Carbenoids

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# C−H Functionalization/Asymmetric Michael Addition Cascade Enabled by Relay Catalysis: Metal Carbenoid Used for C−C Bond Formation**

*Dian-Feng Chen, Feng Zhao, Yue Hu, and Liu-Zhu Gong**

***Abstract:*** *A combination of either ruthenium(II) or rhodium(II) complexes and quinine-derived squaramide enables 3-diazooxindoles, indoles, and nitroalkenes to undergo highly efficient asymmetric three-component reactions, thus affording optically active 3,3′-bis(indole)s through a consecutive C−C bond-forming sequence, which turned out to be applicable to the facile total synthesis of (−)-folicanthine.*

Carbon–carbon bond-forming reactions inarguably constitute the backbone of organic synthesis.[1] Historically, a single-step synthesis of a diverse scope of carbon–carbon bonds from multiple components often enables the direct assembly of complex molecules,[2] and remains important in modern chemistry.[3] As one of the most significant active species, the metal carbenoid, commonly generated from a diazo compound, has long been utilized for the formation of multiple carbon–carbon bonds (such as cyclopropanation).[4] However, their participation in multicomponent reactions (MCRs) has not received much attention until recently. The groups of Van Vranken,[5] Wang,[6] and Yu[7] established migration insertion/coupling reaction cascades of in situ generated palladium(II), copper(I), or rhodium(I) carbenoids (**A**) with aryl halides (Figure 1). Hu and co-workers[8] also found that the metal-associated zwitterionic intermediate of type **B** would undergo an electrophilic trapping reaction with appropriate electrophiles. Interestingly, these two successful multicomponent pathways mechanistically benefit from the high reactivity of metal carbenoids.

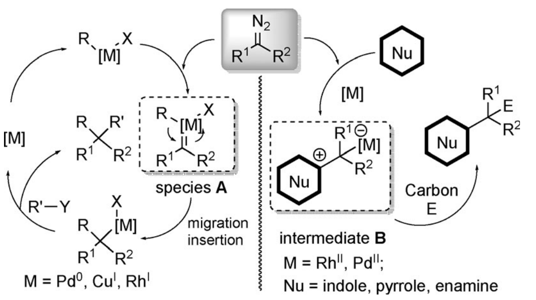
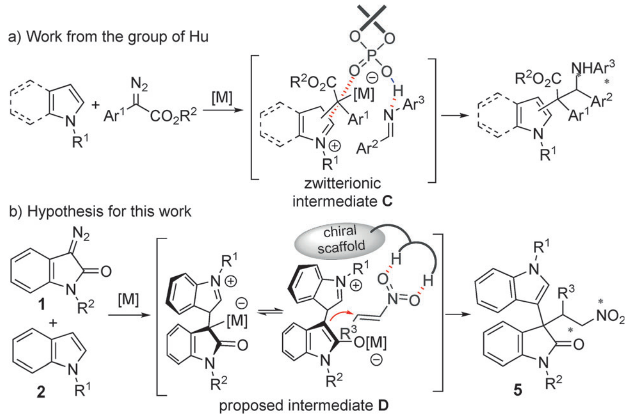


***Figure 1.*** Metal carbenoids in C−C bond-forming MCRs.

Previously, our group and that of Hu have proposed rhodium/chiral phosphoric acid cooperative catalysis for the asymmetric multicomponent Mannich-type reaction of an onium ylide.[9] This concept turns out to be very general for the realization of synthetically important and highly enantioselective multicomponent transformations.[10,11] More significantly, Hu and co-workers applied this concept to enantioselective Mannich-type trapping of zwitterionic intermediates (**C**) generated from metal carbenoids and either indole[8b] or pyrrole[8d] (Scheme 1 a). However, besides imines and carbonyl functionalities, chiral Brønsted acids often feature insufficient activation of other electrophiles, such as Michael reaction acceptors,[12] thus suppressing the development of diverse enantioselective MCRs involving metal carbenoids. As a consequence, the creation of a new metal/organo binary catalyst system to address these formidable issues would be highly valuable. In the light of a highly compatible rhodium/bifunctional squaramide catalysis recently established by our group,[13] we envisaged an unprecedented enantioselective three-component Michael-type cascade reaction.[14] As shown in Scheme 1 b, we hypothesized that the electrophilic reaction of the metal carbenoid derived from 3-diazooxindole **1** with the indole **2** would generate the zwitterion **D**, which might be trapped by nitroalkenes (**3**). This process would be promoted by the chiral bifunctional catalyst **4**, thus leading to the



***Scheme 1.*** Enantioselective and consecutive creation of C−C bonds through metal carbenoids.

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[*] Dr. D.-F. Chen, F. Zhao, Y. Hu, Prof. Dr. L.-Z. Gong
Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, 230026 (China)
E-mail: gonglz@ustc.edu.cn
Homepage: http://staff.ustc.edu.cn/~gonglz/index.html
Prof. Dr. L.-Z. Gong
Collaborative Innovation Center of Chemical Science and Engineering, Tianjin (China)

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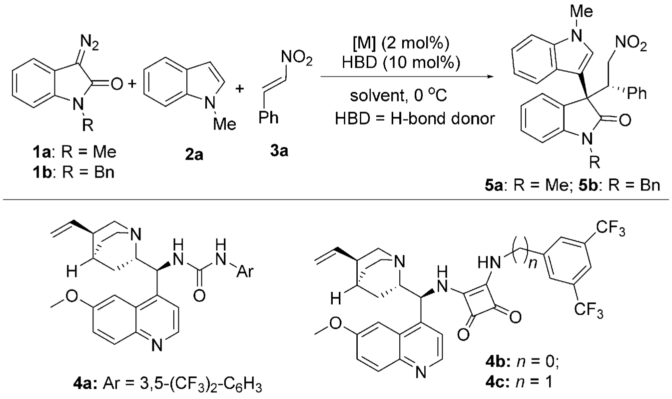
optically active 3,3′-bisindoles derivatives **5** from conveniently prepared starting materials.

To begin, a three-component reaction of *N*-methyl-3-diazooxindole (**1a**) with *N*-methyl indole (**2a**) and nitrostyrene (**3a**) was carried out in the presence of 2 mol% [$Rh_2(OAc)_4$] and 10 mol% **4a** (in $CH_2Cl_2$, 0 °C, Table 1, entry 1). However, the decomposition of the **1a** was not observed, probably because of the deactivation effect within this catalytic system.[15] $Cu(OTf)_2$ and $PdCl_2$ were unable to promote the reaction (entries 2 and 3).[16] To our delight, [{$RuCl_2$(*p*-cymene)}$_2$][17] was found to be highly compatible with **4a**, and capable of complete conversion of **1a** into the desired product **5a** in 72% yield, albeit with moderate stereoselectivity (entry 4). The bifunctional organocatalysts bearing stronger double-hydrogen-bond donors substantially improved the enantioselectivity (entries 5 and 6). In particular, the squaramide **4c** offered the best results (entry 6). The evaluation of solvents found that neither $CHCl_3$ nor toluene was able to give diastereoselectivity (entries 7 and 9). The use of $Et_2O$ slightly improved the diastereoselectivity, but led to an eroded yield (entry 8). Interestingly, a mixture of $CH_2Cl_2$ and $Et_2O$ (1:1) was found to be the solvent of choice, thus allowing the reaction to proceed with high stereoselectivity (entry 10). A variation of the N-protecting group of the 3-diazooxindole from methyl (**1a**) to benzyl (**1b**) largely improved both the diastereo- and enantioselectivity (entry 11). Lowering the temperature led to a much slower reaction and a slightly diminished enantioselectivity (entry 12). Notably, 1 mol% of [{$RuCl_2$(*p*-cymene)}$_2$] and 5 mol% of **4c** indeed provided the best outcomes (entry 13), whereas further decreasing the amount of **4c** resulted in a considerably eroded yield (entry 14).

***Table 1:*** Optimization of reaction conditions.[a]



| Entry | 1 | [M] | HBD | Yield [%][b] | d.r.[c] | *ee* [%][d] |
|---|---|---|---|---|---|---|
| 1 | **1a** | [$Rh_2(OAc)_4$] | **4a** | n.r. | – | – |
| 2 | **1a** | $Cu(OTf)_2$ | **4a** | trace | – | – |
| 3 | **1a** | $PdCl_2$ | **4a** | n.r. | – | – |
| 4 | **1a** | [Ru] | **4a** | 72 | 3.5:1 | 56/57 |
| 5 | **1a** | [Ru] | **4b** | 70 | 2.0:1 | 90/66 |
| 6 | **1a** | [Ru] | **4c** | 90 | 2.0:1 | 93/68 |
| 7[e] | **1a** | [Ru] | **4c** | 42 | 1.0:1 | 88/67 |
| 8[f] | **1a** | [Ru] | **4c** | 65 | 2.5:1 | 88/77 |
| 9[g] | **1a** | [Ru] | **4c** | 55 | 1.0:1 | 88/66 |
| 10[h] | **1a** | [Ru] | **4c** | 91 | 2.5:1 | 93/80 |
| 11[h] | **1b** | [Ru] | **4c** | 98 | 4.0:1 | 97/88 |
| 12[h,i] | **1b** | [Ru] | **4c** | 86 | 4.7:1 | 95/61 |
| 13[h,j] | **1b** | [Ru] | **4c** | 97 | 4.5:1 | 97/90 |
| 14[h,k] | **1b** | [Ru] | **4c** | 60 | 3.5:1 | 95/77 |

[a] Unless indicated otherwise, reactions of **1** (0.10 mmol), **2a** (0.12 mmol), **3a** (0.15 mmol), metal (0.002 mmol), and **4** (0.010 mmol) were carried out in $CH_2Cl_2$ (1 mL) for 12 h. [b] Yield of isolated product. [c] Determined by $^1H$ NMR analysis of crude reaction mixture. [d] Determined by HPLC analysis. [e] $CHCl_3$ was used. [f] $Et_2O$ was used. [g] Toluene was used. [h] $CH_2Cl_2/Et_2O$ (1:1) was used. [i] The reaction was conducted at −20 °C. [j] 1 mol% [Ru] and 5 mol% **4c** were used. [k] 1 mol% [Ru] and 2 mol% **4c** were used. n.r. = no reaction, [Ru] = [{$RuCl_2$(*p*-cymene)}$_2$], Tf = trifluoromethanesulfonyl.

With the optimized reaction conditions in hand, we investigated the generality of this asymmetric organo/metal protocol for all three components (Figure 2). A variety of nitroalkenes were firstly examined, thus resulting in the generation of the products **5c–i** in excellent yields and with high levels of enantioselectivity. For substituted β-nitrostyrenes, the diastereoselectivity was apparently correlated to the substitution pattern of the substituents on the benzene moiety, but it was barely affected by their electronic nature (**5c** and **5d**). For example, *ortho*-substituents (**5f–i**) provided much higher diastereoselectivities (up to 20:1 d.r.) than either the *meta*- or *para*-substituents (**5c–e**). Moreover, furanyl and cinnamyl nitroalkenes also underwent the cascade reaction to furnish **5j** and **5k**, respectively, in high yields and with excellent stereoselectivities.

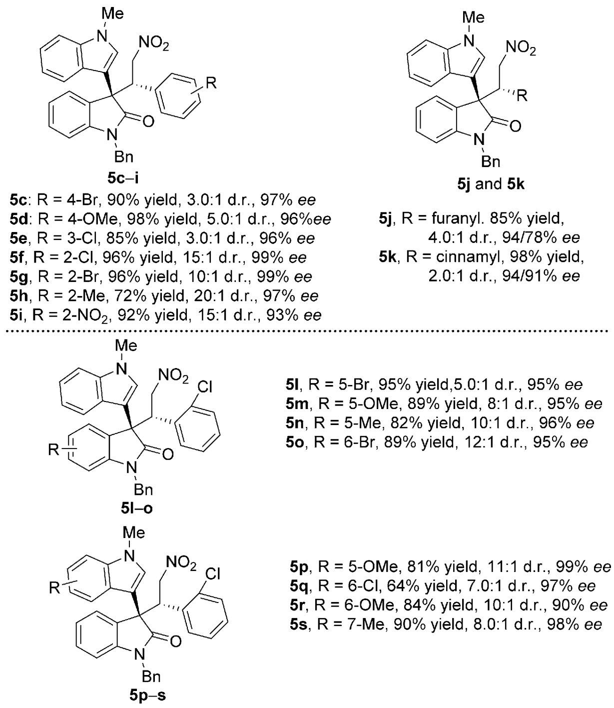
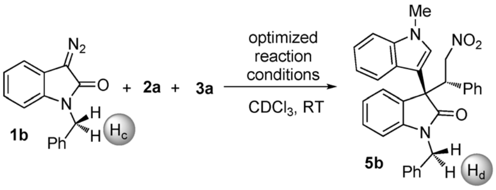


***Figure 2.*** Substrate scope.

Next, the generality for indoles and 3-diazooxindoles was also explored by using 2-chloro-β-nitrostyrene as the Michael acceptor (Figure 2). Basically, clean transformations were observed for C5- and C6-substituted 3-diazooxidoles, thus providing excellent enantioselectivities (**5l–o**). The diastereoselectivity also largely relied on the substitution pattern of the substituent. For instance, 6-bromo-3-diazooxidole favored the *trans*-diastereomer over the 5-bromo-3-diazooxidole (**5l** versus **5o**). Notably, electronically neutral substituent offered higher diastereoselectivity than either an electron-donating or electron-withdrawing substituent (**5f** versus **5l–n**). Substituents on C5, C6, and C7 of the N-methyl indoles **2** were also well tolerated, thus giving **5p–s** with comparable diastereoselectivities and excellent enantioselectivities.

To determine if the proposed trapping process of the zwitterionic intermediate **D** occurs, the reaction of **1b** with **2a** and **3a** in $CDCl_3$ [Eq. (1)] was monitored by $^1H$ NMR spectroscopy. As shown in Figure 3, a doublet at $\delta = 5.05$ ppm ($H_b$) was observed, but then decayed with the concomitant appearance of the final product **5b** (monitored by $H_d$), thus identifying the real intermediate to be the C–H insertion product **6** [see Eq. (2) for structure].[18] The disproportion between $H_a$ to $H_b$ in the spectra may stem from the **4c**-promoted partial enolization of **6** [Eq. (2)]. Moreover, control reactions of **6** and **3a** identified an individual **4c**-catalyzed Michael addition step [Eq. (3)], which suggested a transition metal/organo relay catalysis[19] in this three-component reaction (Table 1, entry 14).



(1)

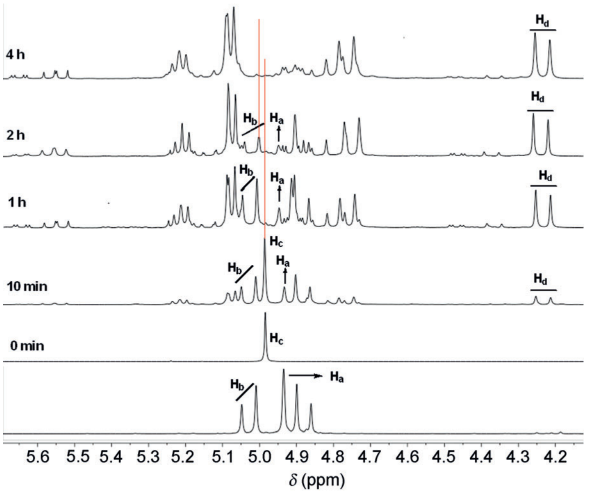
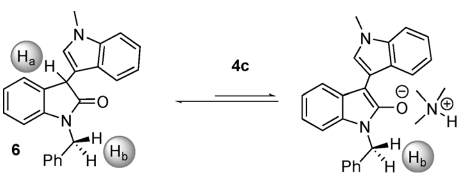


***Figure 3.*** Monitoring of intermediates by $^1H$ NMR spectroscopy.

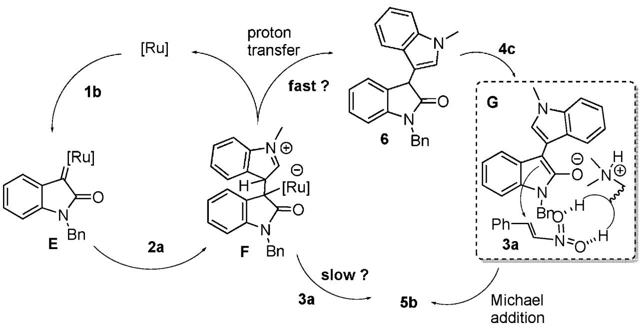


(2)

$$\mathbf{6} + \mathbf{3a} \xrightarrow{\text{reaction conditions}} \mathbf{5b} \qquad (3)$$

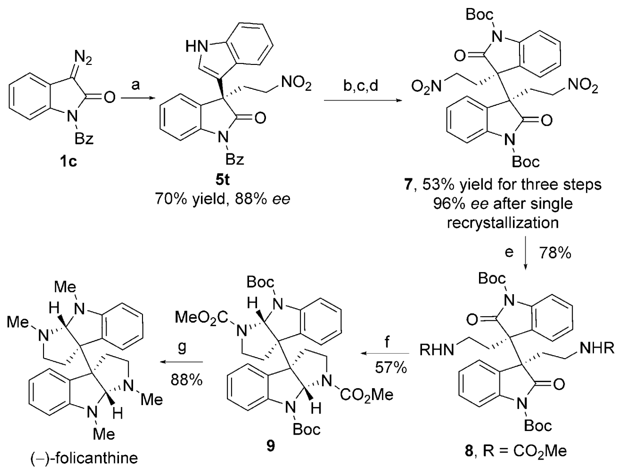
| | |
|---|---|
| 1 mol% [{(p-cymene)$RuCl_2$}$_2$]: | n.r. |
| 5 mol% **4c**: | >99% yield,<br>4.5:1 d.r.<br>97/89% *ee*; |
| 1 mol% [{(p-cymene)$RuCl_2$}$_2$], 5 mol% **4c**: | >99% yield,<br>4.5:1 d.r.<br>97/89% *ee* |

The aforementioned observations and conclusions clearly suggested two catalytic cycles (Scheme 2). The reaction of **2a** with the in situ generated metal carbenoid **E** allowed formation of the zwitterion **F** which underwent a fast proton-transfer process to provide **6** rather than being directly trapped by the activated **3a**. As documented, a chiral bifunctional catalyst, such as **4c**, could promote an enolization of the 3-aryl oxindole,[20] such as **6**, thereby enabling an enantioselective Michael addition to **3a** to furnish the 3,3′-bis(indole) derivative **5b**.



***Scheme 2.*** Proposed relay catalytic cycles.

C3–C3′connected dimeric cyclotryptamine alkaloids, such as chimonanthine and folicanthine,[21] have been found to have significant biological activities and have attracted synthetic interest.[22–24,26] In the progress towards enantioselective construction of the core dimeric hexahydropyrroloindoles, we reported the first catalytic asymmetric total synthesis of (+)-folicanthine.[22a] Later, Kanai and Matsunaga developed a chiral manganese-complex-catalyzed double Michael addition of bis(oxindole) for the synthesis of (+)-folicanthine.[24] Given the potential of the dimeric hexahydropyrroloindole framework within the product of this three-component reaction, we demonstrated a conceivable synthesis of (−)-folicanthine (Scheme 3). The direct assembly of indole, nitroethylene, and the 3-diazooxindole **1c**, catalyzed by $[Rh_2(OAc)_4]$ and **4c**, provided the key intermediate **5t** in 70% yield and with 88% *ee*.[25] A treatment of **5t** with DMSO in mixed HOAc/con. HCl and subsequent reaction with $(Boc)_2O/Na_2CO_3$ in THF successfully resulted in a Boc-protected bis(oxindole) intermediate (see the Supporting Information), which could be further transformed into **7** by a diastereoselevtive Michael addition with nitro-



***Scheme 3.*** Total synthesis of (−)-folicanthine. Conditions: a) indole, nitroethylene, $[Rh_2(OAc)_4]$ (1.0 mol%), **4c** (5.0 mol%), $CH_2Cl_2$, RT; b) conc. HCl, HOAc, DMSO, 50°C; c) $(Boc)_2O$, $Na_2CO_3$, THF, RT; d) nitroethylene, $Mg(OAc)_2\cdot 4H_2O$(5 mol%), benzoic acid, THF, 50°C; e) $NiCl_2/NaBH_4$, methyl dicarbonate, MeOH, 0°C–RT; f) $LiBEt_3H$, toluene, −78–−40°C; 4 M HCl in EtOAc, RT; g) red-Al, toluene, reflux. Boc = *tert*-butoxycarbonyl, DMSO = dimethylsulfoxide, THF = tetrahydrofuran.

ethylene (for three steps, 53% yield; 96% *ee* after single recrystallization). Referring to the known procedure,[24,26] the (−)-folicanthine could be obtained in a 39% overall yield from **7**.

In summary, we have demonstrated a highly enantioselective carbenoid-associated C−H functionalization/Michael addition cascade reaction by virtue of metal/chiral squaramide relay catalysis. In this reaction, two consecutive carbon–carbon bonds were efficiently created in one step, thus affording a variety of optically pure 3,3′-bis(indole) derivatives. Importantly, when the reaction was monitored by $^1$H NMR spectroscopy a C3 carbenoid functionalization from the indole/Michael addition was revealed, as opposed to the expected trapping of the zwitterion. Moreover, on the basis of this metal/organo relay catalytic three-component protocol, a total synthesis of (−)-folicanthine was accomplished in seven steps with 14.5% overall yield.

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**Keywords:** C−H activation · carbenoids · multicomponent reactions · natural products · ruthenium

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[1] W. Brown, C. Foote, B. Iverson, E. Anslyn, *Organic Chemistry*, Cengage Learning, **2009**, 5edth edchap. 24.

[2] For early examples, see: a) P. Biginelli, *Gazz. Chim. Ital.* **1893**, *23*, 360; b) A. Hantzsch, *Justus Liebigs Ann. Chem.* **1882**, *215*, 1; c) I. Ugi, R. Meyr, U. Fetzer, C. Steinbrückner, *Angew. Chem.* **1959**, *71*, 386.

[3] For reviews, see: a) J.-P. Zhu, H. Bienaymé, *Multicomponent Reactions*, Wiley-VCH, Weinheim, **2005**; b) R. C. Cioc, E. Ruijter, R. V. A. Orru, *Green Chem.* **2014**, *16*, 2958–2975.

[4] For reviews, see: a) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861–2904; b) H. M. L. Davies, S. J. Hedley, *Chem. Soc. Rev.* **2007**, *36*, 1109–1119; c) H. M. L. Davies, M. Morton, *Chem. Soc. Rev.* **2009**, *38*, 3061–3071; d) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857–1869; e) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704–724.

[5] a) K. L. Greenman, D. S. Carter, D. L. Van Vranken, *Tetrahedron* **2001**, *57*, 5219–5225; b) S. K. J. Devine, D. L. Van Vranken, *Org. Lett.* **2007**, *9*, 2047–2049; c) R. Kudirka, D. L. Van Vranken, *J. Org. Chem.* **2008**, *73*, 3585–3588; d) S. K. J. Devine, D. L. Van Vranken, *Org. Lett.* **2008**, *10*, 1909–1911; e) R. Kudirka, S. K. J. Devine, C. S. Adams, D. L. Van Vranken, *Angew. Chem.* **2009**, *121*, 3731–3734; *Angew. Chem. Int. Ed.* **2009**, *48*, 3677–3680.

[6] For selected examples, see: a) Q. Xiao, Y. Zhan, J.-B. Wang, *Acc. Chem. Res.* **2013**, *46*, 236–247; b) Y. Xia, Y. Zhang, J.-B. Wang, *ACS Catal.* **2013**, *3*, 2586–2598; c) Z.-H. Zhang, Y.-Y. Liu, M.-X. Guo, X.-K. Zhao, Y. Zhang, J.-B. Wang, *Angew. Chem.* **2010**, *122*, 1157–1160; *Angew. Chem. Int. Ed.* **2010**, *49*, 1139–1142; d) L. Zhou, F. Ye, Y. Zhang, J.-B. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 13590–13591; e) Z.-H. Zhang, Y.-Y. Liu, L. Ling, Y.-X. Li, Y.-A. Dong, M.-X. Guo, X.-K. Zhao, Y. Zhang, J.-B. Wang, *J. Am. Chem. Soc.* **2011**, *133*, 4330–4341; f) Q. Xiao, B.-L. Wang, L.-M. Tian, Y. Yang, J. Ma, Y. Zhang, S.-F. Chen, J.-B. Wang, *Angew. Chem.* **2013**, *125*, 9475–9478; *Angew. Chem. Int. Ed.* **2013**, *52*, 9305–9308; g) F. Ye, M. L. Hossain, Y. Xu, X.-S. Ma, Q. Xiao, Y. Zhang, J.-B. Wang, *Chem. Asian J.* **2013**, *8*, 1404–1407.

[7] Y.-T. Tsoi, Z.-Y. Zhou, W.-Y. Yu, *Org. Lett.* **2011**, *13*, 5370–5373.

[8] a) D. Xing, W.-H. Hu, *Tetrahedron Lett.* **2014**, *55*, 777–783; b) H. Qiu, M. Li, L.-Q. Jiang, F.-P. Lv, L. Zan, C.-W. Zhai, M. P. Doyle, W.-H. Hu, *Nat. Chem.* **2012**, *4*, 733–738; c) D. Xing, C.-C. Jing, X.-F. Li, H. Qiu, W.-H. Hu, *Org. Lett.* **2013**, *15*, 3578–3581; d) D. Zhang, H. Qiu, L.-Q. Jiang, F.-P. Lv, C.-H. Ma, W.-H. Hu, *Angew. Chem.* **2013**, *125*, 13598–13602; *Angew. Chem. Int. Ed.* **2013**, *52*, 13356–13360.

[9] W.-H. Hu, X.-F. Xu, J. Zhou, W.-J. Liu, H.-X. Huang, J. Hu, L.-P. Yang, L.-Z. Gong, *J. Am. Chem. Soc.* **2008**, *130*, 7782–7783.

[10] For a review, see: X. Guo, W.-H. Hu, *Acc. Chem. Res.* **2013**, *46*, 2427–2440.

[11] For selected examples, see: a) Y. Qian, X.-F. Xu, L.-Q. Jiang, D. Prajapati, W.-H. Hu, *J. Org. Chem.* **2010**, *75*, 7483–7486; b) X.-F. Xu, Y. Qian, L.-P. Yang, W.-H. Hu, *Chem. Commun.* **2011**, *47*, 797–799; c) J. Jiang, H.-D. Xu, J.-B. Xi, B.-Y. Ren, F.-P. Lv, X. Guo, L.-Q. Jiang, Z.-Y. Zhang, W.-H. Hu, *J. Am. Chem. Soc.* **2011**, *133*, 8428–8431; d) J. Jiang, X.-C. Ma, S.-Y. Liu, Y. Qian, F.-P. Lv, L. Qiu, X. Wu, W.-H. Hu, *Chem. Commun.* **2013**, *49*, 4238–4240; e) L. Ren, X.-L. Lian, L.-Z. Gong, *Chem. Eur. J.* **2013**, *19*, 3315–3318.

[12] For a limited number of examples, see: a) J. Itoh, K. Fuchibe, T. Akiyama, *Angew. Chem.* **2008**, *120*, 4080–4082; *Angew. Chem. Int. Ed.* **2008**, *47*, 4016–4018; b) T. Sakamoto, J. Itoh, K. Mori, T. Akiyama, *Org. Biomol. Chem.* **2010**, *8*, 5448–5454; c) P. Bachu, T. Akiyama, *Chem. Commun.* **2010**, *46*, 4112–4114.

[13] D.-F. Chen, P.-Y. Wu, L.-Z. Gong, *Org. Lett.* **2013**, *15*, 3958–3961.

[14] There is one example describing asymmetric Michael-type trapping of a metal-associated ylide catalyzed by a chiral zinc(II) complex: X.-Y. Guan, L.-P. Yang, W.-H. Hu, *Angew. Chem.* **2010**, *122*, 2236–2238; *Angew. Chem. Int. Ed.* **2010**, *49*, 2190–2192.

[15] The deactivation effect of catalysts and temperature were responsible for the unsuccessful decomposition of **1a**. For details, see the Supporting Information.

[16] In the presence of **4a**, $PdCl_2$ was unable to decompose **1a**. $Cu(OTf)_2$ could only provide trace amounts of the final product before the reaction was stopped.

[17] For an early use of [{$RuCl_2$(*p*-cymene)}$_2$] in catalytic carbenoid-related transformations, see: Q. Xiao, J.-B. Wang, *Acta Chim. Sin.* **2007**, *65*, 1733 – 1735.

[18] For metal-catalyzed C3 carbenoid functionalization of indoles with 3-diazooxindoles, see: S. Muthusamy, C. Gunanathan, S. A. Babu, E. Suresh, P. Dastidar, *Chem. Commun.* **2002**, 824 – 825.

[19] a) Z.-Y. Han, C. Wang, L.-Z. Gong in *Science of Synthesis Asymmetric Organocatalysis* (Eds.: B. List, K. Maruoka), Georg Thieme, Stuttgart, **2011**, sect. 2.3.6; b) X. Wu, M.-L. Li, L.-Z. Gong, *Acta Chim. Sin.* **2013**, *71*, 1091 – 1100; c) D.-F. Chen, Z.-Y. Han, X.-L. Zhou, L.-Z. Gong, *Acc. Chem. Res.* **2014**, DOI: 10.1021/ar500101a.

[20] The Michael addition of 3-aryl oxindoles to nitroalkenes usually provides moderate stereoselectivities. For selected examples, see: a) X.-L. Liu, Z.-J. Wu, X.-L. Du, X.-M. Zhang, W.-C. Yuan, *J. Org. Chem.* **2011**, *76*, 4008 – 4017; b) M. Ding, F. Zhou, Y.-L. Liu, C.-H. Wang, X.-L. Zhao, J. Zhou, *Chem. Sci.* **2011**, *2*, 2035 – 2039.

[21] a) D. Crich, A. Banerjee, *Acc. Chem. Res.* **2007**, *40*, 151 – 161; b) T. Sevenet, J. Pusset, *The Alkaloids: Chemistry and Pharmacology*, *Vol. 48*, Academic, New York, **1996**, pp. 1 – 73; c) U. Anthoni, C. Christophersen, P. H. Nielsen, *Alkaloids: Chemical and Biological Perspectives*, *Vol. 13*, Pergamon, New York, **1999**, pp. 163 – 236.

[22] For reviews: a) A. Steven, L. E. Overman, *Angew. Chem.* **2007**, *119*, 5584 – 5605; *Angew. Chem. Int. Ed.* **2007**, *46*, 5488 – 5508; b) M. A. Schmidt, M. Movassaghi, *Synlett* **2008**, 313 – 324.

[23] a) C. Guo, J. Song, J.-Z. Huang, P.-H. Chen, S.-W. Luo, L.-Z. Gong, *Angew. Chem.* **2012**, *124*, 1070 – 1074; *Angew. Chem. Int. Ed.* **2012**, *51*, 1046 – 1050; b) Recently, Ma and co-workers reported a chiral phosphoric acid-catalyzed highly enantioselective bromocyclization of tryptamines for the total synthesis of (−)-chimonanthine: W.-Q. Xie, G.-D. Jiang, H. Liu, J.-D. Hu, X.-X. Pan, H. Zhang, X.-L. Wan, Y.-S. Lai, D.-W. Ma, *Angew. Chem.* **2013**, *125*, 13162 – 13165; *Angew. Chem. Int. Ed.* **2013**, *52*, 12924 – 12927.

[24] H. Mitsunuma, M. Shibasaki, M. Kanai, S. Matsunaga, *Angew. Chem.* **2012**, *124*, 5307 – 5311; *Angew. Chem. Int. Ed.* **2012**, *51*, 5217 – 5221.

[25] [$Rh_2(OAc)_4$] was used to promote C3 carbenoid functionalization of nonprotected indole prior to the Michael addition step, as [{(*p*-cymene)$RuCl_2$}$_2$] favored C2 selectivity: W.-W. Chan, S.-H. Yeung, Z.-Y. Zhou, A. S. C. Chan, W.-Y. Yu, *Org. Lett.* **2010**, *12*, 604 – 607.

[26] M. Wada, T. Murata, H. Oikawa, H. Oguri, *Org. Biomol. Chem.* **2014**, *12*, 298 – 306.