OL Organic Letters

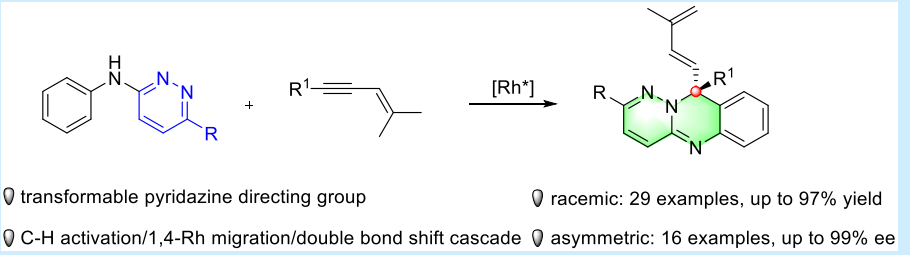
pubs.acs.org/OrgLett Letter

Asymmetric [5+1] Annulation via C−H Activation/1,4-Rh Migration/Double Bond Shift Using a Transformable Pyridazine Directing Group

Man Zhu, Yuyao Zhao, Xingwei Li, and Bingxian Liu*

Cite This: https://doi.org/10.1021/acs.orglett.3c00278 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



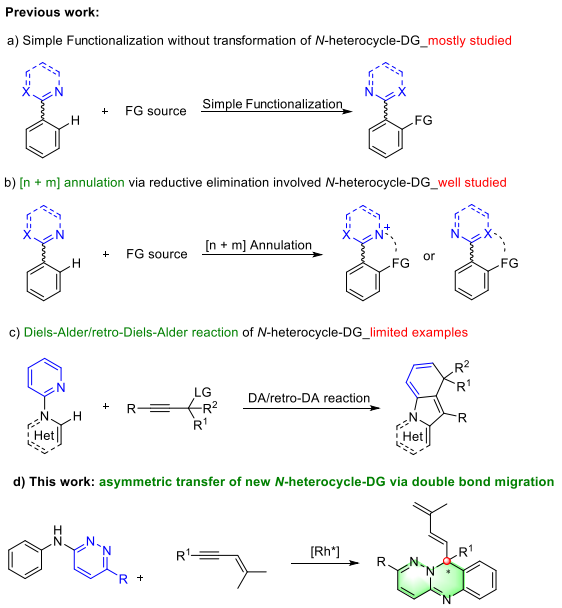
ABSTRACT: *N*-Heterocycle-assisted C−H activation/annulation reactions have provided new concepts for the construction and transformation of azacycles. In this work, we disclose a [5+1] annulation reaction using a novel transformable pyridazine directing group (DG). The DG-transformable reaction mode led to the construction of a new heterocyclic ring accompanied by transformation of the original pyridazine directing group via a C−H activation/1,4-Rh migration/double bond shift pathway, affording the skeleton of pyridazino[6,1-*b*]quinazolines with a good substrate scope under mild conditions. Diverse fused cyclic compounds can be achieved by derivatization of the product. The asymmetric synthesis of the skeleton was also realized to afford the enantiomeric products with good stereoselectivity.

The construction and transformation of azacycles are always hot research topics in organic and pharmaceutical chemistry.[1,2] The directing group-assisted C−H activation/annulation strategy has provided new solutions for accessing diverse azacycles in a straightforward way in recent years.[3] Among them, the annulation reactions directed by *N*-heterocycles have attracted a great deal of attention from chemists because of the widespread presence of *N*-heterocycles in natural products and drug-related molecules. To date, *N*-heterocycles such as pyridine, pyrimidine, and pyrazole have proved to be outstanding directing groups for the C−H activation process. They can easily coordinate to the metal center and form the key cyclic metal complex, which will react with various coupling partners to afford the desired products. To the best of our knowledge, most studies on *N*-heterocycle-assisted C−H activation reactions are focused on a simple functionalization mode without transformation of the *N*-heterocycle directing group (DG) (Scheme 1a).[3a,4] The *N*-heterocycle can also act as a reaction unit involved in the construction of the final new *N*-heterocycle via an [*n*+*m*] annulation process with the original *N*-heterocycle maintained. In these cases, fused N-heterocyclic compounds or quaternary ammonium salts are mostly obtained (Scheme 1b).[3d,i,j,5] Recently, the Ackermann group[6] and the Li group[7] independently used *N*-heterocycles as traceless directing groups. The cyclohexadiene products were afforded via an *N*-heterocycle DG-involved Diels−Alder/retro-Diels−Alder cascade (Scheme 1c). In this attractive reaction mode that can realize heterocycle editing, a new ring is constructed accompanied by transformation of the original *N*-heterocycle DG. However, this type of transformation is still limited, especially for asymmetric construction via a DG-transformable mode.[8] Herein, we report a [5+1] annulation reaction[9] via a C−H activation/1,4-Rh migration/double bond shift pathway using a novel transformable pyridazine directing group, leading to the construction of pyridazino[6,1-*b*]quinazolines.[10] The enantioselective synthesis of the skeleton containing a quaternary carbon stereocenter was also achieved by the use of a chiral rhodium catalyst.

The racemic [5+1] annulation was explored at the beginning. Upon optimization of the reaction conditions, the desired fused heterocyclic product **3aa** was isolated in 83% yield using a chlorinated pyridazine and an alkyl-terminated 1,3-enyne as the substrates in the presence of a rhodium

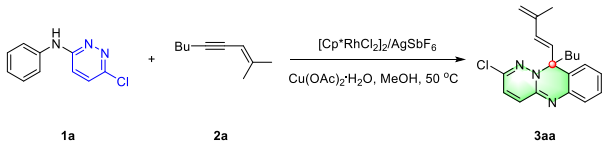
Received: January 27, 2023

Scheme 1. Transformation Modes of *N*-Heterocycle Type Directing Groups



catalyst, $AgSbF_6$, and $Cu(OAc)_2{\cdot}H_2O$ at 50 °C in MeOH (Table 1, entry 1). The optimal conditions were then verified.

Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3aa

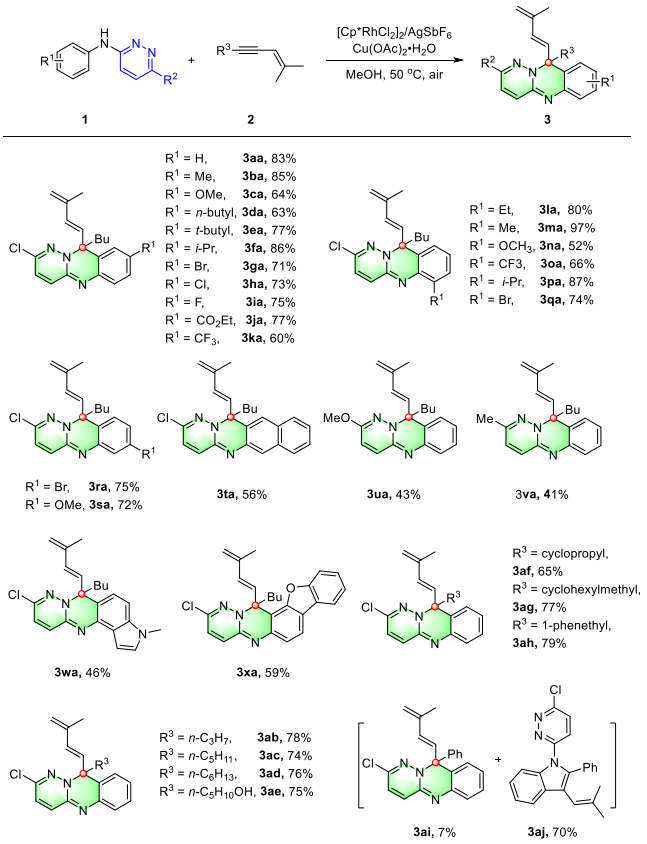
entry	changes to the optimal conditions	yield (%)
1	no changes	83
2	80 °C	80
3	30 °C	72
4	without $Cu(OAc)_2{\cdot}H_2O$	69
5	without $AgSbF_6$	66
6	TFE as the solvent	42
7	1,4-dioxane as the solvent	30
8	DCE as the solvent	40
9	$Cu(OAc)_2$ instead of $Cu(OAc)_2{\cdot}H_2O$	80
10	$Cu(OTf)_2$ instead of $Cu(OAc)_2{\cdot}H_2O$	66
11	AgOAc instead of $Cu(OAc)_2{\cdot}H_2O$	78
12	NaOAc instead of $Cu(OAc)_2{\cdot}H_2O$	58

[a]Reaction conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), and an additive (0.05 mmol) in MeOH (1.0 mL) at 50 °C for 12 h under air. Isolated yields.

The reaction was not sensitive to temperature. Higher and lower reaction temperatures gave the product in acceptable yields (entries 2 and 3, respectively). Neither $AgSbF_6$ nor $Cu(OAc)_2{\cdot}H_2O$ was necessary for the reaction. The product was also isolated in a decreased yield when $AgSbF_6$ or $Cu(OAc)_2{\cdot}H_2O$ was omitted (entries 4 and 5). A screen of the solvents revealed MeOH to be the optimal one (entries 6–8). All of the tested additives with an acetate group were found to be active, leading to **3aa** in moderate to good yields (entries 9–12). The results gave evidence that the acetate group plays an important role in the C–H activation process of the catalytic cycle to improve the reaction efficiency.

The substrate scope of pyridazines and 1,3-enynes was then investigated under the optimal reaction conditions (Scheme 2). Introduction of alkyl, methoxy, ester, trifluoromethyl, or

Scheme 2. Scope of the Racemic [5+1] Annulation Reaction[a]



[a]Reaction conditions: **1** (0.10 mmol), **2** (0.20 mmol), $[Cp^*RhCl_2]_2$ (4 mol %), $AgSbF_6$ (16 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.05 mmol), and MeOH (1.0 mL) at 50 °C for 12 h under air. Isolated yields.

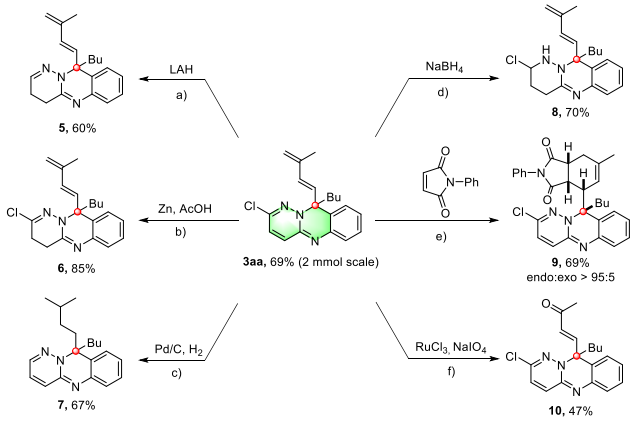
halogen groups to the phenyl rings of pyridazines all tolerated the reaction system, affording the corresponding products in moderate to good yields (**3aa**–**3sa**, 60–97%). Slightly decreased yields were detected with electron-deficient or electron-donating groups, which may be due to the electronic effect of the substituents (**3ca**, **3ja**, **3ka**, **3na**, and **3sa**). The substrates with other aryl rings such as naphthalene and hetero rings were also determined to be suitable (**3ta**, **3wa**, and **3xa**, 46–59%). The substrates containing OMe or Me groups at the pyridazine ring also gave the desired products in moderate yields (**3ua** and **3va**, 43% and 41%). The 1,3-enynes with long alkyl groups all afforded good results (**3ab**–**3ad**, 74–78%). Notably, the introduction of a hydroxyl group did not affect the reaction efficiency, with a 75% yield of the corresponding product isolated (**3ae**, 75%). The cyclopropyl, cyclohexyl, and phenyl groups were also used and gave acceptable results (**3af**–**3ah**, 65–79%). The phenyl-terminated 1,3-enyne was shown to be a substrate that could easily afford the [3+2] annulation product as the major one instead of the [5+1] product. This may be due to the different regioselectivity of the alkyne insertion process for the phenyl-terminated alkyne (**3ai** and **3aj**, 7% and 70%). However, the reaction system is still sensitive to the steric effect so that no desired product was

https://doi.org/10.1021/acs.orglett.3c00278
Org. Lett. XXXX, XXX, XXX–XXX

isolated when the substrate with a 3,5-disubsituted phenyl ring was used.

To demonstrate the utility of this reaction, the scale-up synthesis of **3aa** was conducted with a slightly decreased reaction efficiency (Scheme 3, 2 mmol scale, 69%). The

Scheme 3. Scale-up Synthesis and Derivatizations of Product 3aa[a]



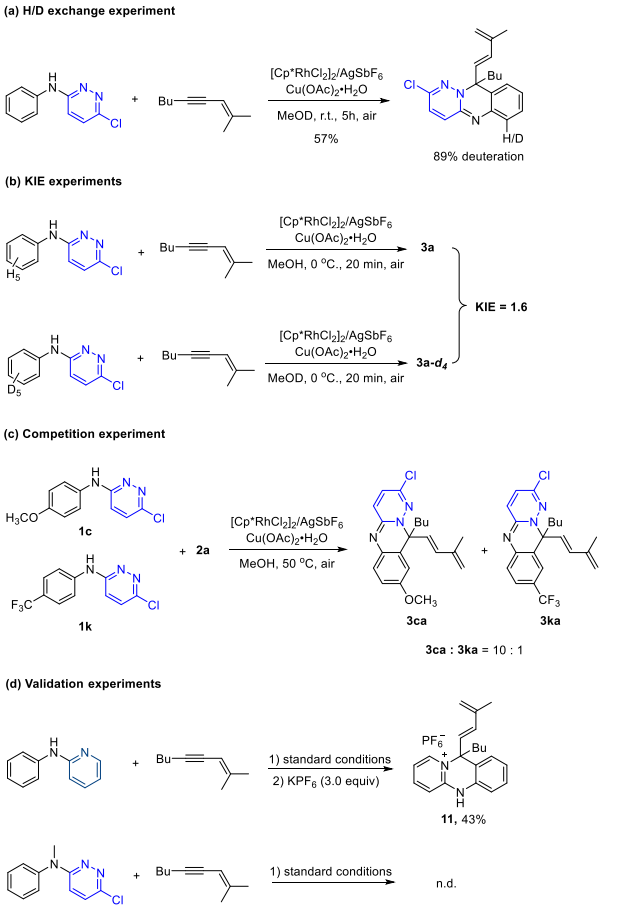
[a]Reaction conditions: (a) LAH, THF; (b) Zn, AcOH, H_2O/THF; (c) Pd/C, H_2, MeOH; (d) $NaBH_4$, AcOH, CH_3CN; (e) *N*-phenylmaleimide, toluene; (f) $RuCl_3$, $NaIO_4$, AcOH, MeCN/H_2O.

derivatization reactions of **3aa** were then carried out. The selective reduction of **3aa** can afford diverse products via dechlorination or hydrogenation of the specific unit under different reduction conditions (Scheme 3, **5**−**8**, 60−85% yield). The Diels−Alder reaction of the diene unit with maleimide gave the [4+2] product with good diastereoselectivity (Scheme 3, **9**, 69%). The oxidation of **3aa** delivered α,β-unsaturated ketone product **10** in 47% yield.

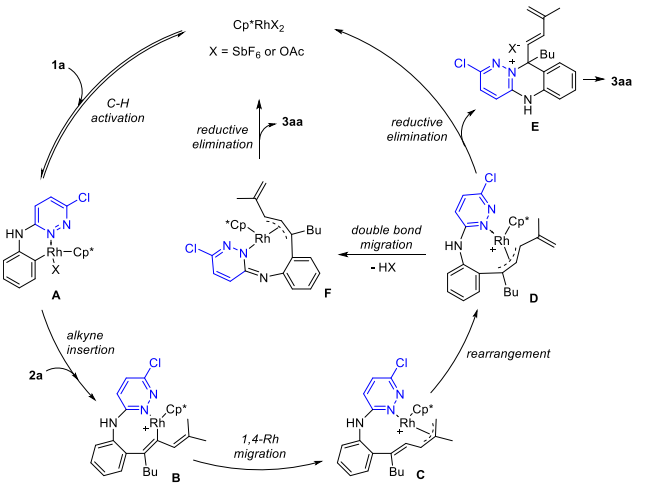
Mechanistic experiments were conducted to gain insight into the catalytic cycle (Scheme 4). Deuteration of the phenyl C−H bond of the product was detected when the reaction was carried out using MeOD as the solvent (Scheme 4a), which indicated the reversibility of the C−H activation process, and the process seemed to be not involved in the rate-determining step in that a low value of 1.6 was achieved by the kinetic isotope effect experiments (Scheme 4b). The competition reaction of the substrates with electron-deficient and electron-donating groups was conducted, giving **3ca** from the electron-rich substrate as the major product (Scheme 4c). To verify the necessity of the pyridazine ring as the directing group, a similar pyridine substrate was synthesized and subjected to the reaction system (Scheme 4d). However, no desired double bond migration product was detected, and a pyridine quaternary ammonium salt can be isolated by treatment of the pyridine substrate with the standard condition followed by the addition of KPF_6. The free NH group also proved to be necessary for the double bond migration, while the *N*-Me-substituted substrate was not applicable.

A plausible mechanism is proposed in Scheme 5 according to the results presented above and the literature.[9,11] Compound **1a** reacted with a rhodium catalyst to afford rhodacycle species **A** via a reversible C−H activation process. Intermediate **A** then underwent alkyne insertion to provide intermediate **B**, which can afford a Rh(III) π-allyl species **D** by 1,4-Rh migration/allyl rearrangement. Intermediate **D** could deliver the final product via two pathways. The direct reductive

Scheme 4. Mechanistic Studies



Scheme 5. Plausible Mechanism



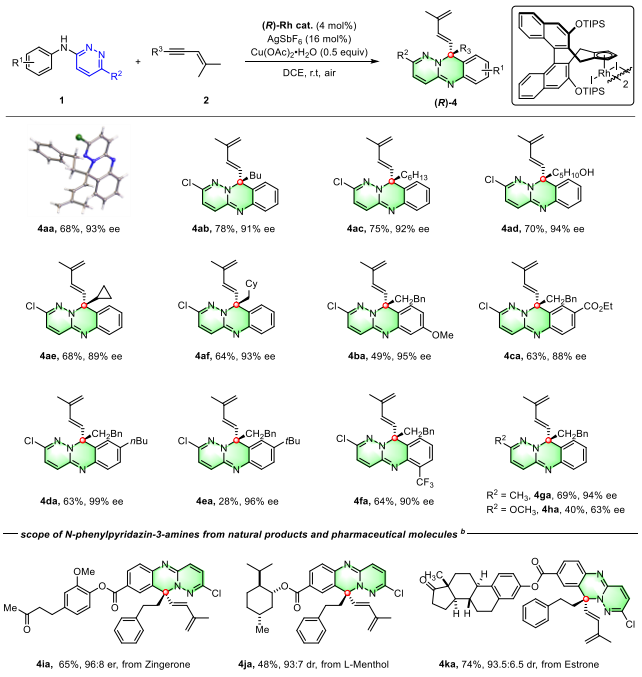
elimination of intermediate **D** generates a salt **E** that can transfer to **3aa** with bases. In an alternative way, intermediate **D** can also afford intermediate **F** by the intramolecular NH cleavage assisted by the X ligand, leaving the HX as a byproduct. The subsequent reductive elimination of intermediate **F** then gave the final product and released a rhodium(I) catalyst.

By assessing the importance of the chiral skeleton and the potential of the asymmetric system, we next investigated the asymmetric [5+1] annulation with Cramer's chiral rhodium

https://doi.org/10.1021/acs.orglett.3c00278
Org. Lett. XXXX, XXX, XXX−XXX

catalyst (see the Supporting Information for details). Enantiomeric pyridazino[6,1-*b*]quinazoline **4aa** was isolated in 68% yield and 93% ee under the optimal reaction conditions (Scheme 6). The substrate scope for the asymmetric system

Scheme 6. Scope of the Asymmetric Coupling System[a]



[a]Reaction conditions: **1** (0.05 mmol), **2** (0.1 mmol), [*R*-Rh] (4 mol %), $AgSbF_6$ (16 mol %), and $Cu(OAc)_2{\cdot}H_2O$ (0.5 equiv) in DCE (1.0 mL) at room temperature for 18 h under air. Isolated yields. [b]DCE (2.0 mL).

was then checked and revealed to be decent with moderate to excellent yield and good enantioselectivity. The absolute configuration of **4aa** was determined by single-crystal X-ray diffraction analysis (CCDC 2234937). The 1,3-enynes with different alkyl substitutions all gave the corresponding products with high ee (**4aa**−**4af**, 64−78% yields, 89−94% ee). The electron-deficient and electron-rich substituents on the phenyl ring of pyridazines all afforded good results with reasonable yields and high ee (**4ba**−**4fa**, 28−69% yields, 88−99% ee). The low efficiency of **4ea** may be caused by the obviously increased steric hindrance of the *tert*-butyl group. The change of the chlorine group at the pyridazine ring to a methyl group had little effect on the reaction (**4ga**, 69% yield, 94% ee). However, the reaction efficiency and selectivity were significantly reduced by the introduction of a methoxy group (**4ha**, 40% yield, 63% ee). Thus, the transmission of the electronic effect of the substitution at the pyridazine ring may also affect the stereodetemining intermediate. Some complex substrates from natural products and pharmaceutical molecules were also tested. Moderate reaction efficiency (48−74% yields) and good stereoselectivity were obtained (**4ia**−**4ka**).

In conclusion, an annulation reaction was realized for the enantiomeric synthesis of fused azacycles containing a quaternary carbon stereocenter. The reaction was conducted under mild conditions using a novel transformable pyridazine directing group. A new azacycle was constructed via a [5+1] annulation process accompanied by the transformation of the original pyridazine directing group via a double bond migration process. The derivatization of the product and the late-stage functionalization of complex substrates demonstrated more applications of the reaction system.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.3c00278.

Experimental procedures; ^1H NMR, ^{13}C NMR, ^{19}F NMR, and NOESY spectra; HPLC chromatograms; crystal structure of **4aa**; and HRMS spectra of representative compounds (PDF)

Accession Codes

CCDC 2234937 contains 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 Author

Bingxian Liu − *NMPA Key Laboratory for Research and Evaluation of Innovative Drug, School of Chemistry and Chemical Engineering, Pingyuan Laboratory, Henan Normal University, Xinxiang, Henan 453007, China;* orcid.org/0000-0001-9872-9876; Email: liubingxian@htu.edu.cn

Authors

Man Zhu − *NMPA Key Laboratory for Research and Evaluation of Innovative Drug, School of Chemistry and Chemical Engineering, Pingyuan Laboratory, Henan Normal University, Xinxiang, Henan 453007, China*

Yuyao Zhao − *NMPA Key Laboratory for Research and Evaluation of Innovative Drug, School of Chemistry and Chemical Engineering, Pingyuan Laboratory, Henan Normal University, Xinxiang, Henan 453007, China*

Xingwei Li − *NMPA Key Laboratory for Research and Evaluation of Innovative Drug, School of Chemistry and Chemical Engineering, Pingyuan Laboratory, Henan Normal University, Xinxiang, Henan 453007, China;* orcid.org/0000-0002-1153-1558

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.3c00278

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge the financial support for this work by the National Key R&D Program of China (2021YFC0864700), the NSFC (21801066, U1804283, and 82130103), the Central Plains Scholars and Scientists Studio Fund (2018002), the project funded by the Natural Science Foundation of Henan (222300420056 and 222300420204), and the China Postdoctoral Science Foundation (2020M682307 and 2021T140183).

REFERENCES

(1) For selected reviews on synthesis of azacycles, see: (a) Mishra, D. R.; Panda, B. S.; Nayak, S.; Panda, J.; Mohapatra, S. Recent Advances in the Synthesis of 5-Membered *N*-Heterocycles via Rhodium Catalysed Cascade Reactions. *ChemistrySelect* **2022**, *7*, No. e202200531. (b) Patil, N. T.; Yamamoto, Y. Coinage Metal-Assisted Synthesis of Heterocycles. *Chem. Rev.* **2008**, *108*, 3395−3442. (c) Chen, W.-W.; Xu, M.-H. Recent advances in rhodium-catalyzed asymmetric synthesis of heterocycles. *Org. Biomol. Chem.* **2017**, *15*, 1029−1050. (d) Hong, F.-L.; Ye, L.-W. Transition Metal-Catalyzed Tandem Reactions of Ynamides for Divergent N-Heterocycle Synthesis. *Acc. Chem. Res.* **2020**, *53*, 2003−2019. (e) Prabagar, B.; Ghosh, N.; Sahoo, A. K. Cyclization and Cycloisomerization of π-Tethered Ynamides: An Expedient Synthetic Method to Construct Carbo- and Heterocycles. *Synlett* **2017**, *28*, 2539−2555. (f) Chen, J.-R.; Hu, X.-Q.; Lu, L.-Q.; Xiao, W.-J. Formal [4 + 1] Annulation Reactions in the Synthesis of Carbocyclic and Heterocyclic Systems. *Chem. Rev.* **2015**, *115*, 5301−5365. (g) Wang, Y.; Zhang, W.-X.; Xi, Z. Carbodiimide-based synthesis of N-heterocycles: moving from two classical reactive sites to chemical bond breaking/forming reaction. *Chem. Soc. Rev.* **2020**, *49*, 5810−5849.

(2) (a) Ling, Y.; Hao, Z.-Y.; Liang, D.; Zhang, C.-L.; Liu, Y.-F.; Wang, Y. The Expanding Role of Pyridine and Dihydropyridine Scaffolds in Drug Design. *Drug Des. Devel. Ther.* **2021**, *15*, 4289−4338. (b) Sudhana, S. M.; Adi, P. J. Synthesis, Biological Evaluation and Molecular Docking Studies of Novel Di-hydropyridine Analogs as Potent Antioxidants. *Curr. Top. Med. Chem.* **2019**, *19*, 2676−2686. (c) Jampilek, J. Heterocycles in Medicinal Chemistry. *Molecules* **2019**, *24*, 3839.

(3) For selected reviews of C−H activation/annulation, see: (a) Sambiagio, C.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. A comprehensive overview of directing groups applied in metal-catalysed C−H functionalisation chemistry. *Chem. Soc. Rev.* **2018**, *47*, 6603−6743. (b) Wang, R.; Xie, X.; Liu, H.; Zhou, Y. Rh(III)-Catalyzed C−H Bond Activation for the Construction of Heterocycles with sp^3-Carbon Centers. *Catalysts* **2019**, *9*, 823−852. (c) Wang, C.; Chen, F.; Qian, P.; Cheng. Recent advances in the Rh-catalyzed cascade arene C−H bond activation/annulation toward diverse heterocyclic compounds. *Org. Biomol. Chem.* **2021**, *19*, 1705−1721. (d) Guo, X.-X.; Gu, D.-W.; Wu, Z.-X.; Zhang, W.-B. Copper-Catalyzed C-H Functionalization Reactions: Efficient Synthesis of Heterocycles. *Chem. Rev.* **2015**, *115*, 1622−1651. (e) Liu, J.; Xiao, X.; Lai, Y.; Zhang, Z. Recent advances in transition metal-catalyzed hetero-annulative difunctionalization of alkenes via C−H activation for the synthesis of heterocycles. *Org. Chem. Front.* **2022**, *9*, 2256−2279. (g) Santhoshkumar, R.; Cheng, C.-H. Reaching Green: Heterocycle Synthesis by Transition Metal-Catalyzed C−H Functionalization in Sustainable Medium. *Chem. - Eur. J.* **2019**, *25*, 9366−9384. (h) Karak, P.; Rana, S. S.; Choudhury, J. Cationic p-extended heteroaromatics via a catalytic C−H activation annulative alkyne-insertion sequence. *Chem. Commun.* **2021**, *58*, 133−154. (i) Gandeepan, P.; Cheng, C.-H. Advancements in the Synthesis and Applications of Cationic *N*-Heterocycles through Transition Metal-Catalyzed C-H Activation. *Chem. - Asian J.* **2016**, *11*, 448−460. (j) Song, L.; Van der Eycken, E. V. Transition Metal-Catalyzed Intermolecular Cascade C−H Activation/Annulation Processes for the Synthesis of Polycycles. *Chem. - Eur. J.* **2021**, *27*, 121−144.

(4) For selected reviews, see: (a) Colby, D. A.; Bergman, R. G.; Ellman, J. A. Rhodium-Catalyzed C−C Bond Formation via Heteroatom-Directed C−H Bond Activation. *Chem. Rev.* **2010**, *110*, 624−655. (b) Gandeepan, P.; Müller, T.; Zell, D.; Cera, G.; Warratz, S.; Ackermann, L. 3d Transition Metals for C−H Activation. *Chem. Rev.* **2019**, *119*, 2192−2452.

(5) For selected papers, see: (a) Davies, D. L.; Ellul, C. E.; Macgregor, S. A.; McMullin, C. L.; Singh, K. Experimental and DFT Studies Explain Solvent Control of C−H Activation and Product Selectivity in the Rh(III)-Catalyzed Formation of Neutral and Cationic Heterocycles. *J. Am. Chem. Soc.* **2015**, *137*, 9659−9669. (b) Ghorai, D.; Choudhury, J. Rhodium(III)−N-Heterocyclic Carbene-Driven Cascade C−H Activation Catalysis. *ACS Catal.* **2015**, *5*, 2692−2696. (c) Dutta, C.; Rana, S. S.; Choudhury, J. Leveraging Metallotropism-Enabled Substrate Activation in Cobalt-Catalyzed Annulation Chemistry: Protic NHC Template Is the Key. *ACS Catal.* **2019**, *9*, 10674−10679. (d) Jayakumar, J.; Vedarethinam, G.; Hsiao, H.-C.; Sun, S.-Y.; Chuang, S.-C. Cascade One-Pot Synthesis of Orange-Red-Fluorescent Polycyclic Cinnolino[2,3-f]-phenanthridin-9-ium Salts by Palladium(II)-Catalyzed C−H Bond Activation of 2-Azobiaryl Compounds and Alkenes. *Angew. Chem., Int. Ed.* **2020**, *59*, 689−694. (e) Villar, J. M.; Suarez, J.; Varela, J. A.; Saa, C. N-Doped Cationic PAHs by Rh(III)-Catalyzed Double C−H Activation and Annulation of 2-Arylbenzimidazoles with Alkynes. *Org. Lett.* **2017**, *19*, 1702−1705. (f) Wang, Y.; Li, B.; Wang, B. Synthesis of Cinnolines and Cinnolinium Salt Derivatives by Rh(III)- Catalyzed Cascade Oxidative Coupling/Cyclization Reactions. *J. Org. Chem.* **2018**, *83*, 10845−10854. (g) Bai, D.; Xia, J.; Song, F.; Li, X.; Liu, B.; Liu, L.; Zheng, G.; Yang, X.; Sun, J.; Li, X. Rhodium(iii)-catalyzed diverse [4 + 1] annulation of arenes with 1,3-enynes via sp^3/sp^2 C−H activation and 1,4-rhodium migration. *Chem. Sci.* **2019**, *10*, 3987−3993. (h) Xu, K.; Fu, Y.; Zhou, Y.; Hennersdorf, F.; Machata, P.; Vincon, I.; Weigand, J. J.; Popov, A. A.; Berger, R.; Feng, X. Cationic Nitrogen-Doped Helical Nanographenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 15876−15881. (i) Karak, P.; Dutta, C.; Dutta, T.; Koner, A. L.; Choudhury, J. Orchestrated catalytic double rollover annulation: rapid access to N-enriched cationic and neutral PAHs. *Chem. Commun.* **2019**, *55*, 6791−6794. (j) Mayakrishnan, S.; Tamizmani, M.; Balachandran, C.; Aoki, S.; Maheswari, N. U. Rh(III)-Catalysed synthesis of cinnolinium and fluoranthenium salts using C−H activation/ annulation reactions: organelle specific mitochondrial staining applications. *Org. Biomol. Chem.* **2021**, *19*, 5413−5425. (k) Chen, X.; Zheng, G.; Song, G.; Li, X. *Adv. Synth. Catal.* **2018**, *360*, 2836.

(6) Zhu, C.; Kuniyil, R.; Ackermann, L. Manganese(I)-Catalyzed C−H Activation/Diels−Alder/retro-Diels−Alder Domino Alkyne Annulation featuring Transformable Pyridines. *Angew. Chem., Int. Ed.* **2019**, *58*, 5338−5342.

(7) Zheng, G.; Sun, J.; Xu, Y.; Zhai, S.; Li, X. Mn-Catalyzed Dehydrocyanative Transannulation of Heteroarenes via C-H Activation: Beyond the Permanent Directing Effects of Pyridines/ Pyrimidines. *Angew. Chem., Int. Ed.* **2019**, *58*, 5090−5094.

(8) Wang, Q.; Zhang, W.-W.; Zheng, C.; Gu, Q.; You, S.-L. Enantioselective Synthesis of Azoniahelicenes by Rh-Catalyzed C−H Annulation with Alkynes. *J. Am. Chem. Soc.* **2021**, *143*, 114−120.

(9) (a) Sun, J.; Yuan, W.; Tian, R.; Wang, P.; Zhang, X.-P.; Li, X. Rhodium(III)-Catalyzed Asymmetric [4 + 1] and [5 + 1] Annulation of Arenes and 1,3-Enynes: Distinct Mechanism of Allyl Formation and Allyl Functionalization. *Angew. Chem., Int. Ed.* **2020**, *59*, 22706−22713. (b) Burns, D. J.; Lam, H. W. Catalytic 1,4-Rhodium(III) Migration Enables 1,3-Enynes to Functionas One-Carbon Oxidative Annulation Partners in C-H. *Angew. Chem., Int. Ed.* **2014**, *126*, 10089−10093. (c) Dooley, J. D.; Lam, H. W. Corrigendum: One-Carbon Oxidative Annulations of 1,3-Enynes by Catalytic C-H Functionalization and 1,4-Rhodium(III) Migration. *Chem. - Eur. J.* **2018**, *24*, 8692. (d) Xu, F.; Kang, W.-F.; Wang, Y.; Liu, C.-S.; Tian, J.-Y.; Zhao, R.-R.; Du, M. Rhodium(III)-Catalyzed Cascade [5 + 1] Annulation/5-exo-Cyclization Initiated by C−H Activation: 1,6-Diynes as One-Carbon Reaction Partners. *Org. Lett.* **2018**, *20*, 3245−3249. (e) Kuppusamy, R.; Muralirajan, K.; Cheng, C.-H. Cobalt(III)-Catalyzed [5 + 1] Annulation for 2H-Chromenes Synthesis via Vinylic C−H Activation and Intramolecular Nucleophilic Addition. *ACS Catal.* **2016**, *6*, 3909−3913. (f) Chen, P.; Nan, J.; Hu, Y.; Ma, Q.; Ma, Y. Ru^{II}-Catalyzed/NH_2-Assisted Selective Alkenyl C−H [5 + 1] Annulation of Alkenylanilines with Sulfoxonium Ylides to Quinolines. *Org. Lett.* **2019**, *21*, 4812−4815. (g) Singh, A.; Shukla, R. K.; Volla, C. M. R. Rh(III)-Catalyzed [5 + 1] annulation of 2-alkenylanilides and 2-alkenylphenols with allenyl acetates. *Chem. Sci.* **2022**, *13*, 2043−2049.

https://doi.org/10.1021/acs.orglett.3c00278
Org. Lett. XXXX, XXX, XXX−XXX

(10) (a) He, Z.-X.; Gong, Y.-P.; Zhang, X.; Ma, L.-Y.; Zhao, W. Pyridazine as a privileged structure: An updated review on anticancer activity of pyridazine containing bioactive molecules. *Eur. J. Med. Chem.* **2021**, *209*, 112946. (b) Liu, X.; Kou, J.; Xiao, Z.; Tian, F.; Hu, J.; Zheng, P.; Zhu, W. Design, Synthesis and Biological Evaluation of 6,7-Disubstituted-4-phenoxyquinoline Derivatives Bearing Pyridazinone Moiety as c-Met Inhibitors. *Molecules.* **2018**, *23*, 1543. (c) Zhang, B.; Liu, X.; Xiong, H.; Zhang, Q.; Sun, X.; Yang, Z.; Xu, S.; Zheng, P.; Zhu, W. Discovery of [1,2,4]triazolo[4,3-a]pyrazine derivatives bearing a 4-oxo-pyridazinone moiety as potential c-Met kinase inhibitors. *New J. Chem.* **2020**, *44*, 9053−9063. (d) Zhang, Q.; Liu, X.; Gan, W.; Wu, J.; Zhou, H.; Yang, Z.; Zhang, Y.; Liao, M.; Yuan, P.; Xu, S.; Zheng, P.; Zhu, W. Discovery of Triazolo-pyridazine/-pyrimidine Derivatives Bearing Aromatic (Heterocycle)-Coupled Azole Units as Class II c-Met Inhibitors. *ACS Omega.* **2020**, *5*, 16482−16490.

(11) Rahim, A.; Feng, J.; Gu, Z. 1,4-Migration of Transition Metals in Organic Synthesis. *Chin. J. Chem.* **2019**, *37*, 929−945.

https://doi.org/10.1021/acs.orglett.3c00278
Org. Lett. XXXX, XXX, XXX−XXX