

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

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Abstract: A combination of either ruthenium(II) or rhodium(II) complexes and quinine-derived squaramide enables 3-diazoindoles, 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 (–)-folicanthaline.

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.

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 1a). 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

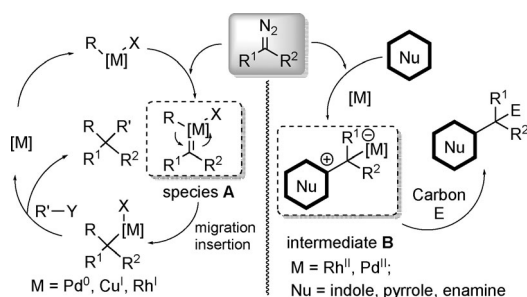
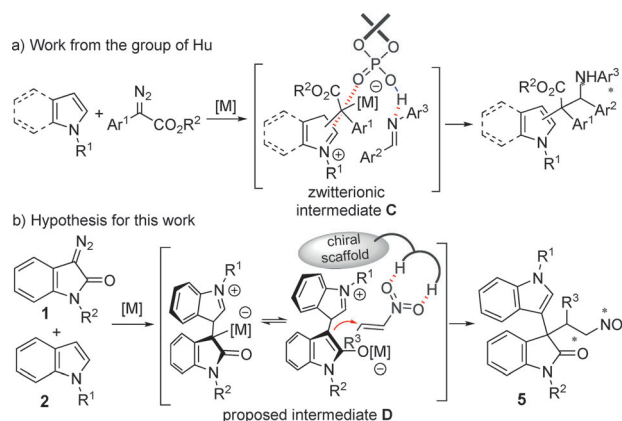


Figure 1. Metal carbenoids in C–C bond-forming MCRs.



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

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[**] We are grateful for financial support from the NSFC (21232007), MOST (973 project 2010CB833300), the Ministry of Education, and CAS.

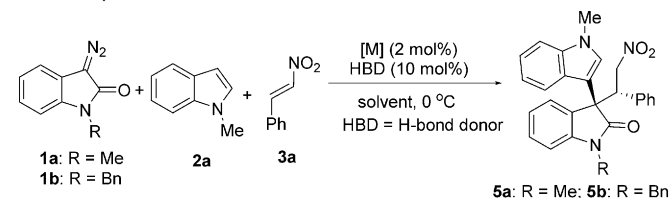
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201406098>.

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 1b, we hypothesized that the electrophilic reaction of the metal carbenoid derived from 3-diazoindole **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

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 % $[\text{Rh}_2(\text{OAc})_4]$ and 10 mol % **4a** (in CH_2Cl_2 , 0 °C, Table 1,

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



1a: R = Me
1b: R = Bn

2a

3a

[M] (2 mol%)
HBD (10 mol%)
solvent, 0 °C
HBD = H-bond donor

5a: R = Me; 5b: R = Bn

4a: Ar = 3,5-(CF₃)₂-C₆H₃

4b: n = 0;
4c: n = 1

Entry	1	[M]	HBD	Yield [%] ^[b]	d.r. ^[c]	ee [%] ^[d]
1	1a	$[\text{Rh}_2(\text{OAc})_4]$	4a	n.r.	—	—
2	1a	$\text{Cu}(\text{OTf})_2$	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] $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ (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] = $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$, Tf = trifluoromethanesulfonyl.

entry 1). However, the decomposition of the **1a** was not observed, probably because of the deactivation effect within this catalytic system.^[15] $\text{Cu}(\text{OTf})_2$ and PdCl_2 were unable to promote the reaction (entries 2 and 3).^[16] To our delight, $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ ^[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 $[\{\text{RuCl}_2(p\text{-cymene})\}_2]$ 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).

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

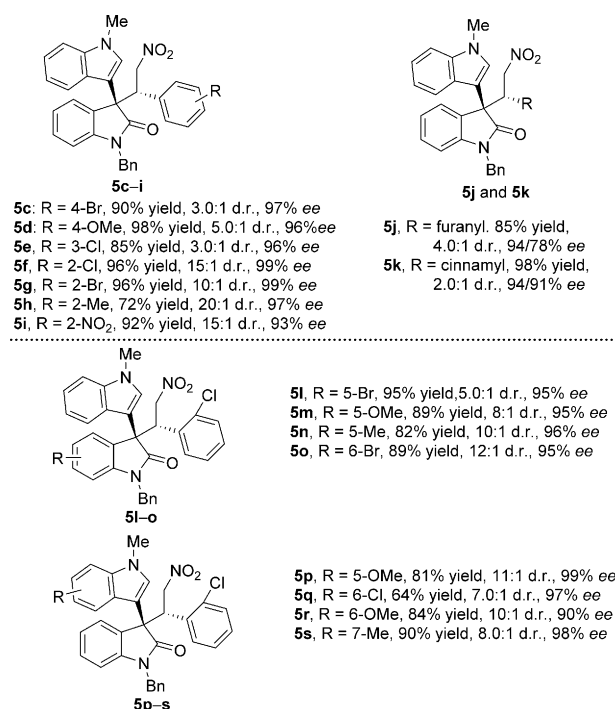


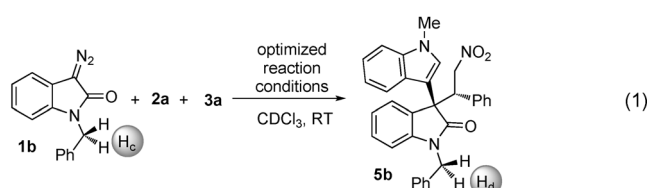
Figure 2. Substrate scope.

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.

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-diazooxindoles, thus providing excellent enantioselectivities (**5l–o**). The diastereoselectivity also largely relied on the substitution pattern of the substituent. For instance, 6-bromo-3-diazooxindole favored the *trans*-diastereomer over the 5-bromo-3-diazooxindole (**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 CDCl₃ [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

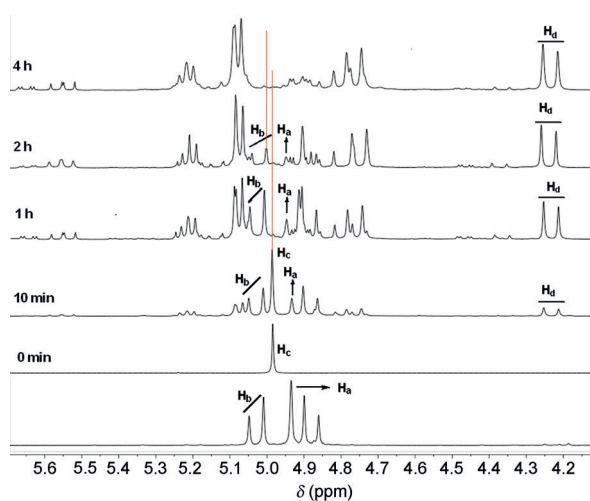
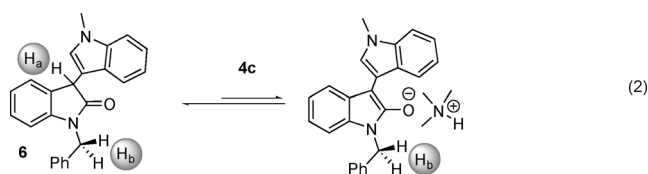
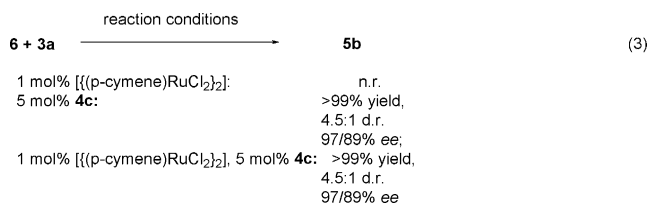


Figure 3. Monitoring of intermediates by ¹H NMR spectroscopy.

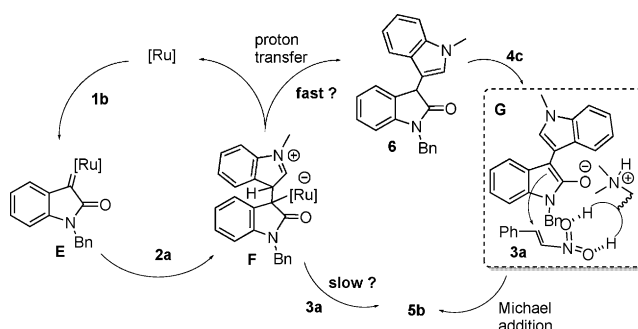
insertion product **6** [see Eq. (2) for structure].^[18] The disproportion between H_a to H_b in the spectra may stem from the **4c**-promoted partial enolization of **6** [Eq. (2)]. Moreover,



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).



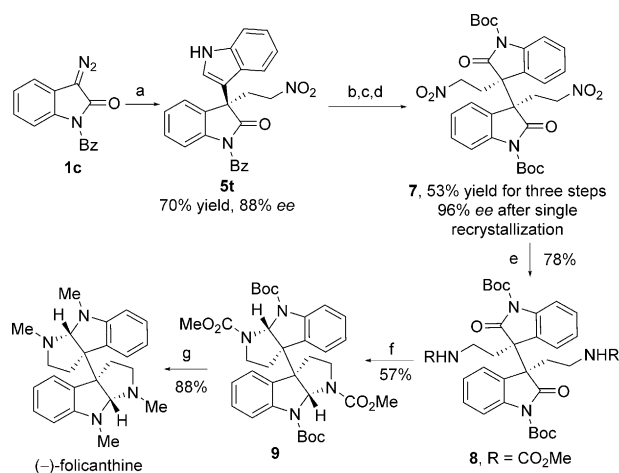
The aforementioned observations and conclusions clearly suggested two catalytic cycles (Scheme 2). The reaction of **2a** with the in situ generated metal carbenoid **E** allowed formation of the zwitterion **F** which underwent a fast proton-transfer process to provide **6** rather than being directly



Scheme 2. Proposed relay catalytic cycles.

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**.

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 [Rh₂(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/Na₂CO₃ in THF successfully resulted in a Boc-protected bis(oxindole) intermediate (see the Supporting Information), which could be further transformed into **7** by a diastereoselective Michael addition with nitro-



Scheme 3. Total synthesis of (–)-folicanthine. Conditions: a) indole, nitroethylene, [Rh₂(OAc)₄] (1.0 mol%), **4c** (5.0 mol%), CH₂Cl₂, RT; b) conc. HCl, HOAc, DMSO, 50 °C; c) (Boc)₂O, Na₂CO₃, THF, RT; d) nitroethylene, Mg(OAc)₂·4 H₂O (5 mol%), benzoic acid, THF, 50 °C; e) NiCl₂/NaBH₄, methyl dicarbonate, MeOH, 0 °C–RT; f) LiEt₃H, 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 ¹H 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.

Received: June 10, 2014

Revised: July 2, 2014

Published online: August 21, 2014

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

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