate D via the SET and following 1,2-alkyl migration to give intermediate E. The relative energies of all intermediates and transitional states along the reaction pathways using different substrates are shown in Scheme 5. For the substrate involving three-membered ring, the intermediate B1 can undergo a ringopening process to generate another radical intermediate C1



Rhl

thermodynamically favorable

-41.6

DOI: 10.1039/C5CC07292A

Scheme 5 DFT studies on the key reaction step.

D3 RhT

-22.9

via transition state TS1 with an energy barrier of 4.0 kcal/mol. Alternatively, the intermediate B1 can undergo SET to a more stable zwitterionic intermediate D1 which undergoes a 1,2alkyl migration to form intermediate E1 by passing through TS2 with an energy barrier of 12.3 kcal/mol. In this case, the energy barrier of ring-opening process to form radical intermediate C1 is much lower, thus this process is kinetically favorable, which may account for why experimentally obtained product is 2. In addition, one possible intermediate I is also investigated theoretically. However, this intermediate is unstable and could not be located. Similarly, the substrates involving four-membered ring and five-membered ring are also investigated. In these two cases, the energy barriers for two reaction pathways are very close (11.0 kcal/mol vs. 11.1 kcal/mol, 17.2 kcal/mol vs. 17.0 kcal/mol), however, the intermediates E2 and E3 are very thermodynamically stable. Thus, for substrates involving four-membered ring and fivemembered ring, the favored pathway is 1,2-alkyl migration, furnishing products 4.

In summary, we have disclosed in this paper that styryl azides could smoothly undergo intramolecular rearrangement in the presence of Rh^{II} complex, producing a series of indole-fused azetidines and 1*H*-carbazoles or related derivatives in moderate to good yields via $Rh_2^{III,II}$ nitrene radical. The

COMMUNICATION

Page 4 of 5

products 2 and 4 have important structural motif in organic and medicinal chemistry. DFT calculations on the key step explain that cyclization and SET pathways are controlled by designed radical clock. The potential utilization and extension of the substrate scope of this synthetic methodology are currently under investigation.

We are grateful for the financial support from the National Basic Research Program of China (973)-2015CB856603, and the National Natural Science Foundation of China (20472096, 21372241, 21361140350, 20672127, 21421091, 21372250, 21121062, 21302203, 20732008 and 21572052).

Notes and references

- 1 (a) R. J. Sundberg, Indoles, Academic, New York, 1996; (b) G. R. Humphrey and J. T. Kuethe, Chem. Rev., 2006, 106, 2875.
- (a) M. Somei and F. Yamada, Nat. Prod. Rep., 2004, 21, 278; (b) T. Kawasaki and K. Higuchi, Nat. Prod. Rep., 2005, 22, 761; (c) K. Higuchi and T. Kawasaki, Nat. Prod. Rep., 2007, 24, 843.
- 3 (a) H. Hayashi, K. Takiuchi, S. Murao, and M. Arai, Agric. Biol. Chem., 1988, 52, 2131; (b) Y. Shiono, K. Akiyama and H. Hayashi, Biosci. Biotechnol. Biochem., 2000, 64, 1519.
- (a) K.-H. Lim, Y.-Y. Low and T.-S. Kam, Tetrahedron Lett., 2006, 47, 5037; (b) K.-H. Lim, O. Hiraku, K. Komiyama, T. Koyano, M. Hayashi and T.-S. Kam, J. Nat. Prod., 2007, 70, 1302.
- X.-H. Cai, Q.-G. Tan, Y.-P. Liu, T. Feng, Z.-Z. Du, W.-Q. Li and 5 X.-D. Luo, Org. Lett., 2008, 10, 577.
- For selected reviews, see: (a) A. Brandi, S. Cicchi, F. M. 6 Cordero and A. Goti, Chem. Rev., 2003, 103, 1213; (b) M. Rubin, M. Rubina and V. Gevorgyan, Chem. Rev., 2007, 107, 3117; (c) L.-X. Shao and M. Shi, Curr. Org. Chem., 2007, 11, 1135; (d) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, Chem. Soc. Rev., 2008, 37, 320; (e) M. Shi, L.-X. Shao, J.-M. Lu, Y. Wei, K. Mizuno and H. Maeda, Chem. Rev., 2010, 110, 5883; (f) H. Pellissier, Tetrahedron, 2010, 66, 8341; (g) M. Shi, J.-M. Lu, Y. Wei and L.-X. Shao, Acc. Chem. Res., 2012, 45, 641; (h) A. Brandi, S. Cicchi, F. M. Cordero and A. Goti, Chem. Rev., 2014, 114, 7317; (i) H. Pellissier, Tetrahedron, 2014, 70, 4991.
- For recent examples of ring expansions and cycloadditions of 7 MCPs, see: (a) M. Shi, L.-P. Liu and J. Tang, J. Am. Chem. Soc., 2006, 128, 7430; (b) M. E. Scott, Y. Bethuel and M. Lautens, J. Am. Chem. Soc., 2007, 129, 1482; (c) K. Chen, Z. Zhang, Y. Wei and M. Shi, Chem. Commun., 2012, 48, 7696; (d) R. J. Felix, D. Weber, O. Gutierrez, D. J. Tantillo and M. R. Gagné, Nat. Chem., 2012, 4, 405; (e) P. A. Inglesby, J. Bacsa, D. E. Negru and P. A. Evans, Angew. Chem., Int. Ed., 2014, 53, 3952; (f) L. Saya, I. Fernández, F. López and J. L. Mascareñas, Org. Lett., 2014, 16, 5008; (g) K. Chen, Z.-Z. Zhu, Y.-S. Zhang, X.-Y. Tang and M. Shi, Angew. Chem., Int. Ed., 2014, 53, 6645; (h) R. Sang, X.-Y. Tang and M. Shi, Org. Chem. Front., 2014, 1, 770. For intramolecular reactions of nitrenes with MCPs, see: (i) Y. Liang, L. Jiao, Y. Wang, Y. Chen, L. Ma, J. Xu, S. Zhang and Z.-X. Yu, Org. Lett., 2006, 8, 5877; (j) W. Li and M. Shi, Tetrahedron, 2007, 63, 11016; (k) D.-H. Zhang, Y. Wei and M. Shi, Eur. J. Org. Chem., 2011, 4940.
- (a) K. W. Fiori and J. Du Bois, J. Am. Chem. Soc., 2007, 129, 8 562; (b) D. N. Zalatan and J. Du Bois, J. Am. Chem. Soc., 2009, 131, 7558; (c) K. P. Kornecki and J. F. Berry, Chem. - Eur. J., 2011, 17, 5827; (d) K. P. Kornecki and J. F. Berry, Eur. J. Inorg. Chem., 2012, 562; (e) K. P. Kornecki and J. F. Berry, Chem. Commun., 2012, 48, 12097.

- X. Zhang, Z. Ke, N. J. DeYonker, H. Xu, Z.-F. Li, X. Xu, X. Zhang, C.-Y. Su, D. L. Phillips and C. Zhao, J. Org. Chem., 2013, 78, 12460.
- 10 The crystal data of 2a have been deposited in CCDC with number 949600.
- 11 F. Guo, L. Wang, P. Wang, J. Yu and J. Han, Asian J. Org. Chem., 2012, 1, 218.
- 12 The crystal data of 4i have been deposited in CCDC with number 1003610.
- 13 For recent examples of metal-catalyzed reactions of azidestyrenes, see: (a) B. J. Stokes, K. J. Richert and T. G. Driver, J. Org. Chem., 2009, 74, 6442; (b) T. G. Driver, Org. Biomol. Chem. 2010, 8, 3831; (c) K. Sun, S. Liu, P. M. Bec and T. G. Driver, Angew. Chem., Int. Ed., 2011, 50, 1702; (d) B. J. Stokes, S. Liu and T. G. Driver, J. Am. Chem. Soc., 2011, 133, 4702; (e) A. L. Pumphrey, H. Dong and T. G. Driver, Angew. Chem., Int. Ed., 2012, 51, 5920; (f) C. Kong, N. Jana and T. G. Driver, Org. Lett., 2013, 15, 824; (g) C. Jones, Q. Nguyen and T. G. Driver, Angew. Chem., Int. Ed., 2014, 53, 785; (h) C. Kong and T. G. Driver, Org. Lett., 2015, 17, 802.
- 14 For recent examples of metal-based carbene or nitrene radicals, see: (a) T. Bach, B. Schlummer and K. Harms, Chem. Commun., 2000, 287; (b) T. Bach, B. Schlummer and K. Harms, Chem. - Eur. J., 2001, 7, 2581; (c) M. P. Doyle, Angew. Chem., Int. Ed., 2009, 48, 850; (d) H. Lu, W. I. Dzik, X. Xu, L. Wojtas, B. de Bruin and X. P. Zhang, J. Am. Chem. Soc., 2011, 133, 8518; (e) V. Lyaskovskyy, A. I. O. Suarez, H. Lu, H. Jiang, X. P. Zhang and B. de Bruin, J. Am. Chem. Soc., 2011, 133, 12264; (f) L.-M. Jin, X. Xu, H. Lu, X. Cui, L. Wojtas and X. P. Zhang, Angew. Chem., Int. Ed., 2013, 52, 5309; (g) L.-M. Jin, H. Lu, Y. Cui, C. L. Lizardi, T. N. Arzua, L. Wojtas, X. Cui and X. P. Zhang, Chem. Sci., 2014, 5, 2422; (h) J. Zhang, J. Jiang, D. Xu, Q. Luo, H. Wang, J. Chen, H. Li, Y. Wang and X. Wan, Angew. Chem., Int. Ed., 2015, 54, 1231.
- 15 For the definition of BS1, see: reference 9.
- 16 M. J. Frisch, et al. Gaussian 09, revision A.01; Gaussian, Inc.: Wallingford, CT, 2009.

Published on 30 October 2015. Downloaded by UNIVERSITY OF OTAGO on 30/10/2015 20:16:21

ChemComm Accepted Manuscript

Journal Name

Substrate-Controlled Rh(II)-Catalyzed Single-Electron-Transfer (SET): Divergent Synthesis of Fused Indoles



Rh(II)-catalyzed diversified ring expansions controlled by single-electron-transfer (SET) have been disclosed in this paper.

Kai Chen, Zi-Zhong Zhu, Jia-Xin Liu, Xiang-Ying Tang,* Yin Wei and Min Shi*