ORGANIC CHEMISTRY







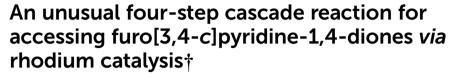
FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue



Cite this: *Org. Chem. Front.*, 2023, **10**, 4658



Yidi Li,‡^{a,e} Huiying Xu, [b]‡^c Zhi Zhou, [b]*^c Lin Huang, b,d Zhenhao Tang,d Wei Yi [b]*^c and Xiaowei Wu [b]*^{a,b,d,e}

The development of efficient cascade reactions is highly important and appealing because of their desirable step-economy and convenience in constructing multiple chemical bonds and complex molecules in one shot. Herein, we report a rare four-step tandem reaction between acrylamides and 4-hydroxy-2-alkynoates to prepare novel furo[3,4-c]pyridine-1,4-diones which are difficult to synthesize by traditional methods. This unique domino reaction includes C–H activation, Lossen rearrangement, annulation, and lactonization. Additionally, this protocol features good functional group tolerance, obtainment of products by simple filtration, room temperature, and air compatibility. DFT calculations were conducted to shed some light on the reaction mechanism.

Received 19th June 2023, Accepted 5th August 2023 DOI: 10.1039/d3qo00909b

rsc.li/frontiers-organic

Introduction

The prevalence of heterocycles in natural products and pharmaceuticals has led to the importance and benefits of synthesizing such compounds efficiently. In the past decades, directing group (DG) assisted C–H activation/annulation reactions *via* transition-metal catalysis for the synthesis of heterocycles have achieved tremendous advances. ^{1,2} DGs play crucial roles in controlling chemical reactivity and regioselectivity in C–H activation reactions. On the other hand, DGs simply adhere to primordial positions and function as auxiliary groups in these reactions without other transformations. Amide-type DGs are frequently applied to C–H activation/annulation reactions for the synthesis of prevalent isoquinolones

and 2-pyridones, where DGs remain static in most cases (Scheme 1a). 1,2a-f,3 The rearrangement or migration of DGs in C–H activation reactions provides an intriguing strategy to construct C–C/C–N bonds and also contributes to the synthesis of novel heterocyclic scaffolds. 4,5 Therefore, it is fascinating to apply this emerging strategy to organic synthesis. Nevertheless, the development of this emerging strategy involving DG rearrangement or migration still falls far behind when compared to the numerous reports of static DGs participating in C–H activation reactions.

Even though DGs could improve chemoselectivity and regioselectivity, they may be present as undesired moieties on products at times, and additional steps are required to remove unwanted DGs. If DGs undergo a rearrangement process, it will not only create a new and efficient avenue for synthesizing heterocycles, but also possibly generate novel heterocycles that traditional approaches can hardly furnish. By taking advantage of the strategy of directing group rearrangement, a series of intriguing spirooxindole pyrrolones were synthesized elegantly by Dai's group (Scheme 1b).6 Acrylamides involving the rearrangement of DGs undergo three processes: C-H activation, directing group rearrangement, and annulation. Recently, we developed an efficient rhodium-catalyzed domino C-H alkenylation, DG migration, and lactonization reaction between N-carbamoyl indoles and 4-hydroxy-2-alkynoates for the synthesis of the furan-2(5H)-one scaffold (Scheme 1c).7 Efficient cascade reactions are highly appealing due to their desirable step-economy and convenience in constructing complex molecules with multiple chemical bonds in one shot.8-11

To our knowledge, the implementation of a multistep cascade reaction involving four distinct processes of C-H acti-

^aDrug Discovery and Development Center, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China.

 $[\]hbox{\it E-mail: zhouzhi@gzhmu.edu.cn, wuxiaowei@simm.ac.cn}$

^bSchool of Pharmaceutical Sciences, Southern Medical University, Guangzhou 510515. China

^cGuangzhou Municipal and Guangdong Provincial Key Laboratory of Protein Modification and Degradation & Molecular Target and Clinical Pharmacology, State Key Laboratory of Respiratory Disease, School of Pharmaceutical Sciences & the Fifth Affiliated Hospital, Guangzhou Medical University, Guangzhou, Guangdong 511436, China. E-mail: yiwei@gzhmu.edu.cn

^dZhongshan Institute for Drug Discovery, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Zhongshan 528400, China

^eUniversity of Chinese Academy of Sciences, No. 19A Yuquan Road, Beijing 100049, China

[†] Electronic supplementary information (ESI) available. CCDC 2281784. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3q000909b

[‡]These authors contributed equally.

Previous work:

a) C(sp²)-H activation/[4+2] annulation assisted by static DGs (well-established)

b) C(sp²)-H activation/DG Lossen rearrangement/annulation with diazo oxindoles

$$\begin{array}{c} 0 \\ R^{1} \\ N \end{array} \begin{array}{c} O \\ P \end{array} \begin{array}{c} O \\ P \end{array} \begin{array}{c} O \\ N \end{array} \begin{array}{c} O \\$$

c) C(sp²)-H activation/DG migration/lactonization with 4-hydroxy-2-alkynoates

This work

d) Unprecedented C(sp²)-H activation/DG Lossen rearrangement/annulation/lactonization cascade

Scheme 1 Transition-metal catalyzed C–H activation/annulation reactions.

vation, directing group rearrangement, annulation, and lactonization has yet to be documented. In this study, we report a rare four-step tandem reaction between acrylamides and 4-hydroxy-2-alkynoates 12 to prepare novel furo[3,4-c]pyridine-1,4-diones which are difficult to synthesize by traditional methods. The four-step tandem reaction involves C–H activation, DG Lossen rearrangement, [4 + 2] annulation, and lactonization. The method can tolerate a variety of functional groups. Furthermore, the products can be easily purified by filtration and the reaction is compatible with both room temperature and air. These features contribute to the practicality and versatility of the protocol.

Results and discussion

We embarked on our studies with the optimization of the reaction conditions for the cyclization between acrylamide ${\bf 1a}$ and ethyl 4-hydroxy-4-phenylbut-2-ynoate ${\bf 2a}$. No desired product ${\bf 3a}$ was obtained when catalyzed by MnBr(CO)5, [RuCl2(p-cym)]2, Cp*Co(CO)I2 and Pd(OAc)2, respectively (Table 1, entries 1–6). Switching to [Cp*IrCl2]2 led to only 6% yield (entry 2). In contrast, the yield of ${\bf 3a}$ was improved to 73%, and 43% of the product could be obtained by simple filtration when using [Cp*RhCl2]2 (entry 5). The structure of ${\bf 3a}$ was confirmed using 1D-NMR and NOESY experiments as well as mass spectra. Solvent screening revealed that TFE outperformed

Table 1 Optimization of reaction conditions^a

Entry	Catalyst	Additive	Solvent	$\mathrm{Yield}^{b,c}\left(\% ight)$
1	MnBr(CO) ₅	NaOAc	TFE	0
2	$[Cp*IrCl_2]_2$	NaOAc	TFE	6
3	Cp*Co(CO)I ₂	NaOAc	TFE	0
4	$[Ru(p-cym)Cl_2]_2$	NaOAc	TFE	0
5	$[Cp*RhCl_2]_2$	NaOAc	TFE	73 (47)
6	Pd(OAc) ₂	NaOAc	TFE	0
7	$[Cp*RhCl_2]_2$	NaOAc	THF	Trace
8	$[Cp*RhCl_2]_2$	NaOAc	MeOH	15
9	$[Cp*RhCl_2]_2$	NaOAc	DCE	32
10	$[Cp*RhCl_2]_2$	NaOAc	CH_3CN	0
11	$[Cp*RhCl_2]_2$	NaOAc	EA	20
12	$[Cp*RhCl_2]_2$	Na_2CO_3	EtOH	0
13	$[Cp*RhCl_2]_2$	Na_2CO_3	TFE	78 (53)
14	$[Cp*RhCl_2]_2$	K_2CO_3	TFE	19 `
15	$[Cp*RhCl_2]_2$	CsOAc	TFE	54 (37)
16	$[Cp*RhCl_2]_2$	KOAc	TFE	46 (33)
17^{d}	$[Cp*RhCl_2]_2$	_	TFE	0
18^e		Na_2CO_3	TFE	0

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (3 mol%), additive (0.2 mmol), under air, solvent (1.0 mL), room temperature, 6 h. ^b Total isolated yield. ^c Isolated yields obtained by simple filtration are shown in parenthesis. ^d Na₂CO₃ was not used. ^e [Cp*RhCl₂]₂ was not used.

other common solvents, such as THF (only trace), MeOH (15% yield), DCE (32% yield with 40% substrate not being consumed) and EA (20% yield) (entries 7–11). When using ethanol and adding Na₂CO₃ as a base, the yield of **3a** was 0% (entry 12). After extensive screening of additives, such as Na₂CO₃, K₂CO₃, CsOAc, and KOAc, Na₂CO₃ was identified as the optimal one (entries 13–16). The control experiments confirmed that no desired reaction occurred in the absence of an additive or rhodium (entries 17 and 18).

With the optimal conditions in hand, we next examined the scope of this cyclization reaction (Scheme 2). Aryl-substituted propynol bearing electron-donating groups are all tolerated in this system, such as CH3, t-Bu, OMe, and CH2CH3, and the corresponding products can be obtained in high yields by direct filtration (3a-3e). To our delight, electron-withdrawing groups including F, Cl, Br, and I were also tolerated well with the isolated yields ranging from 62% to 72% (3f-3i). Although the yield of the product dropped dramatically when the group was changed to cyclopentyl (3k), the reaction was compatible with other different rings (naphthalene, furan, and thiophene) and afforded the products smoothly (3j, 3l, and 3m). We also explored tertiary alkynol and obtained the desired product in a moderate yield (3n). Next, we investigated R¹ of acrylamide 1 bearing electron-donating and electron-withdrawing groups at the para position of the phenyl group, and the reactions proceeded well to generate the corresponding products. In comparison, when the phenyl group was changed to the benzyl

Research Article

Scheme 2 Substrate scope. Reaction conditions: 1 (0.2 mmol), 2 (0.24 mmol), [Cp*RhCl₂]₂ (3 mmol%), Na₂CO₃ (0.2 mmol), under air, trifluoroethanol (1.0 mL), rt, 6-12 h. Total yields are shown, and yields obtained by simple filtration are shown in parentheses.

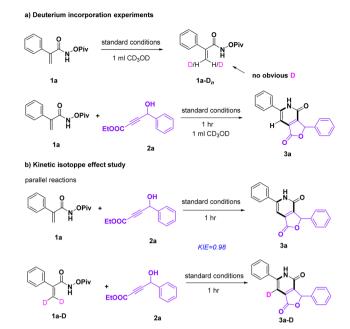
and methyl group, the yield dropped to 47% and 20%, respectively (30-3u). Additionally, the structures of 3h, 3n, 3p, and 3q were further confirmed by NOESY experiments.

Several experiments were conducted to probe the reaction mechanism. In the presence of 1a, Na₂CO₃, [Cp*RhCl₂]₂, and 1.0 ml methanol- d^4 , the experiment of H/D exchange occurring at the olefinic bond of acrylamide was performed (Scheme 3a). And no obvious deuterium incorporation was observed at this position (8% D). In addition, there was also almost no D at the olefinic bond of 3a after adding 2a. The result demonstrated that the cleavage of the C-H bond could be irreversible.

Additionally, two parallel reactions were performed giving a KIE value of 0.98 (Scheme 3b), which suggested that the C-H activation step was less likely to be involved in the rate-determining step.

X= I, 3u, 66% (40%)

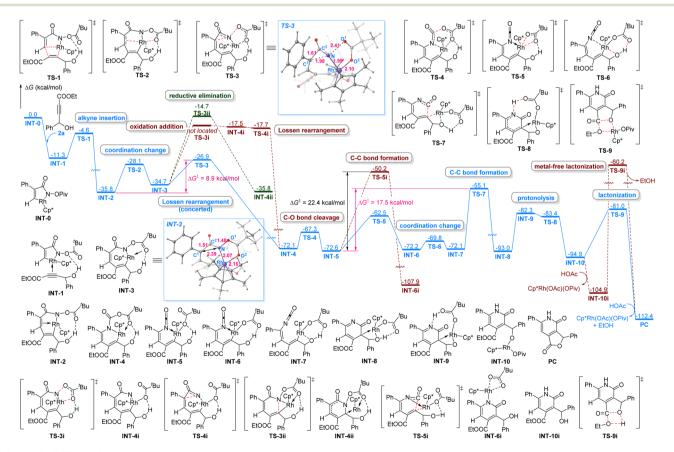
To further obtain the mechanistic features of the unprecedented Rh(III)-catalyzed sequential C-H activation/Lossen rearrangement/[4 + 2] annulation/lactonization cascade, we next performed DFT calculations on the key reaction steps: alkyne insertion, Lossen rearrangement, [4 + 2] annulation and lactonization. As shown in Scheme 4, the five-membered rhodacycle INT-0 derived from C-H activation was rationally



Scheme 3 Deuteration and KIE experiments.

selected as the starting point, which coordinated with propargyl alcohol 2a and produced the intermediate INT-1 (ΔG^{\ddagger} = -11.3 kcal mol⁻¹) involving hydrogen-bonding between the

hydroxyl group of 2a and the pivalate group. Then the C-C unsaturated bond of 2a was inserted into the Rh-C bond via **TS-1** ($\Delta G^{\ddagger} = -4.6 \text{ kcal mol}^{-1}$) to deliver **INT-2** with a free energy of -35.8 kcal mol⁻¹. The subsequent facile coordination change via TS-2 ($\Delta G^{\ddagger} = -28.1 \text{ kcal mol}^{-1}$) produced the unstable intermediate INT-3 which afforded different reaction paths. The concerted Lossen rearrangement/N-O bond cleavage from INT-3 occurred via TS-3 ($\Delta G^{\ddagger} = -26.9 \text{ kcal mol}^{-1}$) which demanded an energy barrier of 8.9 kcal mol⁻¹ (from INT-2 to TS-3) to give the intermediate INT-4 along with a considerable quantity of heat. The relatively elongated N-O¹ bond (1.48 Å vs. 1.42 Å in INT-0) in the geometry of INT-3 and the significantly elongated N-O¹ bond (2.41 Å) and shortened C¹-N bond (1.98 Å) in the transition state TS-3 suggest that the Lossen rearrangement was assisted by the pivalate group and the rhodium center. Alternatively, classic C-N bond reductive elimination via TS-3ii ($\Delta G^{\ddagger} = -14.7 \text{ kcal mol}^{-1}$) involved a higher energy barrier of 21.1 kcal mol⁻¹ (from **INT-2** to **TS-3ii**). Moreover, the Rh(III)-Rh(V)-Rh(III) reaction path involving an oxidative addition process from INT-3 was also ruled out owing to the relatively high free energies of INT-4i/TS-4i. After low-barrier isomerization via TS-4, INT-4 was transformed into the isocyanate intermediate INT-5 from which the direct C-C bond formation/annulation occurred via TS-5i (ΔG^{\ddagger} = -50.2 kcal mol⁻¹) and required a barrier of 22.4 kcal mol⁻¹ (from INT-5 to TS-5i). However, the coordination change via



DFT calculations of the reaction pathways.

TS-5/TS-6 led to a more favorable C-C bond formation reaction via TS-7 ($\Delta G^{\ddagger} = -55.1 \text{ kcal mol}^{-1}$) which only needs an activation energy of 17.5 kcal mol⁻¹. Afterwards, the protonolysis reaction via INT-9/TS-8 was followed by lactonization via TS-9 $(\Delta G^{\ddagger} = -81.0 \text{ kcal mol}^{-1})$. Alternatively, the metal-free lactonization without the rhodium complex goes through TS-9i (ΔG^{\ddagger} = -60.2 kcal mol⁻¹) which is of a much higher barrier and can be ruled out.

In order to shed light on the driving force of the Lossen rearrangement, we examined closely the geometry change along the intrinsic reaction coordinate (IRC) corresponding to TS-3 (see the ESI for details†). The results revealed that at the beginning the N-O1 bond distance increases which seems to drive the C1 atom attack on the N atom. The reaction goes through TS-3 and then the N-O1 bond breaks which is followed by C1-N bond formation and C1-C2 bond cleavage. This gives a chance for the O1 atom to attack the positively charged C² atom. With the assistance of the pivalate group and the rhodium center, the Lossen rearrangement involves multiple σ -bond metathesis processes.

Conclusions

Research Article

In summary, we have developed a rare four-step tandem reaction between acrylamides and 4-hydroxy-2-alkynoates to prepare novel furo[3,4-c]pyridine-1,4-diones. This unique tandem reaction consists of C-H activation, Lossen rearrangement, [4 + 2] annulation, and lactonization. The protocol features good functional group tolerance, obtainment of pure products by simple filtration, room temperature, and air compatibility. In addition, DFT calculations were conducted to shed some light on the reaction mechanism.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Financial support from the Basic and Applied Basic Research Foundation of Guangdong Province (2021A1515110468), Shanghai Pujiang Program (21PJ1415800), Natural Science Foundation of Guangdong Province (2019A1515010935), Highlevel New R&D Institute (2019B090904008), High-level Innovative Research Institute (2021B0909050003), and NSFC (21877020 and 22007020) is gratefully acknowledged. We also thank Wei Zhang from the Zhongshan Institute for Drug Discovery for X-ray crystallographic analysis.

References

1 (a) P. Gandeepan, T. Müller, D. Zell, G. Cera, S. Warratz and L. Ackermann, 3d Transition Metals for C-H Activation,

Chem. Rev., 2019, 119, 2192-2452; (b) D. J. Abrams, P. A. Provencher and E. J. Sorensen, Recent applications of C-H functionalization in complex natural product syn-2018, 47, 8925-8967; Chem. Soc. Rev., (c) C. Sambiagio, D. Schönbauer, R. Blieck, T. D. Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. W. Delord, T. Besset, B. U. W. Maes and M. Schnürch, A comprehensive overview of directing groups applied in metal-catalysed C-H functionalisation chemistry, Chem. Soc. Rev., 2018, 47, 6603-6743; (d) Y. Yang, J. Lan and J. You, Oxidative C-H/C-H Coupling Reactions between Two (Hetero)arenes, Chem. Rev., 2017, 117, 8787-8863; (e) T. Gensch, M. N. Hopkinson, F. Glorius and J. W. Delord, Mild metal-catalyzed C-H activation: examples and concepts, Chem. Soc. Rev., 2016, 45, 2900-2936; (f) P. Augustin, G. Catherine and C. Laurent, Recent Advances in [Cp*M^{III}] (M = Co, Rh, Ir)-Catalyzed Intramolecular Annulation Through C-H Activation, Eur. J. Org. Chem., 2018, 5777-5794; (g) D. Mandal, S. Roychowdhury, J. P. Biswas, S. Maiti and D. Maiti, Transition-metal-catalyzed C-H bond alkylation using olefins: recent advances and mechanistic aspects, Chem. Soc. Rev., 2022, 51, 7358-7426; (h) L. Ackermann, Metallaelectrocatalyzed C-H Activation by Earth-Abundant 3d Metals and Beyond, Acc. Chem. Res., 2020, 53, 84-104.

2 (a) S. Mochida, N. Umeda, K. Hirano, T. Satoh and Miura, Rhodium-catalyzed Oxidative Coupling/ Cyclization of Benzamides with Alkynes via C-H Bond Cleavage, Chem. Lett., 2010, 39, 744-746; (b) T. K. Hyster and T. Rovis, Rhodium-Catalyzed Oxidative Cycloaddition of Benzamides and Alkynes via C-H/N-H Activation, J. Am. Chem. Soc., 2010, 132, 10565-10569; (c) N. Guimond, C. Gouliaras and K. Fagnou, Rhodium(III)-catalyzed isoquinolone synthesis: the N-O bond as a handle for C-N bond formation and catalyst turnover, J. Am. Chem. Soc., 2010, 132, 6908-6909; (d) Y. Su, M. Zhao, K. Han, G. Song and X. Li, Synthesis of 2-pyridones and iminoesters via Rh(III)catalyzed oxidative coupling between acrylamides and alkynes, Org. Lett., 2010, 12, 5462-5465; (e) X. Xu, Y. Liu and C.-M. Park, Rhodium(III)-catalyzed intramolecular annulation through C-H activation: total synthesis of (\pm)-antofine, (\pm)-septicine, (\pm)-tylophorine, and rosettacin, Int. Ed.,2012, 51, (f) N. Quiñones, A. Seoane, R. G. Fandiño, J. L. Mascareñas and M. Gulías, Rhodium(III)-catalyzed intramolecular annulations involving amide-directed C-H activations: synthetic scope and mechanistic studies, Chem. Sci., 2013, 4, 2874-2879; (g) X. Wu, B. Wang, Y. Zhou and H. Liu, Propargyl Alcohols as One-Carbon Synthons: Redox-Neutral Rhodium (III)-Catalyzed C-H Bond Activation for the Synthesis of Isoindolinones Bearing a Quaternary Carbon, Org. Lett., 2017, 19, 1294-1297; (h) X. Wu, B. Wang, S. Zhou, Y. Zhou and H. Liu, Ruthenium-Catalyzed Redox-Neutral [4 + 1] Annulation of Benzamides and Propargyl Alcohols via C-H Bond Activation, ACS Catal., 2017, 4, 2494-2499; (i) L. Grigorjeva and O. Daugulis, Cobalt-catalyzed, amino-

quinoline-directed C(sp²)-H bond alkenylation by alkynes, Chem., Int. Ed., 2014, 53, 10209-10212; (j) A. Lerchen, T. Knecht, M. Koy, C. G. Daniliuc and F. Glorius, A General Cp*CoIII-Catalyzed Intramolecular C-H Activation Approach for the Efficient Total Syntheses of Aromathecin, Protoberberine, and Tylophora Alkaloids, Chem. - Eur. J., 2017, 23, 12149-12152; (k) X. Wu and H. Ji, Rhodium-Catalyzed [4 + 1] Cyclization via C-H Activation for the Synthesis of Divergent Heterocycles Bearing a Quaternary Carbon, J. Org. Chem., 2018, 83, 4650-4656; (l) X. Wu, P. Li, Y. Lu, J. Qiao, J. Zhao, X. Jia, H. Ni, L. Kong, X. Zhang and F. Zhao, 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; (m) Y. Yu, L. Huang, W. Wu and H. Jiang, Palladium-catalyzed oxidative annulation of acrylic acid and amide with alkynes: a practical route to synthesize α-pyrones and pyridines, Org. Lett., 2014, 16, 2146-2149.

- 3 (a) H. Meng, H. Xu, Z. Zhou, Z. Tang, Y. Li, Y. Zhou, W. Yi and X. Wu, Recyclable rhodium-catalyzed C-H activation/[4 + 2] annulation with unconventional regioselectivity at ambient temperature: experimental development and mechanistic insight, Green Chem., 2022, 24, 7012-7021; (b) T. von Münchow, S. Dana, Y. Xu, B. Yuan and L. Ackermann, Enantioselective electrochemical cobaltcatalyzed aryl C-H activation reactions, Science, 2023, 379, 1036–1042; (c) P. Wang, H. Wu, X.-P. Zhang, G. Huang, R. H. Crabtree and X. Li, Sigma-Bond Metathesis as an Unusual Asymmetric Induction Step in Rhodium-Catalyzed Enantiodivergent Synthesis of C-N Axially Chiral Biaryls, J. Am. Chem. Soc., 2023, 145, 8417-8429; (d) Y. Chao, L. Shi, F. Wang, Y. Su, J.-B. Xia and F. Li, Rhodium-Catalyzed Asymmetric (3 + 2 + 2) Annulation via N-H/C-H Dual Activation and Internal Alkyne Insertion toward N-Fused 5/ Bicycles, ACS Catal., 2022, 12, 14194-14208; (e) T. Kurihara, M. Kojima, T. Yoshino and S. Matsunaga, Cp*Rh(III)/Chiral Lewis Base Cooperative Catalysis for Enantioselective Cyclization via C-H Activation, J. Am. Chem. Soc., 2022, 144, 7058-7065; (f) R. K. Shukla, A. M. Nair and C. M. R. Volla, Pd(ii)-catalyzed β - and γ -C-(sp³)-H dienylation with allenyl acetates, *Chem. Sci.*, 2022, 14, 955-962.
- 4 (a) C.-Q. Wang, Y. Zhang and C. Feng, Fluorine Effects on Group Migration via a Rhodium(v) Nitrenoid Intermediate, Angew. Chem., Int. Ed., 2017, 56, 14918-14922; (b) T. Yamada, Y. Shibata and K. Tanaka, Formal Lossen Rearrangement/Alkenylation or Annulation Cascade of Heterole Carboxamides with Alkynes Catalyzed by CpRhIII Complexes with Pendant Amides, Chem. - Eur. J., 2019, 25, 16022-16031; (c) T. Yamada, Y. Shibata, S. Kawauchi, Yoshizaki and K. Tanaka, Formal Lossen Rearrangement/[3 + 2] Annulation Cascade Catalyzed by a Modified Cyclopentadienyl Rh^{III} Complex, Chem. - Eur. J., 2018, 24, 5723-5727; (d) M. Bian, H. Mawjuda, H. Gao, H. Xu, Z. Zhou and W. Yi, Lossen Rearrangement vs C-N

- Reductive Elimination Enabled by Rh(III)-Catalyzed C-H Activation/Selective Lactone Ring-Opening: Chemodivergent Synthesis of Quinolinones and Dihydroisoquinolinones, Org. Lett., 2020, 22, 9677-9682; (e) J.-F. Tan, C. T. Bormann, K. Severin and N. Cramer, Fluoroalkyne Alkynyl Triazenes as Surrogates: Regioselective Access to 4-Fluoro-2-pyridones by a Rh(III)-Catalyzed C-H Activation-Lossen Rearrangement-Wallach Reaction, ACS Catal., 2020, 10, 3790-3796; (f) M. Peng, C.-S. Wang, P.-P. Chen, T. Roisnel, H. Doucet, K. N. Houk and J. F. Soulé, Merging C-H Bond Activation, Alkyne and Rearrangements by Rh(III)-Catalysis: Oxindole Synthesis from Nitroarenes and Alkynes, J. Am. Chem. Soc., 2023, 145, 4508-4516; (g) Y. Li, H. Xu, L. Huang, Z. Zhou, Z. Tang, H. Meng, W. Zhang, W. Yi and X. Wu, Rhodium-catalyzed Regioselective C-H Activation/ Lossen Rearrangement/Annulation for the Green Synthesis of Trisubstituted 2-Pyridones, Org. Chem. Front., 2023, 10, 3000-3009; (h) R. B. Dateer and S. Chang, Selective Cyclization of Arylnitrones to Indolines under External Oxidant-Free Conditions: Dual Role of Rh(III) Catalyst in the C-H Activation and Oxygen Atom Transfer, J. Am. Chem. Soc., 2015, 137, 4908-4911; (i) J.-L. Pan, P. Xie, C. Chen, Y. Hao, C. Liu, H.-Y. Bai, J. Ding, L.-R. Wang, Y. Xia and S.-Y. Zhang, Rhodium(III)-Catalyzed Redox-Neutral Cascade [3 + 2] Annulation of N-Phenoxyacetamides with Propiolates via C-H Functionalization/Isomerization/ Lactonization, Org. Lett., 2018, 20, 7131-7136.
- 5 (a) Y. Wu, C. Pi, Y. Wu and X. Cui, Directing group migration strategy in transition-metal-catalysed direct C-H functionalization, Chem. Soc. Rev., 2021, 50, 3677-3689; (b) X. Zhou, Z. Fan, Z. Zhang, P. Lu and Y. Wang, Construction of Pyrrolo [1,2-a]indoles via Cobalt(III)-Catalyzed Enaminylation of 1-(Pyrimidin-2-yl)-1H-indoles with Ketenimines and Subsequent Base-Promoted Cyclization, Org. Lett., 2016, 18, 4706-4709; (c) S.-Y. Chen, X.-L. Han, J.-Q. Wu, Q. Li, Y. Chen and H. Wang, Manganese(1)-Catalyzed Regio- and Stereoselective 1,2-Diheteroarylation of Allenes: Combination of C-H Activation and Smiles Rearrangement, Angew. Chem., Int. Ed., 2017, 56, 9939–9943; (d) C. Wang, A. Wang and M. Rueping, Manganese Catalyzed C-H **Functionalizations:** Hydroarylations and Alkenylations Involving an Unexpected Heteroaryl Shift, Angew. Chem., Int. Ed., 2017, 56, 9935–9938; (e) C. Zhu, R. Kuniyil, B. B. Jei and L. Ackermann, Domino C-HActivation/Directing Group Migration/Alkyne Annulation: Unique Selectivity by d⁶-Cobalt(III) Catalysts, ACS Catal., 2020, 10, 4444-4450; (f) X. Wang, T. Gensch, A. Lerchen, C. G. Daniliuc and F. Glorius, Cp*Rh(III)/Bicyclic Olefin Cocatalyzed C-H Bond Amidation by Intramolecular Amide Transfer, J. Am. Chem. Soc., 2017, 139, 6506-6512; (g) Y. Wu, Z. Chen, Y. Yang, W. Zhu and B. Zhou, Rh(III)-Catalyzed Redox Neutral Unsymmetrical C-H Alkylation and Amidation Reactions of N-Phenoxyacetamides, J. Am. Chem. Soc., 2018, 140, 42-45.
- 6 B. Ma, P. Wu, X. Wang, Z. Wang, H.-X. Lin and H.-X. Dai, Efficient Synthesis of Spirooxindole Pyrrolones by a

Rhodium(III)-Catalyzed C-H Activation/Carbene Insertion/ Lossen Rearrangement Sequence, Angew. Chem., Int. Ed., 2019, 58, 13335-13339.

Research Article

- 7 F. Zhao, Z. Zhou, Y. Lu, J. Qiao, X. Zhang, X. Gong, S. Liu, S. Lin, X. Wu and W. Yi, Chemo, Regio, and Stereoselective Assembly of Polysubstituted Furan-2(5H) ones Enabled by Rh(III)-Catalyzed Domino C-H Alkenylation/Directing Group Migration/Lactonization: A Combined Experimental and Computational Study, ACS Catal., 2021, 11, 13921-13934.
- 8 A review on cascade reactions: A. Baccalini, G. Faita, G. Zanoni and D. Maiti, Transition Metal Promoted Cascade Heterocycle Synthesis through Functionalization, Chem. - Eur. J., 2020, 26, 9749-9783.
- 9 A review on cascade reactions: L. Song and E. V. Van der Eycken, Transition Metal-Catalyzed Intermolecular Cascade C-H Activation/Annulation Processes for the Synthesis of Polycycles, Chem. - Eur. J., 2021, 27, 121-144.
- 10 K. K. Gollapelli, S. Kallepu, N. Govindappa, J. B. Nanubolu and R. Chegondi, Carbonyl-assisted reverse regioselective cascade annulation of 2-acetylenic ketones triggered by Rucatalyzed C-H activation, Chem. Sci., 2016, 7, 4748-4753.
- 11 Y. Fukui, P. Liu, Q. Liu, Z.-T. He, N.-Y. Wu, P. Tian and G.-Q. Lin, Tunable arylative cyclization of 1,6-enynes triggered by rhodium(III)-catalyzed C-H activation, J. Am. Chem. Soc., 2014, 136, 15607-15614.
- 12 (a) G. Liao, H. Song, X. Yin and B. Shi, Expeditious synthesis of pyrano[2,3,4-de]quinolines via Rh(iii)-catalyzed

cascade C-H activation/annulation/lactonization of quinolin-4-ol with alkynes, Chem. Commun., 2017, 53, 7824-7827; (b) Y. Xu, B. Li, X. Zhang and X. Fan, One-Pot Synthesis of Fused N,O-Heterocycles through Rh(III)-Catalyzed Cascade Reactions of Aromatic/Vinylic N-Alkoxy-Amides with 4-Hydroxy-2-Alkynoates, Adv. Synth. Catal., 2018, 360, 2613-2620; (c) A. Kumar, V. Hanchate and K. R. Prabhu, Rhodium(III)-Catalyzed Cascade Reactions of Imines/ Imidates with 4-Hydroxy-2-alkynoates to Synthesize Regioselective Furanone-Fused Isoquinoline Scaffolds, J. Org. Chem., 2021, 86, 17965–17974; (d) Y.-Y. Wang, M. Liu and L. Dong, Rh(III)-Catalyzed multi-site-selective C-H bond functionalization: condition-controlled synthesis of diverse fused polycyclic benzimidazole derivatives, Org. Chem. Front., 2021, 8, 2487-2493; (e) N. Muniraj, A. Kumar and K. R. Prabhu, Cobalt-Catalyzed Regioselective [4 + 2] Annulation/Lactonization of Benzamides with 4-Hydroxy-2-Alkynoates under Aerobic Conditions, Adv. Synth. Catal., 2020, **362**, 152–159; (f) A. Kumar and K. R. Prabhu, Rhodium(III)-Catalyzed C-H Activation: A Cascade Approach for the Regioselective Synthesis of Fused Heterocyclic Lactone Scaffolds, J. Org. Chem., 2020, 85, 3548-3559; (g) Y. Liu, Z. Yang, R. Chauvin, W. Fu, Z. Yao, L. Wang and X. Cui, One-Pot Synthesis of Furo[3,4-c]indolo[2,1-a]isoquinolines through Rh(III)-Catalyzed Cascade Reactions of 2-Phenylindoles with 4-Hydroxy-2-alkynoates, Org. Lett., 2020, 22, 5140-5144.