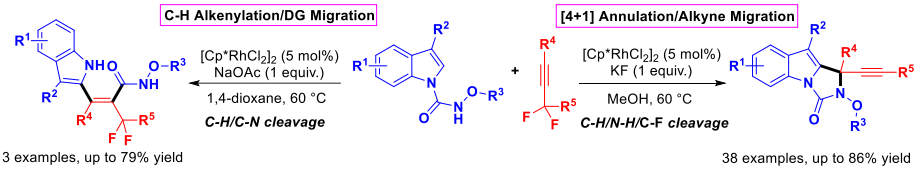
Rh(III)-Catalyzed Divergent Synthesis of Alkynylated Imidazo[1,5-*a*]indoles and α,α-Difluoromethylene Tetrasubstituted Alkenes

Fei Zhao,* Jin Qiao, Yangbin Lu, Xiaoning Zhang, Long Dai, Xin Gong, Hui Mao,* Shiyao Lu, Xiaowei Wu, and Siyu Liu*

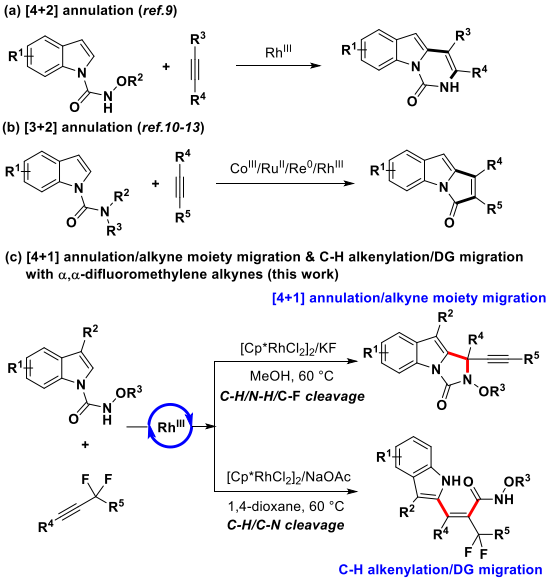
Supporting Information Placeholder



ABSTRACT: Herein, we report the divergent synthesis of alkynylated imidazo[1,5-*a*]indoles and α,α-difluoromethylene tetrasubstituted alkenes through Rh(III)-catalyzed [4+1] annulation/alkyne moiety migration and C–H alkenylation/DG migration, respectively. This protocol features tunable product selectivity, excellent chemo-, regio- and stereoselectivity, broad substrate scope, moderate to high yields, good tolerance of functional groups and mild redox-neutral conditions.

With the remarkable advances made in transition-metal (TM)-catalyzed C–H activations assisted by directing groups (DGs),[1] the direct C–H functionalizations of indoles,[2,3] which are the core structure of many natural products and active pharmaceutical ingredients,[4] have become a powerful tool for the direct modification of indoles, thus allowing the straightforward synthesis of structurally diverse and complex indole compounds from simple and readily available indole materials. Of note, TM-catalyzed C–H annulations of indoles[5] have become an efficient strategy for the assembly of indole-fused polyheterocycles, which are widely found in pharmaceutical agents.[6] In this context, *N*-carbamoyl indoles are popular substrates, not only because the carbamoyl directing group[7] is simple to install, but also because different annulation modes could be allowed. In particular, the C–H annulations of *N*-carbamoyl indoles with alkynes, a common and versatile coupling partner in C–H activations,[8] have contributed significantly to the synthesis of indole-fused polyheterocycles. The reported C–H annulation reactions between *N*-carbamoyl indoles and alkynes could be classified into two categories. (i) [4+2] annulation for the synthesis of pyrimido[1,6-*a*]indol-1(2*H*)-ones via Rh[9] catalysis (Scheme 1a). (ii) [3+2] annulation for the synthesis of 3*H*-pyrrolo[1,2-*a*]indol-3-ones via Co,[10] Ru,[11] Re,[12] Rh[13] catalysis (Scheme 1b). Despite the remarkable achievements made, however, to the best of our knowledge, the [4+1] annulation between *N*-carbamoyl indoles and alkynes for the synthesis of imidazo[1,5-*a*]indoles has never been reported to date. Very recently, α,α-difluoromethylene alkynes were successfully exploited as nontraditional C_1 synthons to participate TM-catalyzed [n+1] annulations.[14] Inspired by these elegant works, together with our interests in indole compound synthesis[15] and Rh(III)-catalyzed C–H activation,[9d,13a,16] herein we present a Rh(III)-

Scheme 1. C–H annulations between *N*-carbamoyl indoles and alkynes



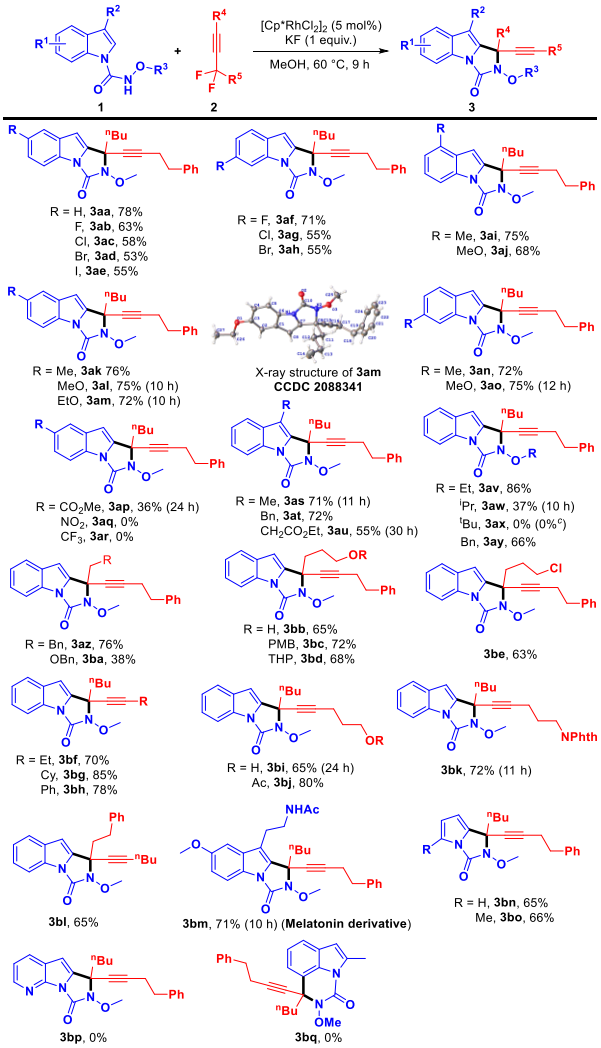
catalyzed [4+1] annulation between *N*-carbamoyl indoles and α,α-difluoromethylene alkynes for the synthesis of imidazo[1,5-*a*]indoles with the $[Cp^*RhCl_2]_2$/KF/MeOH catalytic system (Scheme 1c). This transformation has the following characteristics: (a) α,α-difluoromethylene alkynes were employed as unconventional C_1 synthons to fulfil [4+1] annulation, which is uncommon as alkyne species normally act as C_2 synthons to undergo [n+2] annulation;[17] (b) a chemoselective [4+1] annulation, in which the competitive background reactions such as [4+2] annulation, [3+2] annulation as well as C–H alkenylation[18] were suppressed; (c) a regioselective [4+1] annulation, in which the C–C and C–N

bonds were both formed at the same distal C_{sp}; (d) a defluorinative and redox-neutral [4+1] annulation, in which the cleavage of two C–F bonds enabled the reaction to occur without external oxidants and simultaneously led to an interesting migration of the alkyne moiety; (e) an efficient construction of a quaternary carbon center to access C1-alkynylated imidazo[1,5-*a*]indoles, which are difficult to prepare with traditional methods. These features make this reaction a synthetically novel method for the assembly of the imidazo[1,5-*a*]indole scaffold, despite the elegant construction of this skeleton from indoles with hazardous diazo compounds[9a,19], 4-hydroxyphenylboronic acid under Ag oxidant[20] or malodorous isocyanides under air oxidation.[21] Interestingly, when the catalytic system consisting of $[Cp^*RhCl_2]_2$/NaOAc/1,4-dioxane was employed, the domino C–H alkenylation/carbamoyl DG migration instead of [4+1] annulation took place to provide the challenging α,α-difluoromethylene tetrasubstituted alkenes highly regio- and stereoselectively (Scheme 1c). Notably, the carbamoyl DG not only works as an auxiliary group to achieve C–H activation in this reaction, but also displays as an internal acylation reagent which relocates onto the alkene unit of the products. Despite the elegant synthesis of tetrasubstituted alkenes via Co,[22] Ru,[23] Rh[13,16,24] catalysis, our process stands as an unprecedented example of Rh(III)-catalyzed synthesis of tetrasubstituted alkenes carrying a *gem*-difluoromethylene functionality at the α position. Considering the prevalence of the imidazo[1,5-*a*]indole and tetrasubstituted alkene scaffolds in bioactive molecules (Figure S1),[25,26] our protocol is quite appealing as it allows the divergent synthesis of the challenging C1-alkynylated quaternary imidazo[1,5-*a*]indoles and α,α-difluoromethylene tetrasubstituted alkenes via rhodium catalysis.

Starting with the model substrates indole **1aa** and α,α-difluoromethylene alkyne **2aa**, optimization of the reaction conditions revealed that the [4+1] annulation/alkyne moiety migration product **3aa** and C–H alkenylation/carbamoyl DG migration product **4aa** could be synthesized divergently with the catalytic systems of $[Cp^*RhCl_2]_2$/KF/MeOH and $[Cp^*RhCl_2]_2$/NaOAc/1,4-dioxane, respectively, with excellent chemo-, regio- and stereoselectivity (Table S1).

Subsequently, the substrate scope of Rh(III)-catalyzed [4+1] annulation/alkyne moiety migration was explored (Scheme 2). At first, we checked the scope of indoles with **2aa** as the coupling partner. For example, the reactions of indoles bearing halogens (F, Cl, Br, I) worked well to provide products **3ab-3ah** in 53-71% yields. Similarly, electron-rich indoles bearing Me, MeO, EtO groups reacted smoothly to deliver products **3ai-3ao** in 68-76% yields. Electron-deficient indole carrying CO_2Me group could also undergo this reaction to afford the desired product **3ap**, albeit with a lower yield (36%). By contrast, indoles carrying strong electron-withdrawing groups such as NO_2 and CF_3 failed to react to deliver the desired products **3aq** and **3ar**, but with the recovery of the materials. Of note, the reactions of C3-substituted indoles happened uneventfully to give products **3as-3au** in 55-72% yields in spite of the steric hindrance caused by the C3 substituents. Indoles possessing diverse alkyl groups such as Et, ^{i}Pr, Bn at R^3 were successfully converted into the corresponding products **3av**, **3aw** and **3ay** in 37-86% yields, while indole substrate having a ^{t}Bu group at R^3 failed to react to provide product **3ax** even at a higher temperature. We speculated that the steric hindrance caused by the bulky ^{t}Bu group may prevent the indole substrate from reacting with alkyne **2aa**. Then the scope of α,α-difluoromethylene alkynes was examined with indole **1aa** as the reaction partner. Alkynes with Ph, free or PMB/THP/Bn-protected hydroxyl, or chlorine-substituted alkyl groups at R^4 turned out to be suitable coupling partners, affording products **3az-3be** in 38-76% yields. Likewise, the reactions of alkynes carrying alkyl or aryl groups at R^5 were also reactive, and the desired products **3bf-3bh** were obtained in 70-85% yields. This transformation was also compatible with alkynes bearing an alkyl chain at R^5 in which a free or Ac-protected hydroxyl, or phthaloyl protected amino group could be introduced, providing products **3bi-3bk** in 65-80% yields. Interestingly, when the R^4 and R^5 groups in alkyne **2aa** was swapped, the desired product **3bl** was still obtained in 65% yield. Notably, this reaction could be applied to the modification of natural

Scheme 2. Substrate scope of Rh(III)-catalyzed [4+1] annulation/alkyne moiety migration[a,b]

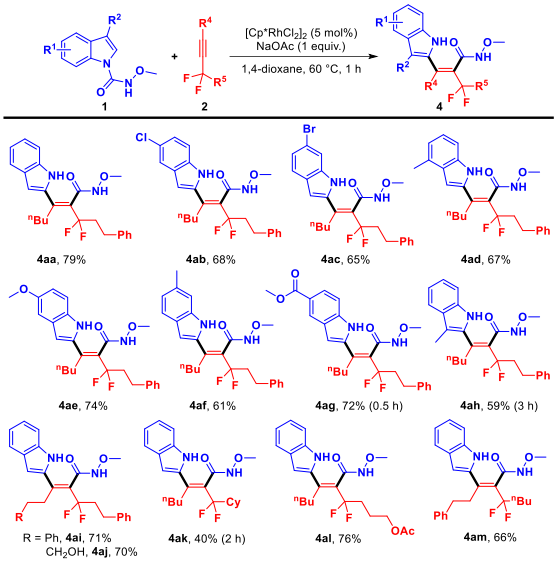


[a]Unless noted, reactions were carried out with **1** (0.25 mmol), **2** (0.325 mmol), $[Cp^*RhCl_2]_2$ (5 mol%) and KF (0.25 mmol) in MeOH (4.0 mL) at 60 °C for 9 h. [b]Isolated yield. [c]Data under 100 °C.

products. As an example, melatonin,[6] an animal hormone, underwent carbamoylation and subsequent Rh(III)-catalyzed [4+1] annulation/alkyne moiety migration with alkyne **2aa** successfully to give product **3bm** in 71% yield. Furthermore, pyrrole substrates could also participate in this transformation, furnishing the desired products **3bn** and **3bo** in 65% and 66% yields, respectively. While *N*-carbamoyl 7-azaindole failed to react to give product **3bp** but with the materials untouched. We also attempted to achieve the annulation at the C7 position of indole by blocking the C2 position with a methyl group to prepare compound **3bq**, but failed. In addition, the reaction between **1aa** and **2aa** could be easily scaled up at a gram scale without the loss of efficiency, indicating the practicality and industrial perspective of this reaction (Supporting Information).

Next, we appraised the scope of Rh(III)-catalyzed C–H alkenylation/DG migration (Scheme 3). For instance, the reactions of a series of indoles carrying halogens (Cl, Br), electron-donating (Me, MeO) or electron-withdrawing groups (CO_2Me) with **2aa** took place smoothly to afford products **4ab-4ah** in 59-74% yields. Similarly, a variety of alkynes bearing unsubstituted or substituted alkyl groups at R^4-R^5 could react well with **1aa** to give products **4ai-4am** in 40-76% yields.

Scheme 3. Substrate scope of Rh(III)-catalyzed C–H alkenylation/DG migration[a,b]

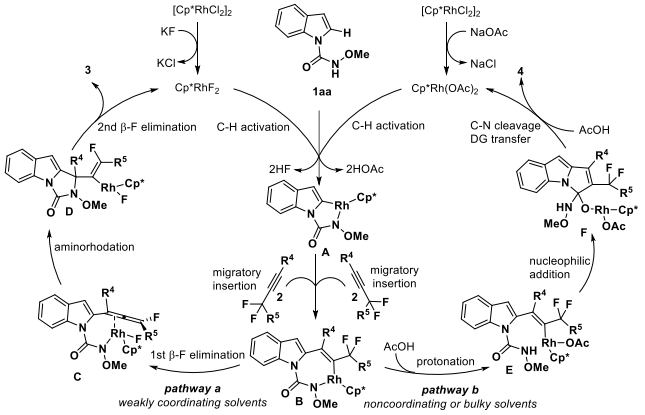


[a]Unless noted, reactions were carried out with **1** (0.25 mmol), **2** (0.325 mmol), $[Cp^*RhCl_2]_2$ (5 mol%) and NaOAc (0.25 mmol) in 1,4-dioxane (4.0 mL) at 60 °C for 1 h. [b]Isolated yield.

A study on the DGs revealed that the alkoxy group like MeO tethered to the amide nitrogen of the indole substrates was indispensable for both transformations (Scheme S1). Isotope labelling experiments were conducted to gain some insights into the reaction mechanism of Rh(III)-catalyzed [4+1] annulation/alkyne moiety migration. When **1aa** was treated in CD_3OD under standard conditions, 52%, 55%, and 18% deuteration was found at positions C2, C3, and C7 of **1aa**, respectively, suggesting the C–H bond cleavage is reversible (Scheme S2). In addition, kinetic isotope effect (KIE) study was also performed (Scheme S3 and S4). The intermolecular competition experiments and two parallel reactions provided the same low KIE values of 1.04, indicating the step of the C–H bond cleavage could not be the rate-limiting step.

Based on the preliminary mechanistic results and literature reports,[14a,17,22] a plausible reaction mechanism was proposed in Scheme 4. At first, chelation assisted C–H activation of **1aa** with rhodium catalyst yields rhodacycle **A**. The following regioselective migratory insertion of the alkyne into the Rh–C bond of rhodacycle **A** gives intermediate **B**. The polarization of the carbon-carbon triple bonds by the *gem*-difluoromethylene functionality was believed to guarantee the regioselectivity. On the other hand, the solvent effect on product selectivity could be rationalized by the different coordinating ability of the solvents.[24] Weakly coordinating solvents such as MeOH could coordinate with the rhodium to stabilize intermediate **B** by forming an 18-electron species. In this case, intermediate **B** could undergo the first β-F-elimination to afford the allene intermediate **C**, which undergoes an intramolecular aminorhodation of the allene unit to produce intermediate **D**. Intermediate **D** undergoes the second β-F-elimination to afford the [4+1] annulation/alkyne moiety migration products **3** with the regeneration of the rhodium catalyst. Alternatively, when noncoordinating or bulky solvents such as 1,4-dioxane is employed, intermediate **B** may trend to undergo protonation to provide intermediate **E**. Then, the intramolecular nucleophilic addition of the carbonyl group by the Rh–C bond of intermediate **E** takes place to offer intermediate **F**. Intermediate **F** then undergoes C–N bond cleavage and protodemetalation to assemble the C–H alkenylation/DG migration products **4** accompanied by the regeneration of the rhodium catalyst.

Scheme 4. Proposed reaction mechanism



In conclusion, we have achieved the divergent synthesis of alkynylated imidazo[1,5-*a*]indoles and α,α-difluoromethylene tetrasubstituted alkenes through Rh(III)-catalyzed [4+1] annulation/alkyne moiety migration and C–H alkenylation/DG migration, respectively. The tunable product selectivity is rationalized by the different reaction pathways decided by the coordinating ability of the solvents. Our method is characterized by excellent chemo-, regio- and stereoselectivity, broad substrate scope, moderate to high yields, good tolerance of functional groups and mild redox-neutral conditions. Pharmacological study of these heterocyclic compounds is currently undergoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, characterization data of the products, and copies of ^{1}H, ^{13}C and ^{19}F NMR spectra (PDF)
X-ray crystal structure of compound **3am** (CIF)

AUTHOR INFORMATION

Corresponding Author

Fei Zhao – *Antibiotics Research and Re-evaluation Key Laboratory of Sichuan Province, Sichuan Industrial Institute of Antibiotics, School of Pharmacy, Chengdu University, Chengdu 610106, China; Jinhua Branch, Sichuan Industrial Institute of Antibiotics, School of Pharmacy, Chengdu University, Jinhua 321007, China;* orcid.org/0000-0003-1841-4466; E-mail: zhaofei@cdu.edu.cn

Hui Mao – *College of Pharmacy, Jinhua Polytechnic, Jinhua 321007, China;* E-mail: maohui1988@126.com

Siyu Liu – *Antibiotics Research and Re-evaluation Key Laboratory of Sichuan Province, Sichuan Industrial Institute of Antibiotics, School of Pharmacy, Chengdu University, Chengdu 610106, China; Jinhua Branch, Sichuan Industrial Institute of Antibiotics, School of Pharmacy, Chengdu University, Jinhua 321007, China;* orcid.org/0000-0002-8076-577X; E-mail: siyu.liu.siia@gmail.com

Authors

Jin Qiao – *Jinhua Branch, Sichuan Industrial Institute of Antibiotics, School of Pharmacy, Chengdu University, Jinhua 321007, China.*

Yangbin Lu – *Jinhua Branch, Sichuan Industrial Institute of Antibiotics, School of Pharmacy, Chengdu University, Jinhua 321007, China.*

Xiaoning Zhang – *Jinhua Branch, Sichuan Industrial Institute of Antibiotics, School of Pharmacy, Chengdu University, Jinhua 321007, China.*

Long Dai – *Jinhua Branch, Sichuan Industrial Institute of Antibiotics, School of Pharmacy, Chengdu University, Jinhua 321007, China.*

Xin Gong – *Antibiotics Research and Re-evaluation Key Laboratory of Sichuan Province, Sichuan Industrial Institute of Antibiotics, School of Pharmacy, Chengdu University, Chengdu 610106, China.*

Shiyao Lu – *Jinhua Branch, Sichuan Industrial Institute of Antibiotics, School of Pharmacy, Chengdu University, Jinhua 321007, China.*

Xiaowei Wu – *Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China; Zhongshan Institute for Drug Discovery, the Institutes of Drug Discovery and Development, Chinese Academy of Sciences, Zhongshan 528400, China;* orcid.org/0000-0001-7248-9149.

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest. CCDC 2088341 contain the supplementary crystallographic data for this paper. These data can be also obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

ACKNOWLEDGMENT

We gratefully acknowledge the financial support from the Natural Science Foundation of Zhejiang Province (Grant LQ19B020003, LY21B020003), National Natural Science Foundation of China (Grant 21602022), Chengdu Talents Program, 1000 Talents Program of Sichuan Province, Longquanyi District Talents Program, Science and Technology Program of Sichuan Province (Grant 2018JY0345), Start-up Funding from Jinhua Branch of Sichuan Industrial Institute of Antibiotics (Grant 1003) and Chengdu University New Faculty Start-up Funding (Grant 2081915037).

REFERENCES

(1) For selected reviews, see: (a) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. Rhodium Catalyzed Chelation-Assisted C–H Bond Functionalization Reactions. *Acc. Chem. Res*. **2012**, *45*, 814–825. (b) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. Transition Metal-Catalyzed C–H Bond Functionalizations by the Use of Diverse Directing Groups. *Org. Chem. Front.* **2015**, *2*, 1107–1295.

(2) For selected reviews on C–H functionalization of indoles, see: (a) Leitch, J. A.; Bhonoah, Y.; Frost, C. G. Beyond C2 and C3: Transition-Metal-Catalyzed C–H Functionalization of Indole. *ACS Catal.* **2017**, *7*, 5618−5627. (b) Petrini, M. Regioselective Direct C-Alkenylation of Indoles. *Chem. Eur. J.* **2017**, *23*, 16115–16151.

(3) For selected recent examples on C–H functionalization of indoles, see: (a) Chen, S.; Zhang, M.; Su, R.; Chen, X.; Feng, B.; Yang, Y.; You, J. C2/C4 Regioselective Heteroarylation of Indoles by Tuning C–H Metalation Modes. *ACS Catal.* **2019**, *9*, 6372–6379. (b) Kona, C. N.; Nishii, Y.; Miura, M. Iridium-Catalyzed Direct C4- and C7-Selective Alkynylation of Indoles Using Sulfur-Directing Groups. *Angew. Chem. Int. Ed*. **2019**, *58*, 9856–9860. (c) Choi, I.; Messinis, A. M.; Ackermann, L. C7-Indole Amidations and Alkenylations by Ruthenium(II) Catalysis. *Angew. Chem. Int. Ed*. **2020**, *59*, 12534–12540. (d) Cembellín, S.; Dalton, T.; Pinkert, T.; Schäfers, F.; Glorius, F. Highly Selective Synthesis of 1,3-Enynes, Pyrroles, and Furans by Manganese(I)-Catalyzed C–H Activation. *ACS Catal.* **2020**, *10*, 197–202.

(4) For selected reviews, see: (a) Zhang, M. Z.; Chen, Q.; Yang, G. F. A Review on Recent Developments of Indole-Containing Antiviral Agents. *Eur. J. Med. Chem*. **2015**, *89*, 421–441. (b) Homer, J. A.; Sperry, J. Mushroom-Derived Indole Alkaloids. *J. Nat. Prod*. **2017**, *80*, 2178–2187.

(5) For selected examples, see: (a) Ackermann, L.; Wang, L.; Lygin, A. V. Ruthenium-Catalyzed Aerobic Oxidative Coupling of Alkynes with 2-Aryl-substituted Pyrroles. *Chem. Sci*. **2012**, *3*, 177–180. (b) Ding, Z.; Yoshikai, N. Mild and Efficient C2-Alkenylation of Indoles with Alkynes Catalyzed by a Cobalt Complex. *Angew. Chem. Int. Ed*. **2012**, *51*, 4698–4701. (c) Yang, X.-F.; Hu, X.-H.; Loh, T.-P. Expedient Synthesis of Pyrroloquinolinones by Rh-Catalyzed Annulation of *N*-Carbamoyl Indolines with Alkynes through a Directed C–H Functionalization/C–N Cleavage Sequence. *Org. Lett.* **2015**, *17*, 1481–1484. (d) Morioka, R.; Nobushige, K.; Satoh, T.; Hirano, K.; Miura, M. Synthesis of Indolo[1,2-*a*][1,8]naphthyridines by Rhodium(III)-Catalyzed Dehydrogenative Coupling via Rollover Cyclometalation. *Org. Lett.* **2015**, *17*, 3130–3133.

(6) For selected reviews, see: Chadha, N.; Silakari, O. Indoles as Therapeutics of Interest in Medicinal Chemistry: Bird's Eye View. *Eur. J. Med. Chem*. **2017**, *134*, 159–184.

(7) For a seminal reference on C–H activation assisted by the carbamoyl directing group, see: (a) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. Pd(II)-Catalyzed Cross-Coupling of sp^3 C−H Bonds with sp^2 and sp^3 Boronic Acids Using Air as the Oxidant. *J. Am. Chem. Soc*. **2008**, *130*, 7190–7191. For a review on C–H activation assisted by the carbamoyl directing group, see: (b) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. A Simple and Versatile Amide Directing Group for C−H Functionalizations. *Angew. Chem. Int. Ed*. **2016**, *55*, 10578–10599.

(8) For selected reviews on C–H functionalization with alkynes, see: (a) Boyarskiy, V. P.; Ryabukhin, D. S.; Bokach, N. A.; Vasilyev, A. V. Alkenylation of Arenes and Heteroarenes with Alkynes. *Chem. Rev.* **2016**, *116*, 5894–5986. (b) Drapeau, M. P.; Gooßen, L. J. Carboxylic Acids as Directing Groups for C–H Bond Functionalization. *Chem. Eur. J*. **2016**, *22*, 18654–18677.

(9) (a) Zhang, Y.; Zheng, J.; Cui, S. Rh(III)-Catalyzed C–H Activation/Cyclization of Indoles and Pyrroles: Divergent Synthesis of Heterocycles. *J. Org. Chem*. **2014**, *79*, 6490–6500. (b) Reddy, C. R.; Yarlagadda, S.; Sridhar, B.; Reddy, B. V. S. Arylative Cyclization of Indole-1-carboxamides with 1,6-Enynes for the Synthesis of Polycyclic Indole Scaffolds. *Eur. J. Org. Chem.* **2017**, 5763–5768. (c) Yamada, T.; Shibata, Y.; Tanaka, K. Functionalized Cyclopentadienyl Ligands and Their Substituent Effects on a Rhodium(III)-Catalyzed Oxidative [4+2] Annulation of Indole- and Pyrrole-1-Carboxamides with Alkynes. *Asian J. Org. Chem*. **2018**, *7*, 1396–1402. (d) Wu, X.; Li, P.; Lu, Y.; Qiao, J.; Zhao, J.; Jia, X.; Ni, H.; Kong, L.; Zhang, X.; Zhao, F. Rhodium-Catalyzed Cascade Reactions of Indoles with 4-Hydroxy-2-Alkynoates for the Synthesis of Indole-Fused Polyheterocycles. *Adv. Synth. Catal.* **2020**, *362*, 2953–2960. (e) Reddy, C. R.; Sathish, P.; Mallesh, K.; Prapurna, Y. L. Construction of Unique Polycyclic 3, 4-Fused Indoles via Rhodium(III)-Catalyzed Domino Annulations. *ChemistrySelect* **2020**, *5*, 12736–12739.

(10) Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M. Pyrroloindolone Synthesis via a Cp*Co^{III}-Catalyzed Redox-Neutral Directed C–H Alkenylation/Annulation Sequence. *J. Am. Chem. Soc*. **2014**, *136*, 5424–5431.

(11) Xie, Y.; Wu, X.; Li, C.; Wang, J.; Li, J.; Liu, H. Ruthenium(II)-Catalyzed Redox-Neutral [3+2] Annulation of Indoles with Internal Alkynes via C–H Bond Activation: Accessing a Pyrroloindolone Scaffold. *J. Org. Chem*. **2017**, *82*, 5263−5273.

(12) Yang, Y.; Wang, C. Re-Catalyzed Annulations of Weakly Coordinating *N*-Carbamoyl Indoles/Indolines with Alkynes via C−H/C−N Bond Cleavage. *Chem. Eur. J*. **2019**, *25*, 8245–8248.

(13) (a) Zhao, F.; Gong, X.; Lu, Y.; Qiao, J.; Jia, X.; Ni, H.; Wu, X.; Zhang, X. Additive-Controlled Divergent Synthesis of Tetrasubstituted 1,3-Enynes and Alkynylated 3*H*-Pyrrolo[1,2-*a*]indol-3-ones via Rhodium Catalysis. *Org. Lett*. **2021**, *23*, 727−733. (b) Kumar, S.; Nunewar, S.; Usama, K. M.; Kanchupalli, V. Rh(III)-Catalyzed [3+2] Annulation and C−H Alkenylation of Indoles with 1,3-Diynes by C−H Activation. *Eur. J. Org. Chem*. **2021**, 2223–2229.

(14) (a) Wang, C.-Q.; Ye, L.; Feng, C.; Loh, T.-P. C–F Bond Cleavage Enabled Redox-Neutral [4+1] Annulation via C–H Bond Activation. *J. Am. Chem. Soc*. **2017**, *139*, 1762–1765. (b) Li, T.; Zhou, C.; Yan, X.; Wang, J. Solvent-Dependent Asymmetric Synthesis of Alkynyl and Monofluoroalkenyl Isoindolinones by CpRh^{III}-Catalyzed C–H Activation. *Angew. Chem. Int. Ed*. **2018**, *57*, 4048–4052.

(15) (a) Zhao, F.; Zhang, D.; Nian, Y.; Zhang, L.; Yang, W.; Liu, H. Palladium-Catalyzed Difunctionalization of Alkynes via C–N and S–N Cleavages: A Versatile Approach to Highly Functional Indoles. *Org. Lett.* **2014**, *16*, 5124–5127. (b) Zhao, F.; Li, J.; Chen, Y.; Tian, Y.; Wu, C.; Xie, Y.; Zhou, Y.; Wang, J.; Xie, X.; Liu, H. Design, Synthesis, and Biological Evaluation of Indoline and Indole Derivatives as Potent and Selective α_{1A}-Adrenoceptor Antagonists. *J. Med. Chem*. **2016**, *59*, 3826–3839.

(16) Wu, X.; Lu, Y.; Qiao, J.; Dai, W.; Jia, X.; Ni, H.; Zhang, X.; Liu, H.; Zhao, F. Rhodium(III)-Catalyzed C–H Alkenylation/Directing Group Migration for the Regio- and Stereoselective Synthesis of Tetrasubstituted Alkenes. *Org. Lett.* **2020**, *22*, 9163–9168.

(17) For reviews, see: (a) Satoh, T.; Miura, M. Oxidative Coupling of Aromatic Substrates with Alkynes and Alkenes under Rhodium Catalysis. *Chem. Eur. J.* **2010**, *16*, 11212–11222. (b) Gulías, M.; Mascareñas, J. L. Metal-Catalyzed Annulations through Activation and Cleavage of C–H Bonds. *Angew. Chem. Int. Ed*. **2016**, *55*, 11000–11019.

(18) For examples on C–H alkenylation of *N*-carbamoyl indoles with alkynes, see: (a) Schipper, D. J.; Hutchinson, M.; Fagnou, K. Rhodium(III)-Catalyzed Intermolecular Hydroarylation of Alkynes. *J. Am. Chem. Soc*. **2010**, *132*, 6910–6911. (b) Sharma, S.; Han, S.; Shin, Y.; Mishra, N. K.; Oh, H.; Park, J.; Kwak, J. H.; Shin, B. S.; Jung, Y. H.; Kim, I. S. Rh-Catalyzed Oxidative C2-Alkenylation of Indoles with Alkynes: Unexpected Cleavage of Directing Group. *Tetrahedron Lett*. **2014**, *55*, 3104–3107. (c) Zhang, W.; Wei, J.; Fu, S.; Lin, D.; Jiang, H.; Zeng, W. Highly Stereoselective Ruthenium(II)-Catalyzed Direct C2-*syn*-Alkenylation of Indoles with Alkynes. *Org. Lett*. **2015**, *17*, 1349–1352. (d) Fei, X.; Li, C.; Yu, X.; Liu, H. Rh(III)-Catalyzed Hydroarylation of Alkyne MIDA Boronates via C–H Activation of Indole Derivatives. *J. Org. Chem*. **2019**, *84*, 6840–6850.

(19) (a) Zhang, Y.; Wang, D.; Cui, S. Facile Synthesis of Isoindolinones via Rh(III)-Catalyzed One-Pot Reaction of Benzamides, Ketones, and Hydrazines. *Org. Lett*. **2015**, *17*, 2494–2497. (b) Chen, X.; Yang, S.; Li, H.; Wang, B.; Song, G. Enantioselective C–H Annulation of Indoles with Diazo Compounds through a Chiral Rh(III) Catalyst. *ACS Catal*. **2017**, *7*, 2392–2396.

(20) Only one example was successfully achieved with 4-hydroxyphenylboronic acid, providing the product with a relatively low yield owing to the decomposition of materials, see: Zheng, J.; Zhang, Y.; Cui, S. Rh(III)-Catalyzed Selective Coupling of *N*-Methoxy-1*H*-indole-1-carboxamides and Aryl Boronic Acids. *Org. Lett*. **2014**, *16*, 3560–3563.

(21) Kong, W.-J.; Chen, X.; Wang, M.; Dai, H.-X.; Yu, J.-Q. Rapid Syntheses of Heteroaryl-Substituted Imidazo[1,5-*a*]indole and Pyrrolo[1,2-*c*]imidazole via Aerobic C2–H Functionalizations. *Org. Lett*. **2018**, *20*, 284–287.

(22) Ikemoto, H.; Tanaka, R.; Sakata, K.; Kanai, M.; Yoshino, T.; Matsunaga, S. Stereoselective Synthesis of Tetrasubstituted Alkenes via a Cp*Co^{III}-Catalyzed C–H Alkenylation/Directing Group Migration Sequence. *Angew. Chem. Int. Ed*. **2017**, *56*, 7156–7160.

(23) Li, M.; Yao, T.-Y.; Sun, S.-Z.; Yan, T.-X.; Wen, L.-R.; Zhang, L.-B. The Ruthenium(II)-Catalyzed C–H Olefination of Indoles with Alkynes: the Facile Construction of Tetrasubstituted Alkenes under Aqueous Conditions. *Org. Biomol. Chem*. **2020**, *18*, 3158–3163.

(24) Liu, G.; Shen, Y.; Zhou, Z.; Lu, X. Rhodium(III)-Catalyzed Redox-Neutral Coupling of *N*-Phenoxyacetamides and Alkynes with Tunable Selectivity. *Angew. Chem. Int. Ed*. **2013**, *52*, 6033–6037.

(25) For bioactive molecules bearing the imidazo[1,5-*a*]indole motif, see: (a) Varasi, M.; Heidempergher, F.; Caccia, C.; Salvati, P. Imidazolylalkyl Derivatives of Imidazo[1,5-*a*]indol-3-one and Their Use as Therapeutic Agents. Patent, WO9532204A1, 1995. (b) Voss, M. E.; Carter, P. H.; Tebben, A. J.; Scherle, P. A.; Brown, G. D.; Thompson, L. A.; Xu, M.; Lo, Y. C.; Yang, G.; Liu, R.-Q.; Strzemienski, P.; Everlof, J. G.; Trzaskos, J. M.; Decicco, C. P. Both 5-Arylidene-2-thioxodihydropyrimidine-4,6(1*H*,5*H*)-diones and 3-Thioxo-2,3-dihydro-1*H*-imidazo[1,5-*a*]indol-1-ones Are Light-Dependent Tumor Necrosis Factor-α Antagonists. *Bioorg. Med. Chem. Lett*. **2003**, *13*, 533–538. (c) Alagille, D.; Pfeiffer, B.; Scalbert, E.; Ferry, G.; Boutin, J. A.; Renard, P.; Viaud-Massuard, M.-C. Design and Synthesis of Indole and Tetrahydroisoquinoline Hydantoin Derivatives as Human Chymase Inhibitors. *J. Enzym. Inhib. Med. Chem*. **2004**, *19*, 137–143. (d) Lennox, W. J.; Qi, H.; Lee, D.-H.; Choi, S.; Moon, Y.-C. Tetrahydrocarbazoles as Active Agents for Inhibiting VEGF Production by Translational Control. Patent, WO2006065480A2, 2006.

(26) For bioactive molecules bearing the tetrasubstituted alkene motif, see: (a) Morand, P.; Bagli, J. F.; Kraml, M.; Dubuc, J. The Effect of Substituted Carboxylic Acids on Hepatic Cholesterogenesis. *J. Med. Chem.* **1964**, *7*, 504–508. (b) Middleton, W. J.; Metzger, D.; Snyder, J. A. 1-Trifluoromethyl-1,2,2-triphenylethylenes. Synthesis and Postcoital Antifertility Activity. *J. Med. Chem.* **1971**, *14*, 1193–1197. (c) Levenson, A. S.; Jordan, V. C. Selective Oestrogen Receptor Modulation. *Eur. J. Cancer.* **1999**, *35*, 1628–1639. (d) Jeanmart, S. A. M.; Bonvalot, D.; Perruccio, F.; Wendeborn, S. V.; Nussbaumer, H.; Rajan, R.; Titulaer, R. Preparation of Acetylenic Compounds as Microbicides. Patent, WO 2013144224 A1, 2013.