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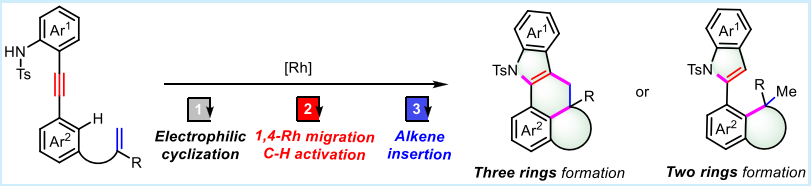
Synthesis of Indole-Fused Polycyclics via Rhodium-Catalyzed Undirected C−H Activation/Alkene Insertion

Songjin Guo, Rui Pan, Zhe Guan, Panpan Li, Libo Cai, Siwei Chen, Aijun Lin,* and Hequan Yao*

Department of Medicinal Chemistry, School of Pharmacy and State Key Laboratory of Natural Medicines (SKLNM), China Pharmaceutical University, Nanjing 210009, P.R. China

Supporting Information



ABSTRACT: A Rh(III)-catalyzed undirected C−H activation/alkene insertion to synthesize diversified indole-fused polycyclics has been developed. Intramolecular electrophilic cyclization generated a 3-indolyl rhodium species that went through an aryl-to-aryl 1,4-rhodium migration to realize the C−H activation. The subsequent [4 + 2] carboannulation or hydroarylation of alkenes could be achieved, respectively, by simply adjusting the additives of the reaction.

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Transition-metal-catalyzed C−H activation/alkene insertion has been widely applied for the synthesis of functional molecules and complex cyclic compounds,[1] which could efficiently circumvent the multistep preparation of the preactivated starting materials, rendering the overall reaction atom and step economical. Recently, Glorius,[2] Guimond,[3] Rovis,[4] Cramer,[5] and Wang[6] have independently described a rhodium- or ruthenium-catalyzed C−H activation/[4 + 2] annulation of alkenes to access the six-membered aza-heterocycles with imines or amides as the directing groups (DGs) (Figure 1a). Moreover, a cobalt-catalyzed carboxylate-directed C−H activation/alkene insertion of benzoic acids and alkenes has been realized by Daugulis's group (Figure 1a).[7] Inspired by Murai's pioneering work on the ruthenium-catalyzed cross-coupling reaction between aromatic ketones and alkenes,[8] heteroatom chelation-assisted C−H activation/hydroarylation of alkenes has been extensively studied in the last two decades (Figure 1b).[9] However, in these previous works, the directing groups were necessary, which could well guarantee the C−H activation. To the best of our knowledge, the undirected C−H activation/alkene insertion,[10] especially the annulation or hydroarylation, has rarely been achieved until now (Figure 1c).

Indole-fused polycyclic scaffolds widely exist in natural products and pharmaceuticals with diverse bioactivities[11] and are utilized in organic synthesis.[12] Nevertheless, most of the existing methods to construct these frameworks either employed elaborately prefunctionalized indoles as the reactants or underwent multistep and complicated process.[13] Thus, exploring a practical and effective method to rapidly assemble them is still highly desirable, yet challenging. Based on our continuous interest in alkene functionalization,[14] herein we disclose an unprecedented rhodium(III)-catalyzed undirected C−H activation/alkene insertion reaction to synthesize diversified indole-fused polycyclics in high atom and step economy (Figure 1d). In this transformation, the in situ generated 3-indolyl rhodium species via rhodium-catalyzed cyclization of 2-ethynylanilines undergoes an aryl-to-aryl 1,4-rhodium migration to achieve the C−H activation, affording an aryl rhodium species, which could add across the alkenes to realize the [4 + 2] carboannulation or hydroarylation of alkenes by simply adjusting the additives of the reaction.

We initiated our investigation with 2-alkynylaniline **1a** as the model substrate (see the Supporting Information (SI) for details). Using $[Cp^*RhCl_2]_2$ (5.0 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv) in DMAC under argon atmosphere, the [4 + 2] carboannulation product **3a** and the hydroarylation product **4a** were achieved in 45% and 28% yields (Table 1, entry 1). The structures of the products **3a** and **4a** were determined by single-crystal X-ray analysis (see the SI for details). To our delight, when the reaction was operated with 0.3 equiv of $Cu(OAc)_2{\cdot}H_2O$ under oxygen atmosphere, product **3a** could be obtained in a yield up to 82% (Table 1, entry 2).[15] Other copper salts, such as CuOAc, CuTc, or $Cu(eh)_2$, impacted the yield of product **3a** (Table 1, entries 3−5), and $Cu(TFA)_2$ significantly inhibited the reaction (Table 1, entry 6). Diversity-oriented synthesis (DOS) is of obvious value in synthetic organic chemistry, which has been identified as an efficient strategy for achieving structural complexity and molecular diversity with the same starting materials. We then looked for appropriate reaction conditions to synthesize product **4a** (Table 1, entries 7−12). Product **4a** could be achieved in 68% yield when NaOAc was tested under argon atmosphere (Table 1, entry 7). Other additives, such as

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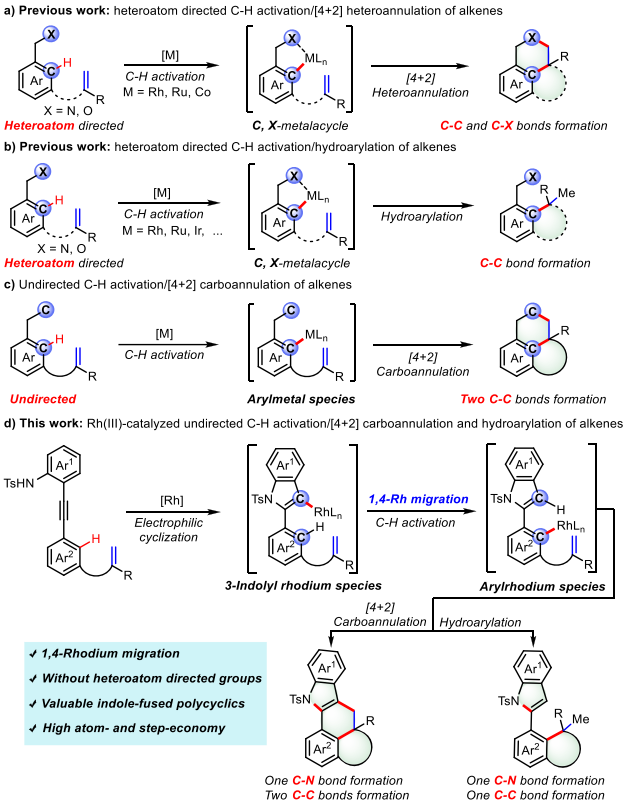
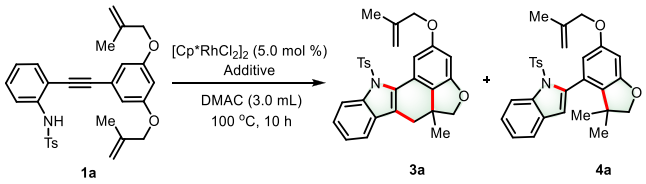


Figure 1. Transition-metal-catalyzed C−H activation/alkene insertion.

Table 1. Screening of Reaction Conditions[a]



entry	additive (equiv)	atmosphere	3a yield[b] (%)	4a yield[b] (%)
1	$Cu(OAc)_2·H_2O$ (2.1)	Ar	45	28
2	**$Cu(OAc)_2·H_2O$ (0.3)**	**O_2 (1 atm)**	**82**	**ND**[c]
3	CuOAc (0.3)	O_2 (1 atm)	70	ND
4	CuTc (0.3)	O_2 (1 atm)	63	ND
5	$Cu(eh)_2$ (0.3)	O_2 (1 atm)	52	ND
6	$Cu(TFA)_2$ (0.3)	O_2 (1 atm)	trace	ND
7	NaOAc (2.1)	Ar	ND	68
8	CsOAc (2.1)	Ar	ND	23
9	AgOAc (2.1)	Ar	ND	trace
10	AgTFA (2.1)	Ar	ND	trace
11	K_3PO_4 (2.1)	Ar	ND	trace
12[d]	**NaOAc (2.1)**	**Ar**	**ND**	**75**

[a]Reaction conditions: **1a** (0.05 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol %), additive (2.1 equiv), DMAC (3.0 mL), 100 °C (oil bath temperature), 10 h. [b]Isolated yields. [c]ND = not determined. [d]80 °C. CuTc = copper(I) thiophene-2-carboxylate; $Cu(TFA)_2$ = copper(II) trifluoroacetate; $Cu(eh)_2$ = copper(II) 2-ethylhexanoate.

CsOAc, AgOAc, AgTFA, and K_3PO_4, were less effective (Table 1, entries 8−11). By reducing the temperature to 80 °C, the yield of the product **4a** could be further increased to 75% (Table 1, entry 12).

Subsequently, we sought to explore the scope and generality of the reaction (Scheme 1). The products **3b−h** with various substituents at the C4- or C5-position of the phenyl ring were achieved in 51−75% yields (Scheme 1a). The *N*-mesyl-protected 2-ethynylaniline **1i** could also participate to offer **3i** in 40% yield. To further increase the molecular diversity, we then embarked on the modification of the alkene moiety (Scheme 1b). The products **3j** and **3k** were obtained in slightly low yields due to the steric effect of the olefins. In addition to forming indole-fused dihydrobenzofurans, other intriguing indole-fused heterocycles, such as indole-fused dihydropyrans **3l** and **3m**, indole-fused isochroman **3n**, and indole-fused benzofuranone **3o** were all achieved in moderate to good yields by altering the alkene chains.

Controlling the regioselectivity of the C−H activation with similar characteristic is always a meaningful and challenging task in organic synthesis. To our delight, when the C-8 position of the benzene ring was fixed with different substituents, such as alkanes, esters, ethers and *tert*-butyldimethylsilyl (TBDMS) ether, the products **3p−w** could be generated exclusively in good efficiency (Scheme 1c).

The scope of hydroarylation products **4** was then investigated (Scheme 1d). The products **4b−e** with methyl, methoxy, and ester groups on the C4- or C5-position of the anilines were isolated in moderate to good yields. *N*-Mesyl-protected 2-ethynylaniline **1f** also performed well to give the product **4f** in 70% yield. The substrate **1g** with an unsymmertic phenyl unit provided the product **4g** in 54% yield. Increasing the steric hindrance of the alkenes caused a slight decrease in reactivity, offering products **4h** and **4i** in 57% and 50% yield, respectively. Furthermore, the indole-fused chroman **4j** could also be reliably synthesized in moderate yield.

To gain insight into the transformation, various control experiments were then performed (Scheme 2). First, the potential intermediate **2a** was synthesized and examined under conditions A or B, while no desired product **3a** or **4a** was observed (Scheme 2a,b). These results ruled out the possibility of **2a** as the intermediate of the reaction. When compound **5** reacted with allyltrimethylsilane **6** or diazo compound **8**, only product **7** or **9** was achieved (Scheme 2c,d). It should be noted that the indole C3-functionalized products were not detected. These two intermediate capturing experiments indicated the existence of aryl rhodium species, which could be generated from 3-indolyl rhodium species via an aryl-to-aryl 1,4-rhodium migration process. When **1p** was subjected to conditions A in the presence of 0.3 mL of D_2O, the compounds $[D]_n$-**2p** and $[D]_1$-**3p** with deuterium installed on the benzene ring B or C were observed (Scheme 2e), which further demonstrated the existence of 3-indolyl rhodium species and aryl rhodium species, and the process of 1,4-rhodium migration was reversible. In conditions B, $[D]_n$-**4a** with deuterium incorporated on the methyl group was detected when the reaction was quenched by D_2O (Scheme 2f); this result indicated that an alkyl rhodium species was formed. The kinetic isotope effect (KIE) experiment between **1a** and D_3-**1a** suggested that the C−H activation was not involved in the rate-limiting step (Scheme 2g).

On the basis of the above experiment results and previous reports,[2−9] a plausible pathway is proposed (Scheme 2h). Initially, the active rhodium(III) species promotes the intramolecular electrophilic cyclization of the nitrogen and the alkyne, furnishing the 3-indolyl rhodium intermediate **II**.[16] Subsequently, the aryl-to-aryl 1,4-rhodium migration occurs to

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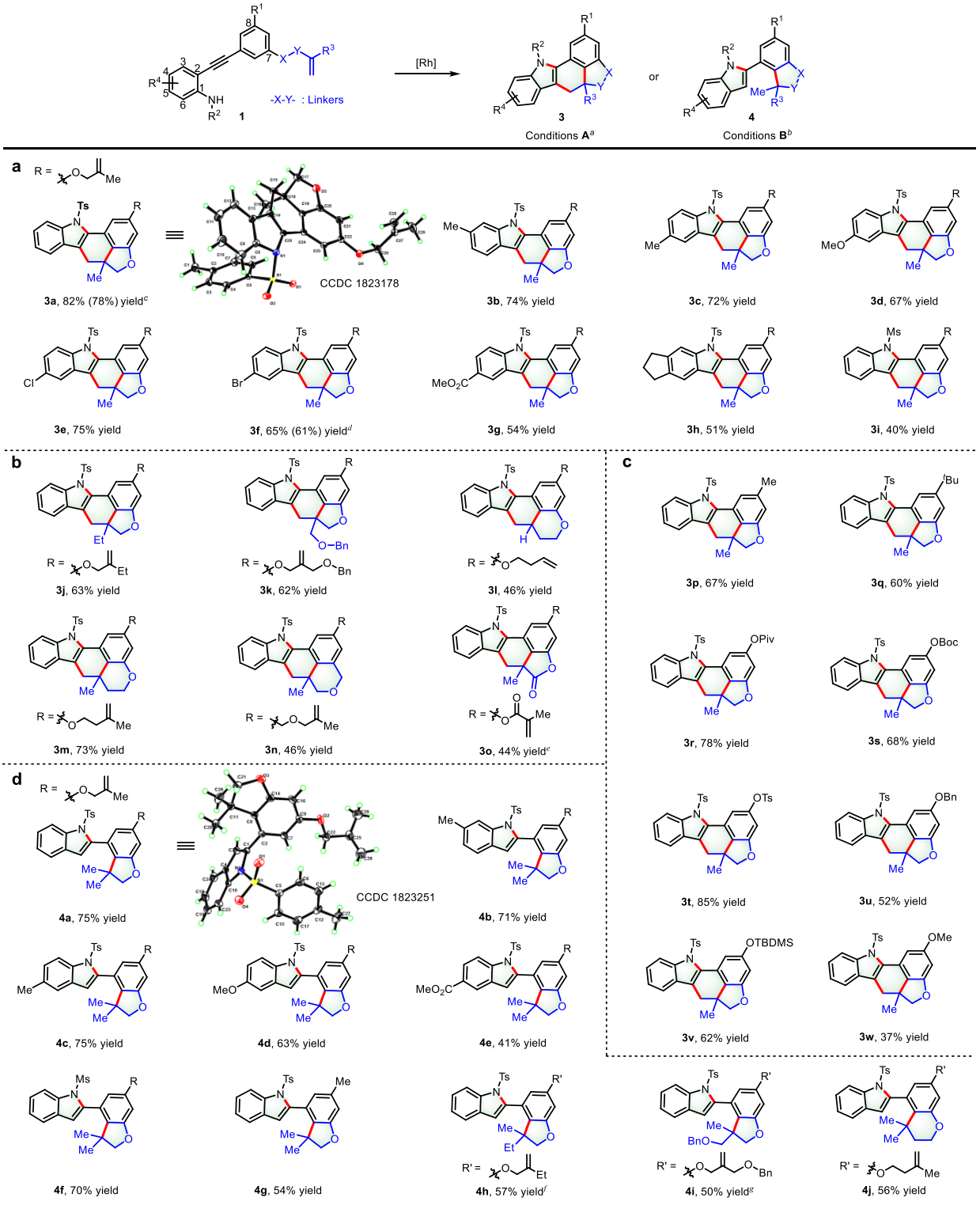
Scheme 1. Substrate Scope*



*(a–c) Substrate scope of the [4 + 2] carboannulation of alkenes. (d) Substrate scope of the hydroarylation of alkenes. [a]Reaction conditions A: **1** (0.05 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol %), $Cu(OAc)_2{\cdot}H_2O$ (30.0 mol %), DMAC (3.0 mL), 100 °C (oil bath temperature) under oxygen atmosphere, 10 h. [b]Reaction conditions B: **1** (0.05 mmol), $[Cp^*RhCl_2]_2$ (5.0 mol %), NaOAc (2.1 equiv), DMAC (3.0 mL), 80 °C (oil bath temperature) under argon atmosphere, 10 h. All cited yields are isolated yields. [c]4.0 mmol scale. [d]3.0 mmol scale. [e]70 °C. [f]dr = 2:1. [g]dr = 1.5:1.

fulfill the C–H bond activation,[17] affording the aryl rhodium species **III** or **IV**. Proto-demetalation of intermediate **II** will form the side products **2**, which could not reverse to generate intermediate **II** again. The alkene coordinates and inserts into the Rh–C bond of intermediate **III**, giving rise to the alkyl rhodium species **V**. In conditions A, the indole C3 C–H activation offers the seven-membered rhodacycle complex **VI**, which upon C–C reductive elimination provides the desired

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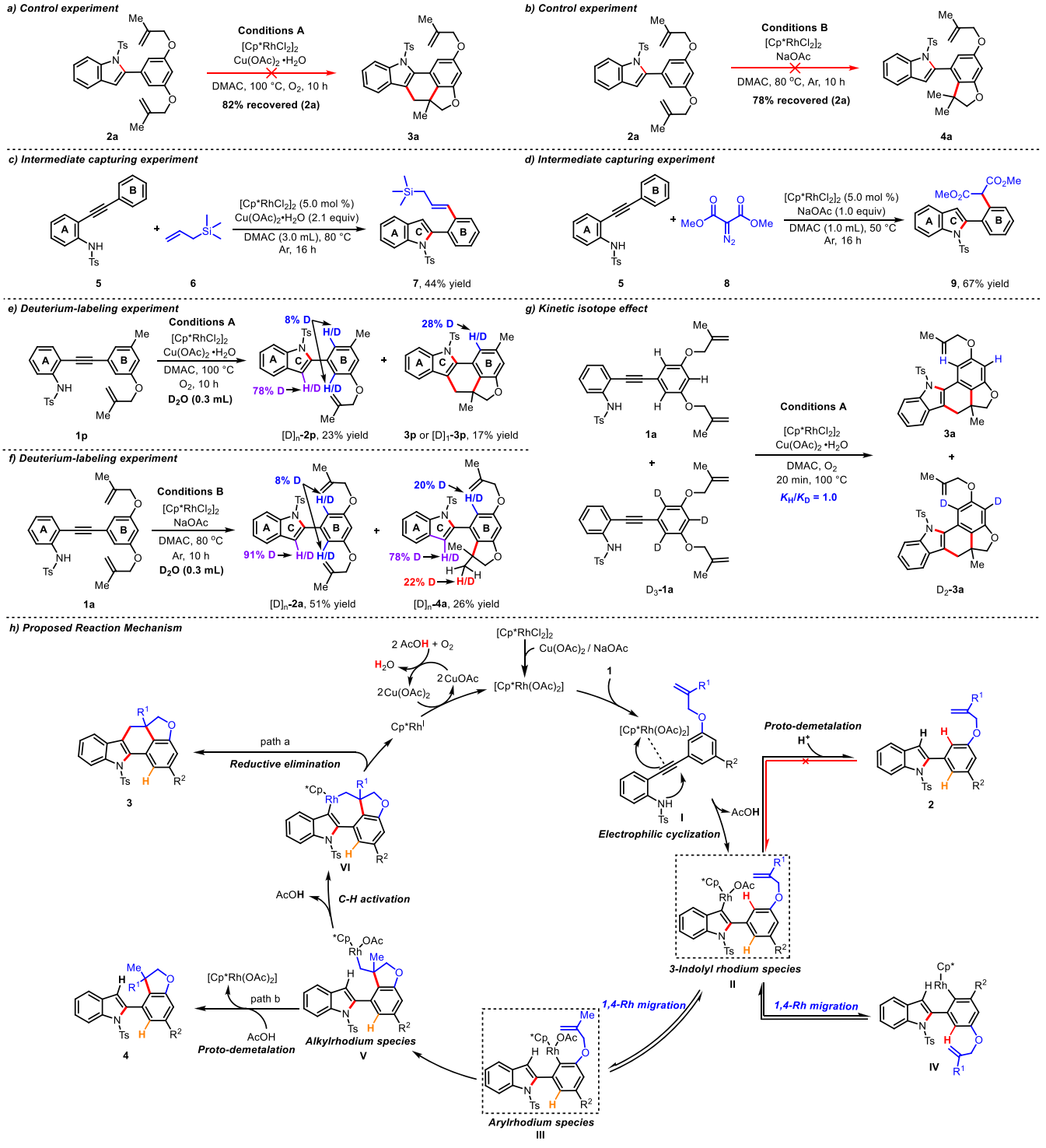
Scheme 2. Reaction Mechanism



products **3**. It is worth noting that the choice of $Cu(OAc)_2/O_2$ as the additives is crucial for the formation of products **3** because it could efficiently eliminate the HOAc to avoid the protonation process and oxidize the rhodium(I) species to regenerate the active rhodium(III) species simultaneously. In conditions B, the alkyl rhodium complex **V** undergoes direct proto-demetalation process to provide products **4** and regenerates the active rhodium(III) catalyst to the next catalytic cycle.

In conclusion, we have presented a convenient method for the divergent construction of indole-fused polycyclic frameworks via a rhodium(III)-catalyzed undirected C−H activation/alkene insertion reaction. The in situ generated 3-indolyl rhodium species enabled the C−H activation through an aryl-to-aryl 1,4-rhodium migration process. The resulting aryl rhodium added across the alkenes, realizing the [4 + 2] carboannulation of alkenes with $Cu(OAc)_2$ and O_2 as the additives and the hydroarylation of alkenes with NaOAc as the additive. The primary mechanism study revealed that the C−H

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activation might not be the rate-limiting step, and the process of 1,4-rhodium migration was reversible.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02198.

Full experimental details, characterization data of new compounds, and copies of NMR spectra (PDF)

Accession Codes

CCDC 1823178 and 1823251 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: hyao@cpu.edu.cn.
*E-mail: ajlin@cpu.edu.cn.

ORCID

Aijun Lin: 0000-0001-5786-4537
Hequan Yao: 0000-0003-4865-820X

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews, see: (a) Huang, H.; Ji, X.; Wu, W.; Jiang, H. *Chem. Soc. Rev.* **2015**, *44*, 1155. (b) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2016**, *55*, 10578. (c) Dong, Z.; Ren, Z.; Thompson, S. J.; Xu, Y.; Dong, G. *Chem. Rev.* **2017**, *117*, 9333.

(2) (a) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350. (b) Shi, Z.; Boultadakis-Arapinis, M.; Koester, D. C.; Glorius, F. *Chem. Commun.* **2014**, *50*, 2650.

(3) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449.

(4) (a) Hyster, T. K.; Knörr, L.; Ward, T. R.; Rovis, T. *Science* **2012**, *338*, 500. (b) Davis, T. A.; Hyster, T. K.; Rovis, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 14181. (c) Hyster, T. K.; Dalton, D. M.; Rovis, T. *Chem. Sci.* **2015**, *6*, 254. (d) Romanov-Michailidis, F.; Sedillo, K. F.; Neely, J. M.; Rovis, T. *J. Am. Chem. Soc.* **2015**, *137*, 8892. (e) Semakul, N.; Jackson, K. E.; Paton, R. S.; Rovis, T. *Chem. Sci.* **2017**, *8*, 1015. (f) Piou, T.; Romanov-Michailidis, F.; Romanova-Michaelides, M.; Jackson, K. E.; Semakul, N.; Taggart, T. D.; Newell, B. S.; Rithner, C. D.; Paton, R. S.; Rovis, T. *J. Am. Chem. Soc.* **2017**, *139*, 1296.

(5) (a) Ye, B.; Cramer, N. *Science* **2012**, *338*, 504−506. (b) Wodrich, M. D.; Ye, B.; Gonthier, J. F.; Corminboeuf, C.; Cramer, N. *Chem. - Eur. J.* **2014**, *20*, 15409.

(6) (a) Li, B.; Ma, J.; Wang, N.; Feng, H.; Xu, S.; Wang, B. *Org. Lett.* **2012**, *14*, 736. (b) Wu, J.-Q.; Zhang, S.-S.; Gao, H.; Qi, Z.; Zhou, C.-J.; Ji, W.-W.; Liu, Y.; Chen, Y.; Li, Q.; Li, X.; Wang, H. *J. Am. Chem. Soc.* **2017**, *139*, 3537.

(7) Nguyen, T. T.; Grigorjeva, L.; Daugulis, O. *Angew. Chem., Int. Ed.* **2018**, *57*, 1688.

(8) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.

(9) For selected examples, see: (a) Matsumoto, T.; Taube, D. J.; Periana, R. A.; Taube, H.; Yoshida, H. *J. Am. Chem. Soc.* **2000**, *122*, 7414. (b) Lail, M.; Arrowood, B. N.; Gunnoe, T. B. *J. Am. Chem. Soc.* **2003**, *125*, 7506. (c) Martinez, R.; Chevalier, R.; Darses, S.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 8232. (d) Martinez, R.; Simon, M.-O.; Chevalier, R.; Pautigny, C.; Genet, J.-P.; Darses, S. *J. Am. Chem. Soc.* **2009**, *131*, 7887. (e) Kakiuchi, F.; Kochi, T.; Mizushima, E.; Murai, S. *J. Am. Chem. Soc.* **2010**, *132*, 17741. (f) Davis, T. A.; Hyster, T. K.; Rovis, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 14181. (g) Kim, J.; Park, S.-W.; Baik, M.-H.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 13448.

(10) For selected examples (intermolecular reaction) of the undirected C−H activation/alkene insertion, see: (a) Vora, H. U.; Silvestri, A. P.; Engelin, C. J.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 2683. (b) Wang, P.; Verma, P.; Xia, G.; Shi, J.; Qiao, J. X.; Tao, S.; Cheng, P. T. W.; Poss, M. A.; Farmer, M. E.; Yeung, K.-S.; Yu, J.-Q. *Nature* **2017**, *551*, 489. (c) Chen, X.-Y.; Wu, Y.; Zhou, J.; Wang, P.; Yu, J.-Q. *Org. Lett.* **2019**, *21*, 1426.

(11) For selected reviews, see: (a) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278. (b) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73. (c) Brancale, A.; Silvestri, R. *Med. Res. Rev.* **2007**, *27*, 209. (d) Sharma, V.; Kumar, P.; Pathak, D. *J. Heterocycl. Chem.* **2010**, *47*, 491.

(12) For selected examples, see: (a) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1. (b) Zhang, H.; Wang, X.-N.; Lin, L.-P.; Ding, J.; Yue, J.-M. *J. Nat. Prod.* **2007**, *70*, 54. (c) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Nat. Prod. Rep.* **2013**, *30*, 694. (d) Showalter, H. D. H. *J. Nat. Prod.* **2013**, *76*, 455.

(13) For selected examples, see: (a) Vice, S. F.; Friesen, R. W.; Dmitrienko, G. I. *Tetrahedron Lett.* **1985**, *26*, 165. (b) Artis, D. R.; Cho, I.-S.; Jaime-Figueroa, S.; Muchowski, J. M. *J. Org. Chem.* **1994**, *59*, 2456. (c) Bi, Y.-Z.; Zhang, L. H.; Hamaker, L. K.; Cook, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 9027. (d) Jiricek, J.; Blechert, S. *J. Am. Chem. Soc.* **2004**, *126*, 3534. (e) Miller, K. A.; Martin, S. F. *Org. Lett.* **2007**, *9*, 1113. (f) Craig, D.; Goldberg, F. W.; Pett, R. W.; Tholen, N. T. H.; White, A. J. P. *Chem. Commun.* **2013**, *49*, 9275.

(14) (a) Yuan, Z.; Feng, Z.; Zeng, Y.; Zhao, X.; Lin, A.; Yao, H. *Angew. Chem., Int. Ed.* **2019**, *58*, 2884. (b) Han, C.; Fu, Z.; Guo, S.; Fang, X.; Lin, A.; Yao, H. *ACS Catal.* **2019**, *9*, 4196.

(15) For selected examples, see: (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (b) Yu, D.-G.; Suri, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 8802. (c) Zhang, T.-Y.; Liu, C.; Chen, C.; Liu, J.-X.; Xiang, H.-Y.; Jiang, W.; Ding, T.-M.; Zhang, S.-Y. *Org. Lett.* **2018**, *20*, 220.

(16) For selected examples, see: (a) Huang, J.; Macdonald, S. J. F.; Harrity, J. P. A. *Chem. Commun.* **2010**, *46*, 8770. (b) Byers, P. M.; Rashid, J. I.; Mohamed, R. K.; Alabugin, I. V. *Org. Lett.* **2012**, *14*, 6032. (c) Zhao, P.; Wang, F.; Han, K.; Li, X. *Org. Lett.* **2012**, *14*, 3400. (d) Ling, F.; Li, Z.; Zheng, C.; Liu, X.; Ma, C. *J. Am. Chem. Soc.* **2014**, *136*, 10914. (e) Mizukami, A.; Ise, Y.; Kimachi, T.; Inamoto, K. *Org. Lett.* **2016**, *18*, 748. (f) Hu, Z.; Tong, X.; Liu, G. *Org. Lett.* **2016**, *18*, 2058. (g) Sun, J.; Wang, K.; Wang, P.; Zheng, G.; Li, X. *Org. Lett.* **2019**, *21*, 4662. (h) Tian, M.; Bai, D.; Zheng, G.; Chang, J.; Li, X. *J. Am. Chem. Soc.* **2019**, *141*, 9527.

(17) For selected examples, see: (a) Oguma, K.; Miura, M.; Satoh, T.; Nomura, M. *J. Am. Chem. Soc.* **2000**, *122*, 10464. (b) Matsuda, T.; Shigeno, M.; Murakami, M. *J. Am. Chem. Soc.* **2007**, *129*, 12086. (c) Shintani, R.; Iino, R.; Nozaki, K. *J. Am. Chem. Soc.* **2014**, *136*, 7849. (d) Burns, D. J.; Lam, H. W. *Angew. Chem., Int. Ed.* **2014**, *53*, 9931. (e) Burns, D. J.; Best, D.; Wieczysty, M. D.; Lam, H. W. *Angew. Chem., Int. Ed.* **2015**, *54*, 9958. (f) Korkis, S. E.; Burns, D. J.; Lam, H. W. *J. Am. Chem. Soc.* **2016**, *138*, 12252. (g) Rahim, A.; Feng, J.; Gu, Z. *Chin. J. Chem.* **2019**, DOI: 10.1002/cjoc.201900180.

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Org. Lett. XXXX, XXX, XXX−XXX