

RSC Advances



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. This *Accepted Manuscript* will be replaced by the edited, formatted and paginated article as soon as this 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 [Terms & Conditions](#) and the [Ethical guidelines](#) 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.

COMMUNICATION

Mg(ClO₄)₂-Promoted [4 + 3] Cycloaddition of Oxindole Derivatives with Conjugated Dienes: Concise Synthesis of Spirocycloheptane Oxindole Derivatives

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

DOI: 10.1039/x0xx00000x

Yun Liu, Zhou Sun, Song Li, Kuirong Xiang, Yuan Zhang,* and Ying Li*

www.rsc.org/

We herein reported a novel Mg(ClO₄)₂-promoted intermolecular [4 + 3] cycloaddition reaction of oxindole derivatives and cyclopentadiene. This new strategy provides a convenient approach to the concise synthesis of a series of spirocycloheptane oxindole derivatives, with moderate to good yields and high diastereoselectivities.

The spirooxindole skeletons have drawn tremendous attention among synthetic and medicinal chemists during the past few years due to their functional diversity and their significance in organic synthesis as crucial intermediates.¹ Among them, the spirocycloheptane oxindole frameworks represent ubiquitous structural motifs in a broad range of alkaloids and bioactive compounds (Figure 1). Most of these alkaloids have been found to exhibit remarkable biological and pharmacological activities. For example, the gelsemine, which was first isolated from Carolina jasmine (*Gelsemium sempervirens*)² in 1876,³ have recently been found to exhibit potent and specific antinociception in chronic pain by acting at the three spinal glycine receptors.⁴ In this context, the development of flexible synthetic methods for the synthesis of spirocycloheptane oxindole skeletons would thus be beneficial for the synthesis of those bioactive alkaloids.⁵ Although the chemistry of spirooxindole has been studied quite extensively, the investigations are mostly focused on the construction of spirocyclopentane⁶ or spirocyclohexane oxindole⁷ moieties. To date, there has been limited work on the direct construction of spirocycloheptane oxindole frameworks from oxindole derivatives.^{8,9}

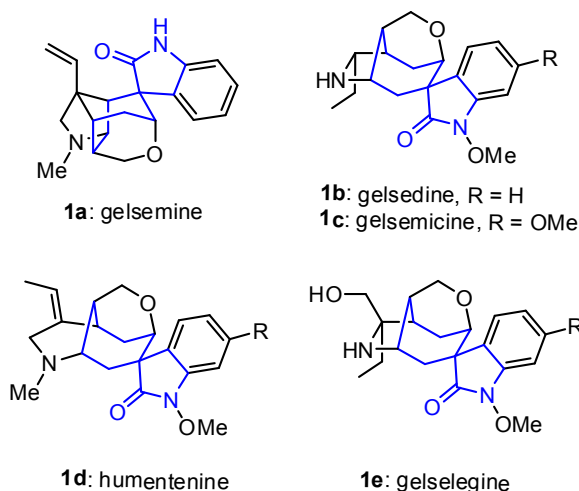


Figure 1. Structures of natural products possessing the spirocycloheptane oxindole skeleton.

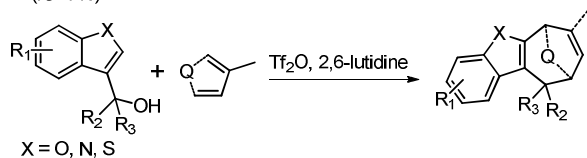
The [4 + 3]-cycloaddition between allylic cations and conjugated dienes has been proved to be a powerful method for the direct synthesis of seven-membered rings.¹⁰⁻¹³ The acid-catalysed [4 + 3] cycloaddition reactions of furfuryl alcohols and 1,3-diene were first reported by Pattenden in 2009 to construct the 5,5,7-tricyclic skeletons.^{13f} The substituted furfuryl alcohols could undergo acid-catalysed hydrolysis transformations, and accompanied by displacement of the hydroxyl group, then leading to the furanoxonium ion intermediates, which could react with 1,3-diene via a [4 + 3] cycloaddition.^{10e} Our group have recently disclosed the intermolecular [4 + 3] cycloaddition of heterocyclic compounds (such as benzofuran, benzothiophene and indole)^{14b,c} with conjugated dienes to construct various 6,5,7-polycyclic skeletons and their application in the total synthesis of Liphagal and Frodonin B.^{14a} In continuation of our previous work, we envisaged that a [4 + 3] cycloaddition reaction between oxindole derived allylic cations and conjugated dienes would result in the straightforward formation of spirocycloheptane oxindoles. Herein, we report a highly diastereoselective [4 + 3] cycloaddition route to the synthesis of spirocycloheptane oxindoles (Scheme 1).

State Key Laboratory of Applied Organic Chemistry & College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou, 730000, P. R. China. E-mail: liying@lzu.edu.cn;

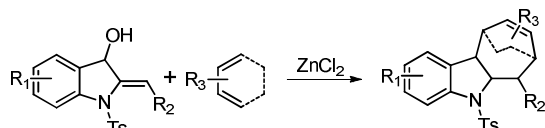
†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Previous work

- a) TiF_2O -promoted [4+3] cycloaddition to construct 6,5,7-polycyclic skeleton (ref 14b)

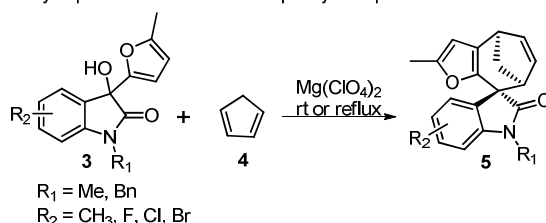


- b) ZnCl_2 -promoted one pot [4+3] cycloaddition reactions (ref 14c)



This work

- c) $\text{Mg}(\text{ClO}_4)_2$ -promoted [4+3] cycloaddition of oxindole derivatives with cyclopentadiene to construct spirocycloheptane oxindole frameworks



Scheme 1. [4+3] Cycloaddition reactions of heterocyclic compounds with conjugated dienes.

Table 1. Optimization of the reaction condition.^a

Entry	Conditions	Solvent	T(°C)	Yield(%) ^b
1	TFA	DCM	-78 to 0	trace ^c
2	CSA	DCM	-78 to rt	NR ^d
3	HClO_4	DCM	-78	ND ^d
4	SnCl_4	DCM	-78 to rt	18
5	ZnCl_2	DCM	rt	30
6	$\text{Mg}(\text{ClO}_4)_2$	DCM	0	<5
7	$\text{Mg}(\text{ClO}_4)_2$	DCM	rt	58
8	$\text{Mg}(\text{ClO}_4)_2$	DCM	reflux	ND ^d
9	$\text{Mg}(\text{ClO}_4)_2$	THF	rt	20
10	$\text{Mg}(\text{ClO}_4)_2$	Et_2O	rt	25

^a Unless otherwise noted, all reaction was performed with **3** (0.1 mmol, 1.0 eq), **4** (1.0 mmol, 10.0 eq) and Lewis acids or Brønsted acids (0.15 mmol, 1.5 eq) in solvent (15 mL). ^b Yield of isolated product. ^c Determined by ^1H NMR (400 MHz) analysis (starting material was decomposed). ^d NR = no reaction (starting material was recovered); ND = not determined (starting material was decomposed).

We initiated our studies using oxindole derivative **3a**¹⁵ as dienophiles and cyclopentadiene **4** as conjugated dienes to explore the cycloaddition conditions. Compounds **3a** could be readily prepared from N-substituted isatins and 2-methyl furan (for details see ESI). Selected representative screening results for this model reaction are presented in Table 1. Initially, a variety of frequently used Brønsted acids as well as Lewis acids were examined for the cycloaddition reaction at room temperature in DCM. However, Brønsted acids and most of Lewis acids resulted in no reaction at all (for details see ESI). Lewis acids such as SnCl_4 and ZnCl_2 could promote the reaction, but resulted in low yields, probably due to the polymerization of dienes or decomposition of the starting materials in these conditions (Table 1, entries 4 and 5). Finally, $\text{Mg}(\text{ClO}_4)_2$ was proved to be the optimum Lewis acid. Upon treatment with 1.5 equiv of anhydrous $\text{Mg}(\text{ClO}_4)_2$ in DCM at ambient temperature, **3a** underwent cycloaddition with **4** to afford the spirooxindole **5a** in 58% yield within 2h (Table 1, entry 8). Further optimization of the reaction conditions by changing the temperature and solvents did not improve the yields (Table 1, entries 6-10).

Having established the optimal reaction conditions, we then investigated the reactivity of a series of oxindole compounds **3a-l** towards cyclopentadiene **4** (Figure 2). As is shown in Figure 2, this novel [4+3] cycloaddition reaction was found to be applicable for a series of oxindole substrates, and a number of spirocycloheptane oxindole derivatives were afforded in moderate to good yields. The electronic properties of R_1 group on the N-atom of oxindole derivatives clearly influenced the reactivity of substrates. The substrates with electron-donating groups ($\text{R}_1 = \text{Me}/\text{Bn}$) afforded products **5** in good yields (Figure 2, **5a-5b**), whereas those with electron-withdrawing groups ($\text{R}_1 = \text{Ac}$) could not afford the desired products. Similarly, electronic effects of R_2 also substantially affected the yields. In general, the presence of halogen atoms on the phenyl ring obviously reduced the reactivity of substrates (Figure 2, **5d-5j**), therefore the higher temperatures were needed for these reactions. While the electron-donating substituents had positive effects (Figure 2, **5c** and **5k**). However, the reaction could not proceed when the substituents on the phenyl ring were two fluorine atoms (Figure 2, **5l**). Notably, this [4+3] cycloaddition reaction showed excellent diastereoselectivities for all substrates, and the relative configuration could be determined by the single X-ray crystallographic analysis data of **5a** (Figure 2).

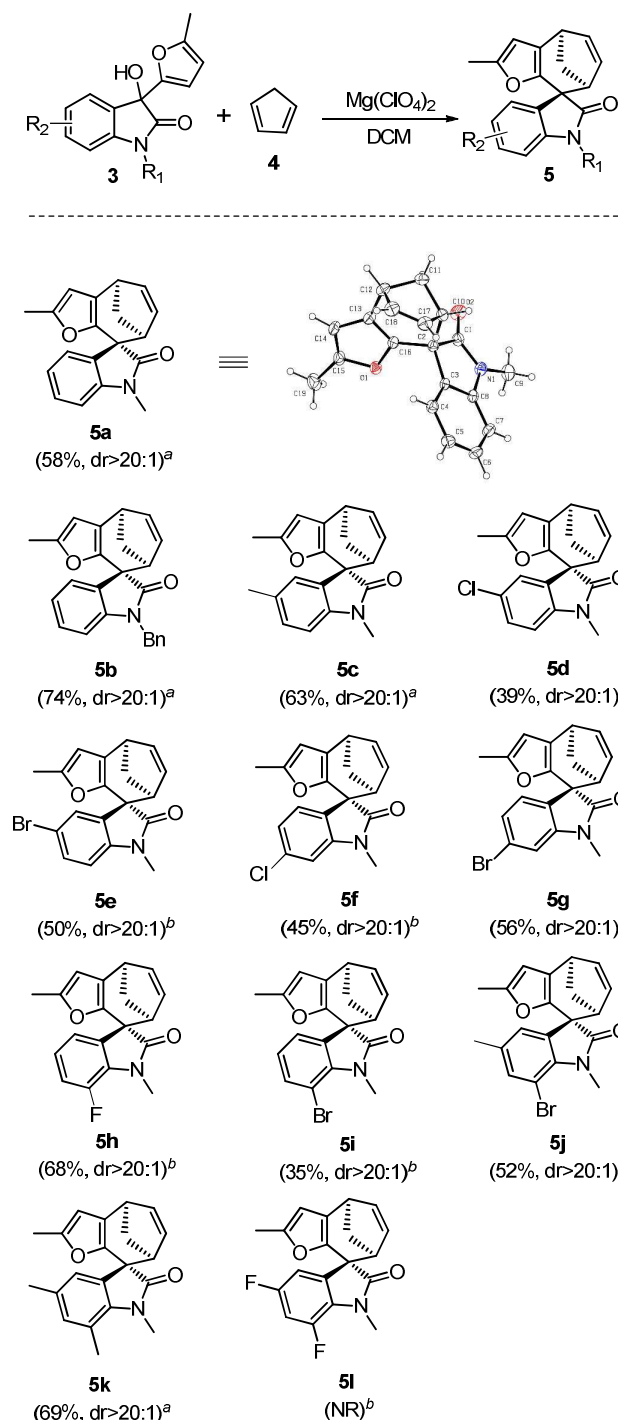
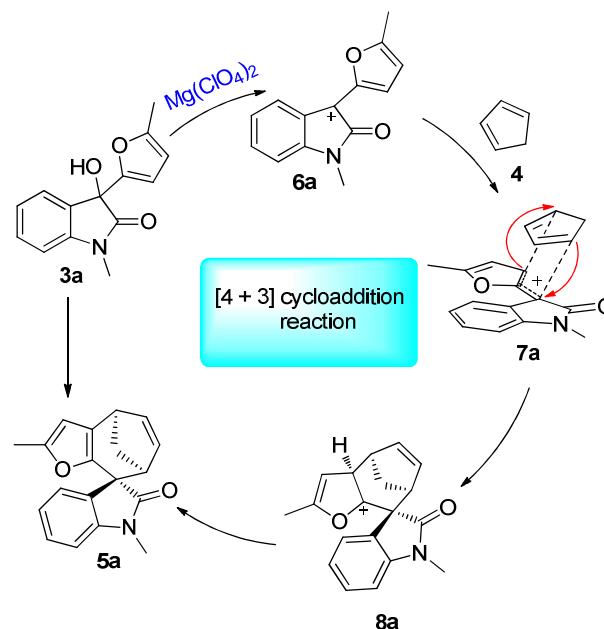


Figure 2. Scope of the [4 + 3] cycloaddition reaction.

^a Unless otherwise noted, the reaction was performed with **3** (0.1 mmol, 1.0 eq), **4** (1.0 mmol, 10.0 eq), and $\text{Mg}(\text{ClO}_4)_2$ (0.15 mmol, 1.5 eq) in DCM (15 mL) at rt. ^b The reaction was performed at refluxing temperature. ^c Diastereomeric ratios were determined by ¹H NMR (400 MHz) analysis. In the experimental results, the diastereoisomer could not be detected in ¹H NMR spectra, therefore we identified the dr as >20:1.

The details of the [4 + 3] cycloaddition mechanism have not yet been fully understood. The theoretical results proposed by Winne et al. pointed to a two-step cationic cyclization process,^{16a} and this can also be supported by Wu's report via

the DFT calculations.^{16b} On the basis of our previous research^{14,16e} and literature reports,^{16a-d} a possible mechanism was proposed, as is shown in Scheme 2. Firstly, an allylic cation intermediate **6a** could be achieved from the oxindole compounds under Lewis acid conditions. Then, an intermolecular [4 + 3] cycloaddition between **6a** and dienes **4** via endo-cycloaddition transition state **8a** resulted in the spirocycloheptane oxindole skeleton **5a**. Most intermolecular oxyallyl cation-type reactions usually prefer an exo- (or extended) addition mode; while in our experiment, we proposed the transformation was taking place under kinetic control (performed at room temperature or ca 40 °C), which probably prefer the endo-transition state for maximizing the π - π stacking interaction between the oxindole cation and conjugated cyclopentadiene.¹⁷



Scheme 2. A plausible mechanism for the [4 + 3] cycloaddition reaction.

Conclusions

In summary, we have developed a novel and convenient approach for the construction of spirocycloheptane oxindole skeletons through a $\text{Mg}(\text{ClO}_4)_2$ -promoted [4 + 3] cycloaddition of oxindole derivatives with conjugated dienes. This method could achieve the concise synthesis of a series of spirocycloheptane oxindoles in moderate yields with high diastereoselectivities. We believe that the strategy demonstrated here may be utilized in the further synthesis of natural products and potential bioactive compounds containing spirocycloheptane oxindole skeletons. Further investigations towards the refinement of the reaction mechanism, as well as applications in total synthesis, are now under way in our lab and will be reported in due course.

Notes and references

The authors acknowledge the financial support provided by the National Natural Science Foundation of China (Nos. 21472078, 21272099, and 21572092). We thank professor Zhi-Xiang. Xie (Lanzhou University) for helpful discussion.

- For reviews of spirooxindole skeletons, see: (a) D.-J. Cheng, Y. Ishihara, B. Tan and C. F. Barbas III, *ACS Catal.*, 2014, **4**, 743; (b) A. K. Franz, N. V. Hanhan and N. R. Ball-Jones, *ACS Catal.*, 2013, **3**, 540; (c) C. V. Galliford and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2007, **46**, 8748.
- For reviews of Gelsemium alkaloid, see: (a) B.-F. Zhang, G.-X. Chou and Z.-T. Wang, *Helvetica. Chimica. Acta.*, 2009, **92**, 1889; (b) J.-M. Yu, T. Wang, X.-X. Liu, J. Deschamps, J. Flippen-Anderson, X.-B. Liao and J. M. Cook, *J. Org. Chem.*, 2003, **68**, 7565; (c) H. Takayama and S. Sakai, *J. Syn. Org. Chem. Jpn.*, 1990, **48**, 876.
- Sonnenschein, F. L. *Ber. Dtsch. Chem. Ges.* 1876, **9**, 1182.
- J.-Y. Zhang, N. Gong, J.-L. Huang, L.-C. Guo, and Y.-X. Wang, *Pain.*, 2013, **154**, 2452.
- For recent selected examples of synthesis of gelsemine alkaloids: (a) H. Lin and S. J. Danishefsky, *Angew. Chem. Int. Ed.*, 2003, **42**, 36; (b) A. Madin, C. J. O'Donnell, T. B. Oh, D. W. Old, L. E. Overman and M. J. Sharp, *Angew. Chem. Int. Ed.*, 1999, **38**, 2934; (c) S. Yokoshima, H. Tokuyama and T. Fukuyama, *Angew. Chem. Int. Ed.*, 2000, **39**, 4073; (d) X. Zhou, T. Xiao, Y. Iwama and Y. Qin, *Angew. Chem. Int. Ed.*, 2012, **51**, 4909; (e) S. Atarashi, J. K. Choi, D. C. Ha, D. J. Hart, D. Kuzmich, C. S. Lee, S. Ramesh and S. C. Wu, *J. Am. Chem. Soc.*, 1997, **119**, 6226; (f) W. G. Earley, J. E. Jacobsen, A. Madin, G. P. Meier, C. J. O'Donnell, T. Oh, D. W. Old, L. E. Overman and M. J. Sharp, *J. Am. Chem. Soc.*, 2005, **127**, 18046; (g) T. Fukuyama and G. Liu, *J. Am. Chem. Soc.*, 1996, **118**, 7426; (h) A. Madin, C. J. O'Donnell, T. Oh, D. W. Old, L. E. Overman and M. J. Sharp, *J. Am. Chem. Soc.*, 2005, **127**, 18054; (i) F. W. Ng, H. Lin and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2002, **124**, 9812; (j) A. J. Pearson and X.-L. Wang, *J. Am. Chem. Soc.*, 2003, 125, 13326; (k) X. Chen, S. Duan, C. Tao, H. Zhai and F.-G. Qiu, *Nat. Commun.*, 2015, **6**, 7204.
- For recent selected examples of spirocyclopentane oxindole skeletons, see: (a) J. Dugal-Tessier, E. A. O'Bryan, T. B. H. Schroeder, D. T. Cohen and K. A. Scheidt, *Angew. Chem. Int. Ed.*, 2012, **51**, 4963; (b) X. Zhao, X. Liu, Q. Xiong, H. Mei, B. Ma, L. Lin and X. Feng, *Chem. Commun.*, 2015, **51**, 16076; (c) R. Zhou, K. Zhang, Y. Chen, Q. Meng, Y. Liu, R. Li and Z. He, *Chem. Commun.*, 2015, **51**, 14663; (d) Y.-M. Cao, F.-F. Shen, F.-T. Zhang and R. Wang, *Chem. Eur. J.*, 2013, **19**, 1184; (e) W. Guo, X. Wang, B. Zhang, S. Shen, X. Zhou, P. Wang, Y. Liu and C. Li, *Chem. Eur. J.*, 2014, **20**, 8545. (f) J. Xu, L.-D. Shao, D. Li, X. Deng, Y.-C. Liu, Q.-S. Zhao and C. Xia, *J. Am. Chem. Soc.*, 2014, **136**, 17962; (g) Y. Tian, L. Tian, X. He, C. Li, X. Jia and J. Li, *Org. Lett.*, 2015, **17**, 4874; (h) C. Zheng, W. Yao, Y. Zhang and C. Ma, *Org. Lett.*, 2014, **16**, 5028.
- For recent selected examples of spirocyclohexane oxindole skeletons, see: (a) T.-P. Gao, J.-B. Lin, X.-Q. Hu and P.-F. Xu, *Chem. Commun.*, 2014, **50**, 8934; (b) W. Yang and D.-M. Du, *Chem. Commun.*, 2013, **49**, 8842; (c) W. Cao, X. Liu, J. Guo, L. Lin and X. Feng, *Chem. Eur. J.*, 2015, **21**, 1632; (d) H.-L. Cui and F. Tanaka, *Chem. Eur. J.*, 2013, **19**, 6213; (e) Y. Shi, A. Lin, H. Mao, Z. Mao, W. Li, H. Hu, C. Zhu and Y. Cheng, *Chem. Eur. J.*, 2013, **19**, 1914; (f) Y.-Y. Han, W.-Y. Han, X. Hou, X.-M. Zhang and W.-C. Yuan, *Org. Lett.*, 2012, **14**, 4054; (g) S. Zhao, J.-B. Lin, Y.-Y. Zhao, Y.-M. Liang and P.-F. Xu, *Org. Lett.*, 2014, **16**, 1802.
- (a) P. Drouhin, T. E. Hurst, A. C. Whitwood and R. J. Taylor, *Org. Lett.*, 2014, **16**, 4900; (b) L. Wang, Y. Su, X. Xu and W. Zhang, *Eur. J. Org. Chem.* 2012, **33**, 6606; (c) Gorokhovik, L. Neuville and J.-P. Zhu, *Org. Lett.*, 2011, **13**, 5536; (d) J. R. Fuchs and R. L. Funk, *Org. Lett.*, 2005, **7**, 677; (e) A. C. Peterson and J. M. Cook, *Tetrahedron Lett.*, 1994, **35**, 2651; (f) V. Nair, P. M. Treesa, N. P. Rath, A. C. Kunwar, K. S. KiranKumar, A. RaviSankar, M. Vairamani and S. Prabhakar, *Tetrahedron*, 2002, **58**, 7221.
- G. Zhan, M. L. Shi, Q. He, W. Du and Y. C. Chen, *Org. Lett.*, 2015, **17**, 4750-4753.
- For reviews of [4 + 3] cycloaddition reactions, see: (a) M. Harmata, *Acc. Chem. Res.*, 2001, **34**, 595; (b) J. K. Cha and J. Oh, *Curr. Org. Chem.*, 1998, **2**, 217; (c) M. Harmata, *Chem. Commun.*, 2010, **46**, 8886; (d) M. Harmata, *Chem. Commun.*, 2010, **46**, 8904; (e) M. J. Palframan and G. Pattenden, *Chem. Commun.*, 2014, **50**, 7223.
- For recent selected examples of [4 + 3] cycloaddition reactions, see: (a) L. Chen, G.-M. Yang, J. Wang, Q.-F. Jia, J. Wei and Z.-Y. Du, *RSC Adv.*, 2015, **5**, 76696; (b) C. S. Jeffrey, D. Anumandla and C. R. Carson, *Org. Lett.*, 2012, **14**, 5764; (c) C. S. Jeffrey, K. L. Barnes, J. A. Eickhoff and C. R. Carson, *J. Am. Chem. Soc.*, 2011, **133**, 7688; (d) E. H. Krenske, K. N. Houk and M. Harmata, *J. Org. Chem.*, 2015, **80**, 744; (e) B. Lo and P. Chiu, *Org. Lett.*, 2011, **13**, 864; (f) A. G. Lohse and R. P. Hsung, *Chem. Eur. J.*, 2011, **17**, 3812; (g) A. G. Lohse, R. P. Hsung, M. D. Leider and S. K. Ghosh, *J. Org. Chem.*, 2011, **76**, 3246; (h) J. M. Winne, S. Catak, M. Waroquier and V. Van Speybroeck, *Angew. Chem. Int. Ed.*, 2011, **50**, 11990; (i) O. A. Ivanova, E. M. Budynina, A. O. Chagarovskiy, A. E. Kaplun, I. V. Trushkov and M. Y. Melnikov, *Adv. Synth. Catal.*, 2011, **353**, 1125.
- For recent selected examples of [4 + 3] cycloaddition reactions, see: (a) B. W. Gung, D. T. Craft, L. N. Bailey and K. Kirschbaum, *Chem. Eur. J.*, 2010, **16**, 639; (b) X. Han, H. Li, R. P. Hughes and J. Wu, *Angew. Chem. Int. Ed.*, 2012, **51**, 10390; (c) D. Shu, W. Song, X. Li and W. Tang, *Angew. Chem. Int. Ed.*, 2013, **52**, 3237; (d) B. Song, L.-H. Li, X.-R. Song, Y.-F. Qiu, M.-J. Zhong, P.-X. Zhou and Y.-M. Liang, *Chem. Eur. J.*, 2014, **20**, 5910.
- For recent selected examples of [4 + 3] cycloaddition reactions, see: (a) A. H. E. Hassan, J. K. Lee, A. N. Pae, S. J. Min and Y. S. Cho, *Org. Lett.*, 2015, **17**, 2672; (b) D. R. Laplace, B. Verbracken, K. Van Hecke and J. M. Winne, *Chem. Eur. J.*, 2014, **20**, 253; (c) Y. Lian, L. C. Miller, S. Born, R. Sarpog and H. M. L. Davies, *J. Am. Chem. Soc.*, 2010, **132**, 12422; (d) J. Wang, S.-G. Chen, B.-F. Sun, G. Q. Lin and Y.-J. Shang, *Chem. Eur. J.*, 2013, **19**, 2539; (e) J. Xu, E. J. E. Caro-Diaz and E. A. Theodorakis, *Org. Lett.*, 2010, **12**, 3708; (f) G. Pattenden and J. M. Winne, *Tetrahedron Letters*, 2009, **50**, 7310.
- (a) J. Zhang, L. Li, Y. Wang, W. Wang, J. Xue and Y. Li, *Org. Lett.*, 2012, **14**, 4528; (b) W. Gong, Y. Liu, J. Zhang, Y. Jiao, J. Xue and Y. Li, *Chem.-Asian J.*, 2013, **8**, 546; (c) J. Zhang, J. Shao, J. Xue, Y. Wang and Y. Li, *RSC Adv.*, 2014, **4**, 63850.
- We have tried many types of allylic alcohols: such as ethenyl-, alkynyl-, phenyl-, thienyl-, furyl-, benzothiophenyl- group, etc. The unsubstituted furyl-oxindole derivatives could not exist stably for the C2 position of furan is the most reactive site towards electrophiles. And the others could not react with cyclopentadiene under the optimal reaction conditions to achieve the expected spirocycloheptane oxindole skeletons (for details see ESI).
- (a) J. M. Winne, S. Catak, M. Waroquier and V. van Speybroeck, *Angew. Chem. Int. Ed.*, 2011, **50**, 11990; (b) X. Han, H. Li, R. P. Hughes and J. Wu, *Angew. Chem. Int. Ed.*, 2012, **51**, 10390; (c) M. J. Palframan and G. Pattenden, *Tetrahedron Lett.*, 2013, **52**, 324; (d) G. Pattenden and M. Palframan, *Synlett*, 2013, **24**, 2720. (e) In the experimental results, when we used thiophenes as dienes, only a Friedel-Crafts intermolecular alkylation reaction occurred, giving an ordinary electrophilic adducts **9a** (determined by the single X-ray crystallographic analysis, for details see ESI). We expected that these results might support for a two-step

Journal Name

COMMUNICATION

pathway mechanism of the intermolecular [4 + 3] cycloaddition reactions (for details see ESI).

- 17 (a) M. Harmata,* S. Elomari, and C. L. Barnes, *J. Am. Chem. Soc.*, 1996, **118**, 2860; (b) J. I. Garcia, J. A. Mayoral, and L. Salvatella,* *Acc. Chem. Res.* 2000, **33**, 658.

Novel $\text{Mg}(\text{ClO}_4)_2$ -promoted [4 + 3] cycloaddition reaction of oxindole derivatives and cyclopentadiene was achieved for the construction of spirocycloheptane oxindole skeleton.

