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Received ooth January 2012, Accepted ooth January 2012 Xing Guang Li,<sup>*a*</sup> Min Sun,<sup>*a*</sup> Kai Liu,<sup>*a*</sup> Qiao Jin<sup>*a*</sup> and Pei Nian Liu<sup>*a*,\*</sup>

benzamides and diazo compounds to form

isocoumarins and  $\alpha$ -pyrones

Rh(III)-catalyzed C-H activation/cyclization of

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Rhodium-catalyzed intermolecular cyclization of benzamides and diazo compounds via C–H activation has been achieved to construct C–C/C–O bonds for the first time. The process provides a facile approach for the construction of isocoumarins and  $\alpha$ -pyrones without the need of high temperature or adding oxidant.

Rhodium-catalyzed C-H activation/cyclization has emerged as a powerful and promising tool for the construction of diversified heterocyclic systems in organic synthesis.<sup>1</sup> As good partners for C-H activation coupling or cyclization, diazo compounds are easily prepared, stable and reactive and therefore widely used in synthetic organic chemistry.<sup>2</sup> In 2012, Yu developed the first example of Rh(III)-catalyzed intermolecular cross-coupling of diazomalonates with arene C-H bonds.3 After this pioneering work, Li, 4a Wang,4b Yi,4c Chang4d and Zhou4e reported studies on Rh(III)-catalyzed cross-coupling of diazomalonates with arene C-H. Notably, Rovis and co-workers uncovered the cyclization of benzamides and diazo compounds to construct y-lactams via Rh(III)-catalyzed C-C/C-N bonds formation (Scheme 1, eq. 1).<sup>5</sup> Even more recent examples of Rh(III)-catalyzed cyclization using diazo compounds coupling/cyclization partners have come from the groups of Glorius,  $^6$  Cui,  $^7$  Cramer,  $^8$  Wang,  $^9$  Yu $^{10}$  and Yi,  $^{11}$  but all these elegant transformations are restricted to C-C/C-N bonds formation to generate N-heterocycles such as isoindolinones, isoquinoline Noxides, azepinones and 1-aminoindoles (Scheme 1, eq. 2).<sup>6-11</sup> To the best of our knowledge, C-C/C-O bonds formation via Rh(III)catalyzed C-H activation/cyclization of aromatics with diazo compounds has not been reported yet.

Isocoumarin and  $\alpha$ -pyrone are important structural motifs in many pharmaceuticals because of their various biological and medicinal activities.<sup>12</sup> However, their synthesis frequently requires specific pre-activated C–X or C–M reagents as substrates.<sup>13</sup> Oxidative annulations of aryl carboxylic acids and alkynes can be achieved in the presence of Rh,<sup>14</sup> Ru<sup>15</sup> or Ir<sup>16</sup> catalyst, but these reactions require stoichiometric oxidants and high temperatures above 100 °C.

As part of our continuing efforts in heterocycle construction,<sup>17</sup> we report here a mild procedure for generating various isocoumarins and  $\alpha$ -pyrones. The process involves Rh(III)-catalyzed C–H activation of benzamides and subsequent intermolecular cyclization

with diazo compounds via C–C/C–O bonds formation (Scheme 1, eq. 3).

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**Scheme 1** Rh(III)-catalyzed C–H activation/cyclization using diazo compounds as cyclization partners.

Initially, N.N-dimethylbenzamide was treated with *tert*-butyl 2-diazo-3-oxobutanoate (2a) in the presence of [Cp\*RhCl<sub>2</sub>]<sub>2</sub> (2.5 mol%), AgSbF<sub>6</sub> (10 mol%) and AcOH (2.0 equiv.) in DCE at 100 °C for 12 h. We were pleased to obtain the unexpected isocoumarin derivative 3a in 8% yield, and its structure was fully characterized and confirmed by the single crystal X-ray analysis (see ESI, CCDC: 1035334). Then we screened various amido groups to determine whether they played a significant role in this novel cyclization reaction (Table 1, entries 2-7). The pyrrolidinyl group performed much better than any other groups we tested. The catalysts  $[Cp*Rh(CH_3CN)_3](SbF_6)_2$  and [Cp\*RhCl<sub>2</sub>]<sub>2</sub> showed similar activity, whereas Cp\*Rh(OAc)<sub>2</sub>, Pd(OAc)<sub>2</sub> or [RuCl<sub>2</sub>(p-cymene)]<sub>2</sub> showed little or even no activity in this transformation (entries 8-11). Therefore we selected [Cp\*RhCl<sub>2</sub>]<sub>2</sub> as the catalyst and investigated various additives (entries 12-18). AcOH promoted the reaction to 54% yield, while Ac<sub>2</sub>O led to better 66% yield. Using a 4:1 mixture of Ac<sub>2</sub>O/AcOH improved the yield to 77%. Lowering the temperature further increased the yield to 87% (entry 20). The further result demonstrated that the reaction could also be

conducted under air atmosphere with **3a** giving 72% yield (entry 22). Once conditions had been optimized, scaling up the reaction proved straightforward to afford product **3a** in 74% isolated yield (0.58 g, entry 23).

Table 1 Optimization of reaction conditions<sup>a</sup>.

	0 R +	O O 'Bu	Catalyst, AgSbF <sub>6</sub> Additive DCE, 100 °C	O CO2'Bu
	1	2a		3a
Entry	R	Catalyst	Additive (equiv)	Yield $(\%)^b$
1	NMe <sub>2</sub>	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	AcOH (2.0)	8
2	NEt <sub>2</sub>	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	AcOH (2.0)	0
3	NHOMe	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	AcOH (2.0)	Trace
4	piperidinyl	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	AcOH (2.0)	6
5	morpholinyl	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	AcOH (2.0)	7
6	N(OMe)Me	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	AcOH (2.0)	9
7	pyrrolidinyl	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	AcOH (2.0)	52
$8^c$	pyrrolidinyl	[Cp*Rh(CH <sub>3</sub> C	AcOH (2.0)	49
		$N_{3}](SbF_{6})_{2}$		
9	pyrrolidinyl	$Cp*Rh(OAc)_2$	AcOH (2.0)	Trace
10	pyrrolidinyl	$Pd(OAc)_2$	AcOH (2.0)	0
11	pyrrolidinyl	[RuCl <sub>2</sub> (p-	AcOH (2.0)	Trace
		cymene)] <sub>2</sub>		
12	pyrrolidinyl	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	TFA (2.0)	Trace
13	pyrrolidinyl	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	AgOAc (2.0)	0
14	pyrrolidinyl	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	NaOAc (2.0)	24
15	pyrrolidinyl	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	KOAc (2.0)	21
16 <sup>a</sup>	pyrrolidinyl	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	AcOH (2.0)	54
17 <sup>a</sup>	pyrrolidinyl	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	$(Ac)_2O(2.0)$	66
18 <sup>a</sup>	pyrrolidinyl	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	$(Ac)_2O(1.6), AcOH(0.4)$	77
19 <sup><i>a</i>,<i>e</i></sup>	pyrrolidinyl	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	$(Ac)_2O(1.6), AcOH(0.4)$	81
$20^{a_{J}}$	pyrrolidinyl	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	$(Ac)_2O(1.6), AcOH(0.4)$	87
$21^{a,g}$	pyrrolidinyl	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	$(Ac)_2O(1.6), AcOH(0.4)$	25
$22^{a,j,n}_{a,j,i}$	pyrrolidinyl	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	$(Ac)_2O(1.6), AcOH(0.4)$	72
$23^{a,j,i}$	pyrrolidinyl	[Cp*RhCl <sub>2</sub> ] <sub>2</sub>	$(Ac)_2O(1.6), AcOH(0.4)$	74

<sup>*a*</sup> Reaction conditions: **1** (0.3 mmol), **2a** (0.6 mmol), catalyst (2.5 mol%), AgSbF<sub>6</sub> (10 mol%), DCE (2 mL), 100 °C, 12 h, under N<sub>2</sub>. <sup>*b*</sup> Yields based on <sup>1</sup>H NMR analysis using phenyltrimethylsilane as the internal standard. <sup>*c*</sup> 5.0 mol% catalyst was used. <sup>*d*</sup> **1a** (0.6 mmol) and **2a** (0.3 mmol) were used. <sup>*e*</sup> At 80 °C. <sup>*f*</sup> At 60 °C. <sup>*g*</sup> At 40 °C. <sup>*h*</sup> Under air atomosphere. <sup>*i*</sup> Performed on a 3.0 mmol scale; isolated yield was shown.

After optimizing reaction conditions, we explored the scope of the substrates for this Rh(III)-catalyzed C-H activation/cyclization reaction of benzamides and diazo compounds (Table 2). Various 1benzoylpyrrolidines 1 substituted at the para-position with electrondonating substituents (-Me, -OMe, -NMe<sub>2</sub>) reacted smoothly to afford the desired products 3b-d in excellent 83-93% yields. In contrast, substrates with strong electron-withdrawing groups (-CF<sub>3</sub>, -NO<sub>2</sub>) at the same position inhibited the reaction, affording products 3h and 3i in lower respective yields of 64% and 63%. Nevertheless, substrates with halo-substituents (-F, -Cl, -Br) at the same position reacted smoothly with 2a to afford the corresponding products 3e-g in 78-90% yields. Ortho-methyl-substituted benzamide also participated in the reaction, providing the desired product 3j in good yield. Interestingly, coupling-cyclization of meta-fluoro-substituted benzamide and 2a occurred exclusively at the less sterically hindered position of the benzamide, generating 3k in 68% yield. Moreover, C-H annulation involving 3,4-dichloro-substituted benzamide occurred at the less hindered position, generating 31 as the single isomer in low yield. Naphthalene and heterocyclic derivatives were also well tolerated in this transformation, and moderate to good yields of the corresponding products 3m and 3n were obtained.

To further evaluate the scope of the C–H activation/cyclization process, a range of diazo compounds 2 were reacted with 1a to form various isocoumarin products. Diazo substrates bearing alkyl groups such as methyl, *n*-propyl, chloromethyl, *i*-propyl and cyclopropyl

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afforded the corresponding products **30-s** in 74-81% yields, except low yield of 34% for **3q**. Similarly, aryl-substituted substrates reacted under the optimal conditions to provide products **3t** and **3u** in excellent yields. Interestingly, the reaction of **11a** with **2**-tila20 substituted 1,3-dione substrates also proceeded to afford the corresponding products **3v** and **3w** in 38% and 93% yield, respectively.

Notably, the annulation reaction with **2a** tolerated the alkenyl substrate, producing  $\alpha$ -pyrone **4a** in 76% yield. Employing 2-methyl-1-(pyrrolidin-1-yl)prop-2-en-1-one as the substrate to explore with different diazo compounds provided various  $\alpha$ -pyrones **4b-4g** in moderate to good yields. However, other alkenyl substrates such as ethenyl, (*E*)-(2-methyl)-ethenyl, (*E*)-(2-phenyl)-ethenyl and cyclohexenyl substrates showed much less or even no reactivity with **2a** in the reaction.

 Table 2 Rh(III)-catalyzed C-H activation/cyclization of benzamides

 1 and diazo compounds 2.



 $^a$  Reaction conditions: 1 (0.6 mmol), 2 (0.3 mmol), [Cp\*RhCl<sub>2</sub>]<sub>2</sub> (2.5 mol%), AgSbF<sub>6</sub> (10 mol%), DCE (2 mL), 60  $^o$ C, 12 h, under N<sub>2</sub>.

To gain insight into the mechanism of this transformation, we conducted several control experiments. The competition experiment

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between differently 4-substituted (4-OMe and 4-CF<sub>3</sub>) benzamides was carried out under standard conditions and gave the products 3c in 77% yield and 3h 10% yield. The results showed the electrondonating substituent of the benzamide is beneficial for this transformation (Scheme 2, eq. 1). Then the reaction of 2a with the same amounts of both 1a and 1a-d5 was explored under standard conditions for 30 min. A significant KIE value of 3.5 was measured based on <sup>1</sup>H NMR analysis (Scheme 2, eq. 5). Moreover, separate reactions of 2a with either 1a or  $1a-d_5$  were performed in parallel, and a similar KIE value of 2.7 was obtained (Scheme 2, eq. 6). These results suggest that C-H cleavage may be involved in the ratedetermining step. Moreover, when we mixed diethyl 2diazomalonate 2b with 1a under standard conditions, the reaction did not proceed (Scheme 2, eq. 7). This suggests that the final lactonization of ketone plays a vital role in the coupling/cyclization cascade transformation.



**Scheme 2** Mechanistic studies for the C–H activation/cyclization of benzamides and diazo compounds.

On the basis of these observations and literature precedents,<sup>1, 3-11</sup> a plausible mechanism is proposed (Scheme 3). Firstly, the *o*- C–H of **1a** is cleaved directly by the Cp\*RhX<sub>2</sub> species to afford intermediate **A**,<sup>18</sup> followed by the formation of the Rh(III)-carbene species **B**. Then, migration insertion of the carbene into the Rh–C bond gives the six-membered rhodacyclic intermediate **C**, which can tautomerize to intermediate **D**. Finally, Rh- or Ag-assisted lactonization via addition-elimination furnishes the product **3** or **4** with the release of pyrrolidine (detected by GC-MS). However, another possible process where the intermediate **C** can be protonated by acetic acid along with the regeneration of the Rh catalyst and **E**.<sup>9</sup> Then product **3** or **4** could be produced through the enolization and esterification.

In summary, we have developed the first Rh(III)-catalyzed C–H activation/cyclization of benzamides with diazo compounds to form C–C/C–O bonds, generating useful isocoumarins and  $\alpha$ -pyrones under mild conditions. In this strategy, the amide functions efficiently as the directing group in C–H activation, constraining the substrates to undergo formation of an intermolecular C–C bond and an intramolecular C–O bond. Diverse substrates were applied in this transformation to produce various isocoumarins and  $\alpha$ -pyrones in moderate to good yields. We believe the results will inspire the use

of C-H activation/cyclization to construct heterocycles in a variety of future applications.



**Scheme 3** Plausible reaction mechanism for the C–H activation/cyclization of benzamides and diazo compounds.

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## Notes and references

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- For reviews on Rh(III) catalyzed C–H activation, see: (a) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624;
   (b) T. Satoh and M. Miura, *Chem. Eur. J.*, 2010, **16**, 11212; (c) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (d) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814; (e) G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651; (f) N. Kuhl, N. Schröder and F. Glorius, *Adv. Synth. Catal.*, 2014, **356**, 1443.
- 2 (a) T. Ye and M. A. McKervey, *Chem. Rev.*, 1994, 94, 1091; (b) M. P. Doyle, M. A. McKervey and T. Ye, *Wiley: New York*, 1998; (c) Z. Zhang and J. Wang, *Tetrahedron*, 2008, 64, 6577; (d) Q. Xiao, Y. Zhang and J. Wang, *Acc. Chem. Res.*, 2013, 46, 236.
- 3 W.-W. Chan, S.-F. Lo, Z. Zhou and W.-Y. Yu, J. Am. Chem. Soc., 2012, 134, 13565.
- 4 (a) X. Yu, S. Yu, J. Xiao, B. Wan and X. Li, *J. Org. Chem.*, 2013, 78, 5444; (b) F. Hu, Y. Xia, F. Ye. Z. Liu, C. Ma, Y. Zhang and J. Wang, *Angew. Chem. Int. Ed.*, 2014, 53, 1364; (c) J. Shi, Y. Yan, Q. Li, H. E.

1 2

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Xu and W. Yi, *Chem. Commun.*, 2014, **50**, 6483; (d) J. Jeong, P. Patel, H. Hwang and S. Chang, *Org. Lett.*, 2014, **16**, 4598; (e) W. Ai, X. Yang, Y. Wu, X. Wang, Y. Li, Y. Yang and B. Zhou, *Chem. Eur. J.*, 2014, DOI: 10.1002/chem.201405077.

- 5 T. K. Hyster, K. E. Ruhl and T. Rovis, J. Am. Chem. Soc., 2013, 135, 5364.
- 6 Z. Shi, D. C. Koester, M. Boultadakis-Arapinis and F. Glorius, J. Am. Chem. Soc., 2013, 135, 12204.
- 7 S. Cui, Y. Zhang, D. Wang and Q. Wu, Chem. Sci., 2013, 4, 3912.
- 8 B. Ye and N. Cramer, Angew. Chem. Int. Ed., 2014, 53, 7896.
- 9 Y. Liang, K. Yu, B. Li, S. Xu, H. Song and B. Wang, Chem. Commun., 2014, 50, 6130.
- 10 H.-W. Lam, K.-Y. Man, W.-W. Chan, Z. Zhou and W.-Y. Yu, Org. Biomol. Chem., 2014, 12, 4112.
- 11 J. Shi, J. Zhou, Y. Yan, J. Jia, X. Liu, H. Song, H. E. Xu and Wei Yi, *Chem. Commun.*, 2015, DOI: 10.1039/C4CC08407A.
- (a) R. D. Barry, *Chem. Rev.*, 1964, 64, 229; (b) H. Matsuda, H. Shimoda, and M. Yoshikawa, *Bioorg. Med. Chem.*, 1999, 7, 1445; (c) R. S. Mali and K. N. Babu, *J. Org. Chem.*, 1998, 63, 2488; (d) H. Zhang, H. Matsuda, A. Kumahara, Y. Ito, S. Nakamura and M. Yoshikawa, *Bioorg. Med. Chem. Lett.*, 2007, 17, 4972; (e) S. Pal, V. Chatare and M. Pal, *Curr. Org. Chem.*, 2011, 15, 782.
- Selected references: (a) R. C. Larock, M. J. Doty and X. Han, J. Org. Chem., 1999, 64, 8770; (b) T. Yao and R. C. Larock, J. Org. Chem., 2003, 68, 5936; (c) D. K. Rayabarapu, P. Sukula and C.-H. Cheng, Org. Lett., 2003, 5, 4903; (d) K. Cherry, J. L. Parrain, J. Thibonnet, A. Duchene and M. Abarbri, J. Org. Chem., 2005, 70, 6669; (e) M. Lessi, T. Masini, L. Nucara, F. Bellina and R. Rossi, Adv. Synth. Catal., 2011, 353, 501; (f) J. Luo, Y. Lu, S. Liu, J. Liu and G. J. Deng, Adv. Synth. Catal., 2011, 353, 2604.
- (a) K. Ueura, T. Satoh and M. Miura, *Org. Lett.*, 2007, 9, 1407; (b) K. Ueura, T. Satoh and M. Miura, *J. Org. Chem.*, 2007, 72, 5362; (c) M. Shimizu, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2009, 74, 3478; (d) S. Mochida, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2009, 74, 6295; (f) X. G. Li, K. Liu, G. Zou and P. N. Liu, *Adv. Synth. Catal.*, 2014, 356, 1496.
- (a) L. Ackermann, J. Pospech, K. Graczyk and K. Rauch, *Org. Lett.*, 2012, **14**, 930; (b) R. K. Chinnagolla and M. Jeganmohan, *Chem. Commun.*, 2012, **48**, 2030.
- 16 D. A. Frasco, C. P. Lilly, P. D. Boyle and E. A. Ison, ACS Catal., 2013, 3, 2421.
- 17 (a) D. Y. Li, X. F. Mao, H. J. Chen, G. R. Chen and P. N. Liu, Org. Lett., 2014, 16, 3476; (b) D. Y. Li, H. J. Chen and P. N. Liu, Org. Lett., 2014, 16, 6176; (c) H. X. Siyang, X. R. Wu, X. Y. Ji, X. Y. Wu and P. N. Liu, Chem. Commun., 2014, 50, 8514; (d) X. G. Li, K. Liu, G. Zou and P. N. Liu, Eur. J. Org. Chem. 2014, 7878; (e) D. Y. Li, X. S. Shang, G. R. Chen and P. N. Liu, Org. Lett., 2013, 15, 3848.
- 18 F. Wang, Z. Qi, J. Sun, X. Zhang and X. Li, Org. Lett., 2013, 15, 6290.

View Article Online DOI: 10.1039/C4CC09314C

4 | J. Name., 2012, 00, 1-3