

Cite this: *Chem. Sci.*, 2024, 15, 20064

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 16th October 2024  
Accepted 4th November 2024

DOI: 10.1039/d4sc07036d

rsc.li/chemical-science

# Ru(II)-catalyzed regioselective oxidative Heck reaction with internal olefins that tolerated strongly coordinating heterocycles†

Ci Chen,<sup>‡</sup> Qiaoya Zhang,<sup>‡</sup> Zhiwei Huang, Wensen Ouyang,<sup>ID</sup> Yang Gao,<sup>ID</sup> Jiye Luo,<sup>ID</sup> Yuan Liu,<sup>ID</sup> Yanping Huo,<sup>ID</sup> Qian Chen<sup>ID</sup> and Xianwei Li<sup>ID</sup>\*

The oxidative Heck reaction of strongly coordinating heterocycles with internal olefins often led to elusive reactivity and regioselectivity. Herein, by judicious choice of X-type directing groups under Ru(II) catalysis, we achieved the regioselective oxidative Heck reaction of strongly coordinating heterocycles with sterically demanding internal olefins. It was postulated that the "match/mismatch effect" of sterically demanding internal olefins as coupling partners and subsequent kinetically favoured Michael addition or oxidative aromatization act as driving forces to facilitate the desired reactivity and site-selectivity.

## Introduction

The directing strategy-enabled oxidative Heck reaction (Fujiwara–Moritani reaction) has proven to be reliable for the expedient construction of olefins and ring systems, featuring step-economy and exquisite reactivity and selectivity.<sup>1</sup> Despite significant advancement in the development of metal catalysts and directing groups, there remained some limitations: (1) sterically demanding internal olefins<sup>2</sup> as coupling partners often exhibited low reactivity, probably due to the low binding affinity of internal olefins toward the metallocycle species and sluggish migratory insertion; (2) elusive reactivity and regioselectivity posed by the unproductive coordination of Lewis basic nitrogen and sulfur atoms of the heterocycle substrates; (3) costly stoichiometric metal oxidants<sup>3</sup> were commonly employed which offset the synthetic advantages.

Currently, only limited success was obtained using sterically demanding internal olefins for the oxidative Heck reaction by meticulous design of directing groups and ligands under metal catalysis. Yu<sup>2a–g</sup> developed MPAA (mono-*N*-protected amino acids) and heterocycle ligands to promote the oxidative Heck reaction enabled by weak coordination compatible with internal olefin coupling partners.

Moreover, regioselective enhancement of strongly coordinating heterocycles remained synthetically appealing and challenging. In this context, Yu and Dai developed a Pd-

catalyzed C–H activation with isonitriles that overrides the limitation of strongly coordinating heterocycles, using *N*-OMe amides as the sole ionic ligands and directing groups, where the formed localized Pd<sup>II</sup>X<sub>2</sub> active species could cleave the specific C–H bonds.<sup>4a</sup> Ackermann demonstrated Co(III)-catalyzed imide enabled C–H amidation and annulation cascade with well-tolerated heterocycles.<sup>4b–d</sup> Glorius reported Ru-catalyzed C–H annulation with propargyl alcohol carbonates and an array of *N*-heterocycles.<sup>4e</sup> Recently, using a well-designed *N,N* bidentate tautomerizable pyridine-based ligand, Yu realized Pd(II)-catalyzed C–H oxygenation of heterocycles with molecular oxygen, in which strongly coordinating heterocycles are compatible (Scheme 1).<sup>4f</sup>

Despite great advancement witnessed for the directed oxidative Heck reaction, including the development of green catalytic systems and synthetic application towards biologically active molecules,<sup>5–8</sup> sterically demanding internal olefins with compatible strongly coordinating heterocycles remained underexplored.

Herein, by judicious choice of X-type directing groups, imide esters, we developed the Ru(II)-catalyzed oxidative Heck reaction<sup>7,8</sup> of heterocycles with internal olefins, using the Na<sub>2</sub>CO<sub>3</sub>·H<sub>2</sub>O<sub>2</sub> oxidant and biomass-derived solvent. Significantly, regioselective modification of complex pharmaceuticals that contained multiple functionalities, *e.g.*, celecoxib that contained strongly coordinating heterocycles, was realized.

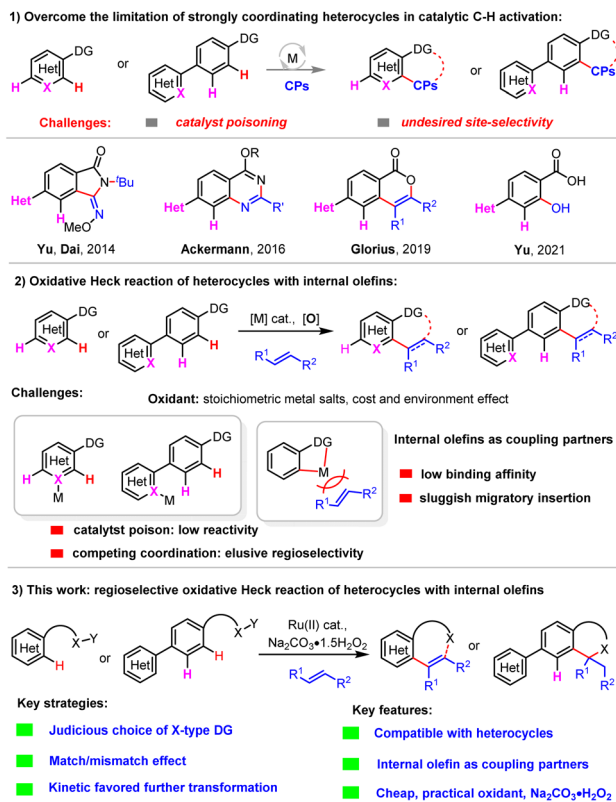
## Results and discussion

We commenced our study on the oxidative Heck reaction by using imide ester **1a**<sup>9,10</sup> and internal olefin **2a** as the model substrates. Optimization of reaction conditions revealed that with Ru[(*p*-cymene)Cl<sub>2</sub>]<sub>2</sub> and AgNTf<sub>2</sub> as the catalyst, NaOAc as the base, Na<sub>2</sub>CO<sub>3</sub>·1.5H<sub>2</sub>O<sub>2</sub> as the practical and inexpensive

School of Chemical Engineering and Light Industry, Guangdong University of Technology, No. 100 Waihuai Xi Road Guangzhou Higher Education Mega Center, Guangzhou, 510006, China. E-mail: xwli@gdut.edu.cn

† Electronic supplementary information (ESI) available. CCDC 2360579. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d4sc07036d>

‡ C. Chen and Q. Zhang contributed equally to this work.



**Scheme 1** Regioselective oxidative Heck reaction with internal olefins that tolerated strongly coordinating heterocycles.

oxidant, and biomass-derived GVL ( $\gamma$ -valerolactone) as the sustainable solvent, the desired olefin **3a** was obtained in good yield (Table 1, entry 1). The Ru(II) complex exhibited comparable reactivity, whereas other metal complexes such as Pd(II), Ni(II), Ir(III) complex candidates showed no reactivity (entries 2 and 3). Control experiments indicated that the Ru(II) catalyst was essential, and AgSbF<sub>6</sub> could also serve as a halide scavenger to facilitate the generation of cationic Ru(II) catalytically active species (entries 4–6).

The utilization of acid, including HOAc, HOPiv or acetate salts such as NaOTFA or NaOPiv instead of NaOAc gave no improvement in the yield of **3a** (entries 7–9). The Cu(II) salt and Ag(I) oxidant effectively promoted the reaction with moderate yields, while DTBP prohibited the reactivity. It is noteworthy that Na<sub>2</sub>CO<sub>3</sub>·1.5H<sub>2</sub>O<sub>2</sub> could serve as the synthetically practical oxidant (entries 10–12). DCE was also an amenable solvent to give comparable efficiency (entry 12). Reactions with decreased temperature furnished the desired product **3a** in much lower yields (entry 13). Notably, only trace production of **3a** was observed under Jeganmohan's conditions<sup>7</sup> (entry 14).

We then moved to examine reactivity of various directing groups for the oxidative Heck reaction with internal olefins conducted under optimal Ru(II) catalysis (Scheme 2). Notably, nitrile showed no reactivity (**1-A**), indicating that this transformation proceeded *via* the imidate ester directed oxidative Heck reaction where base promoted elimination of EtOH gave the desired product **3a**. Moreover, ketone (**1-B**), ester (**1-C**) or

**Table 1** Oxidative Heck reaction of heterocycles with internal olefins<sup>a</sup>

Entry	Variation of standard conditions	Yield <sup>b</sup> (%)
1	Standard conditions	76
2	Pd(OAc) <sub>2</sub> , NiCl <sub>2</sub> or [IrCp*Cl <sub>2</sub> ] <sub>2</sub> as the catalyst	n.r.
3	[RhCp*Cl <sub>2</sub> ] <sub>2</sub> as the catalyst	73
4	AgSbF <sub>6</sub> instead of AgNTf <sub>2</sub>	65
5	Without [Ru(p-cymene)Cl <sub>2</sub> ] <sub>2</sub>	n.r.
6	Without AgNTf <sub>2</sub>	27
7	Without NaOAc	Trace
8	HOAc, PivOH instead of NaOAc	30, 38
9	NaOTFA, NaOPiv instead of NaOAc	56, 67
10	Without Na <sub>2</sub> CO <sub>3</sub> ·1.5H <sub>2</sub> O <sub>2</sub>	24
11	AgOAc, DTBP or Cu(OAc) <sub>2</sub> as the oxidant	68, trace, 66
12	DCE, acetone, <sup>t</sup> BuOH, EA as the solvent	72, 34, 53, 22
13	30 °C, 60 °C or 80 °C	Trace, trace, 46
14	1-AdCO <sub>2</sub> H (0.5 equiv.), EtOH	<10

<sup>a</sup> Standard conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), [Ru(p-cymene)Cl<sub>2</sub>]<sub>2</sub> (2 mol%), AgNTf<sub>2</sub> (5 mol%), NaOAc (30 mol%), Na<sub>2</sub>CO<sub>3</sub>·H<sub>2</sub>O<sub>2</sub> (2.0 equiv.), GVL (1.0 mL), 100 °C, 12 h. <sup>b</sup> Isolated yield.

carboxylic acid (**1-D**), and other X-type ligands such as N-OPiv amide (**1-E**) or NMe<sub>2</sub> (**1H**) showed no reactivity.

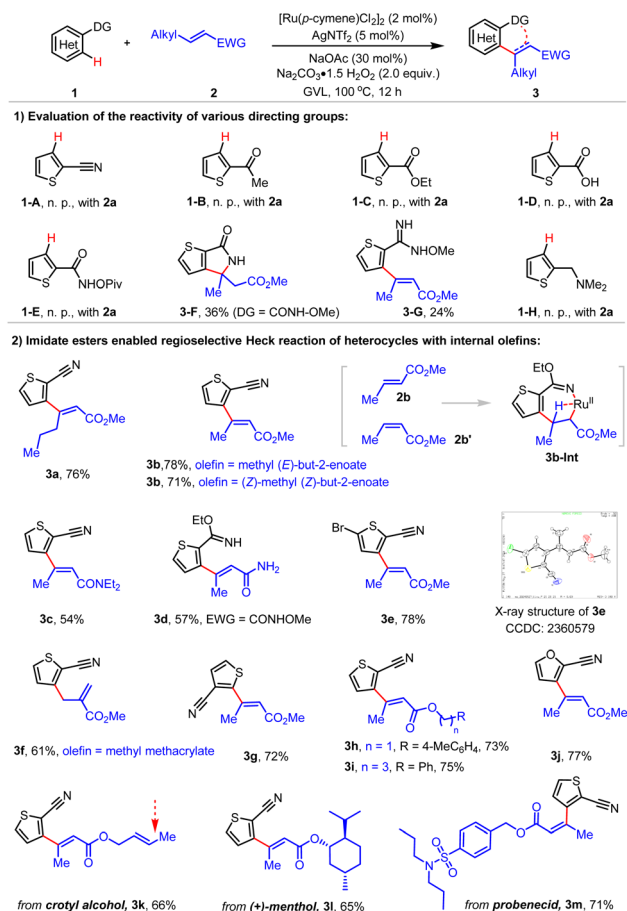
The oxidative Heck reaction followed by Michael addition proceeded smoothly for internal oxidizing N-OMe amide (**3-F**). N-OMe-2-carboximidamide was also applicable for the stereoselective construction of tri-substituted olefins (**3-G**).

C2- and C3-substituted thiophenes (**3a–3e**) and furans (**3j**) led to tri-substituted olefins with exquisite stereoselectivity, which was confirmed by X-ray analysis (**3e**). Internal olefins including (*E*)-hex-2-enoates (**3a**), (*E*)-but-2-enoates (**3e–3i**) and (*E*)-but-2-enamides (**3c** and **3d**) acted as amenable coupling partners. Notably, the reactions of both (*E*)-but-2-enoate **2b** and methyl (*Z*)-but-2-enoate **2b'** as the coupling partners furnished the identical product **3b**, indicating that intermediate **3b-Int** that was enabled by imidate ester **1a** under this Ru(II) catalysis might be involved. Additionally, the oxidative Heck reaction with methyl methacrylate took place at the allylic C(sp<sup>3</sup>)-H position, affording  $\alpha$ -olefin **3f** as the sole product. Site-selective functionalization of natural products and drugs, including crotonate (**3k**), (+)-menthol (**3l**) and probenecid (**3m**) was also achieved.

Preliminary mechanistic studies indicated that the oxidative Heck reaction of *N*-phenyl pyrazole **1a-I** with terminal olefin **2o** proceeded smoothly, while the use of internal olefin **2a** led to low conversion with recovery of starting material **1a-I** (Scheme 3(1)). The observed results might be attributed to the low binding affinity of sterically demanding internal olefins to the *in situ* formed metallocycles *via* directed C–H activation, and subsequent sluggish migratory insertion.

Intriguingly, imidate ester **1d** was applicable in the oxidative Heck reaction with internal olefin **2a**, affording isoindole



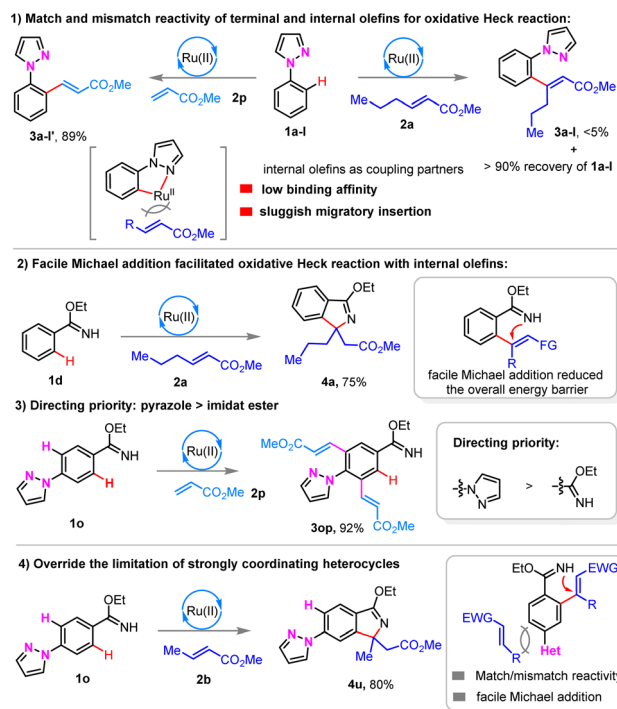


Scheme 2 Regioselective oxidative Heck reaction of heterocycles with internal olefins.

product **4a** in a high yield (Scheme 3(2)). Moreover, the oxidative Heck reaction of pyrazole substituted acrylamide ester **1o** with terminal olefin **2m** gave olefination product **3op** exclusively, indicating that the directing priority is that pyrazole is superior to imidate ester (Scheme 3(3)). Significantly, sterically demanding internal olefins **2** led to complementary regioselectivity (Scheme 3(4)).

The facile Michael addition was envisaged to reduce the overall energy barrier, thus facilitating the oxidative Heck reaction with sterically demanding internal olefins. Consequently, terminal and sterically demanding internal olefins showed the 'match and mismatch effect'<sup>4e</sup> for the directing strategy enabled oxidative Heck reaction, respectively, even using strongly coordinating heterocycles. Furthermore, this 'match/mismatch effect' could be tuned by the incorporation of X-type directing groups, in which the following facile transformation could accelerate the overall oxidative Heck reaction with internal olefins, and thus, compatible with strongly coordinating heterocycles.

We thus investigated the imidate ester assisted oxidative Heck reaction (Scheme 4). The internal olefins bearing stronger electron-withdrawing nitrile (**4c**) exhibited better performance than ester, while crotonamide showed low reactivity (**4b**), which



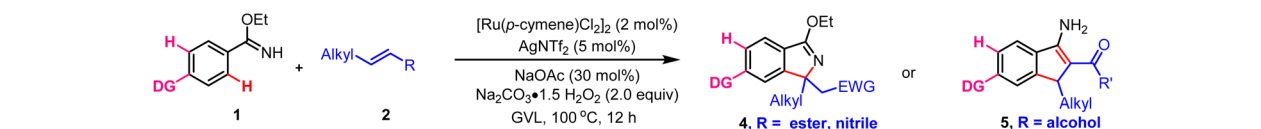
Scheme 3 Preliminary mechanistic studies.

is probably due to the relative reactivity of these olefins for the further Michael addition step. Synthetically versatile functionalities including fluoride (**4e**), bromide (**4h**), iodide (**4f**), and nitro (**4g**) were tolerated. This oxidative Heck showed high regioselectivity and took place at less steric positions (**4i** and **4j**). The reactions with fused ring systems including naphthalene (**4k**), indole (**4l** and **4m**), dibenzo[*b,d*]thiophene (**4n** and **4o**) proceeded smoothly. Notably, imidate esters exhibited directing priority to the competing coordinating ketone (**4q**), ester (**4r**), N-Ts aniline (**4s**), and *O*-bridged pyridine (**4t**) in this transformation. The oxidative Heck reaction of imidate esters with internal olefins is accessible in the presence of strongly coordinating heterocycles including pyrazole (**4u** and **4v**). For *meta*-pyrazole acrylamide ester that contained multiple reactive C-H bonds, the oxidative Heck reaction with internal olefins took place exclusively at the *ortho* position to imidate ester with less steric hindrance (**4w**). Significantly, commonly strongly coordinating pyridine could be also compatible for this imidate ester enabled oxidative Heck reaction with internal olefins (**4x**).

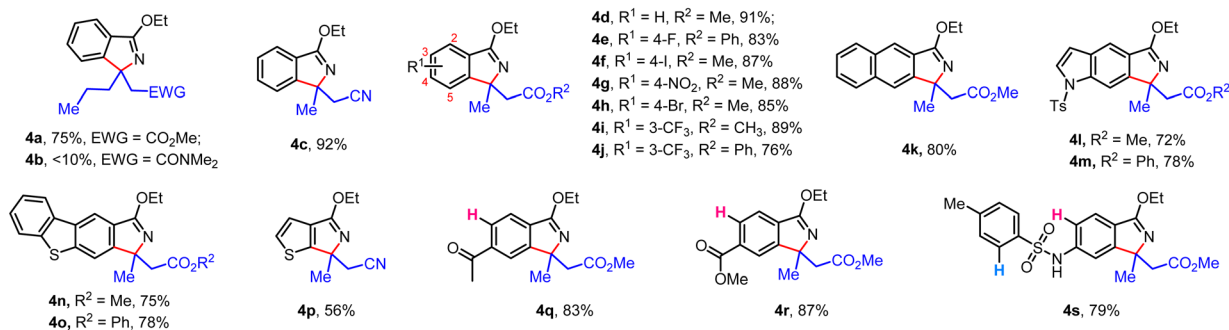
We then performed site-selective functionalization of key skeletons of materials and drugs (Scheme 4(4)). For instance, 2,5-diaryl-1,3,4-oxadiazoles, potent scaffolds for electron transfer materials (ETM), underwent the regioselective oxidative Heck reaction successfully (**4y**). Triphenylamine (TPA), an electroluminescent material, was also an amenable substrate (**4z**). Natural products and drugs including (+)-menthol (**4zb**), probenecid (**4zc**), and cholesterol (**4zd**) derived internal olefins could serve as coupling partners for this oxidative Heck reaction.

Celecoxib analogue derived imidate ester, bearing diverse reactive C-H bonds, could assist the regioselective oxidative

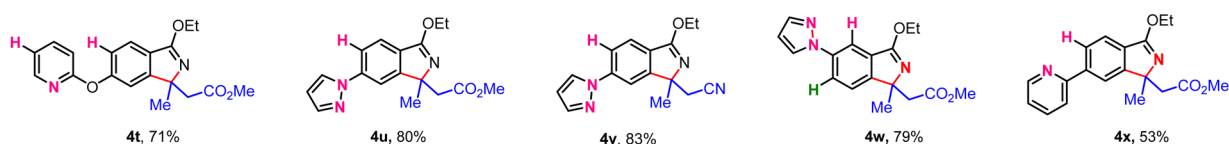




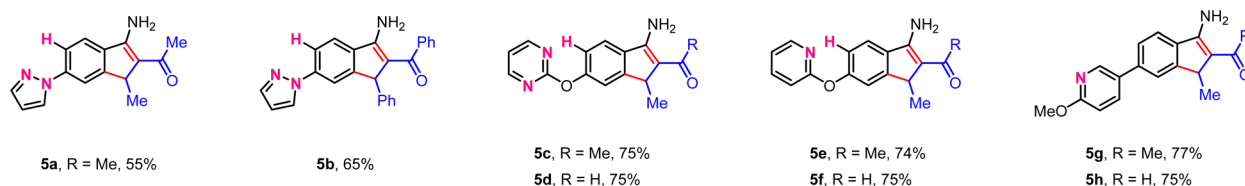
## 1) [4+1] oxidative Heck reaction with sterically demanding internal olefins:



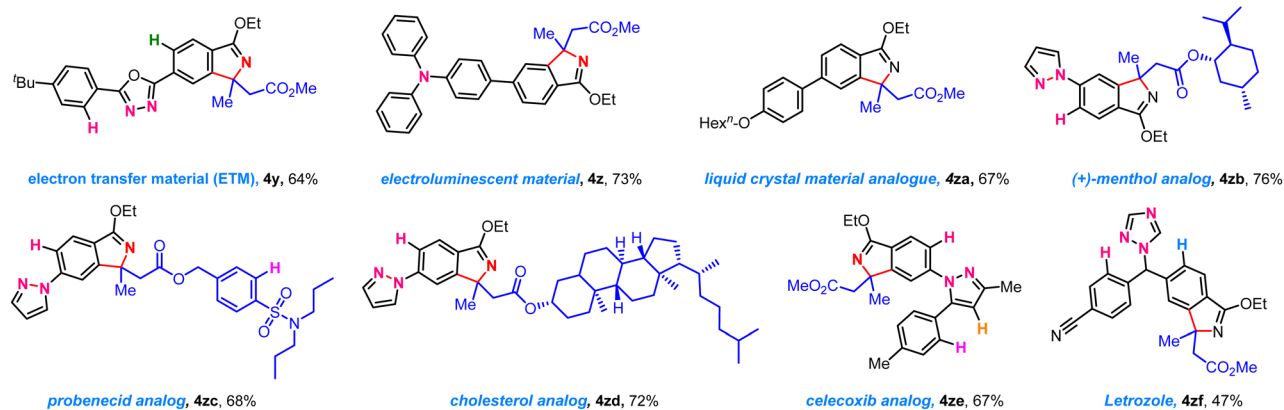
## 2) Tolerance of strongly coordinating heterocycles for [4+1] oxidative Heck reaction:



## 3) [3+2] oxidative Heck reaction with sterically demanding internal olefins:



## 4) Site-selective modification of material and drug molecules:



Scheme 4 Regioselective oxidative Heck reaction with internal olefins.

Heck reaction with internal olefins (4ze). Late-stage modification of the letrozole drug analogue, which contained triazole and nitrile functionalities (4zf), was achieved. The observed high reactivity and regioselectivity for complex drugs and materials further demonstrated the synthetic potential of this oxidative Heck reaction with sterically demanding internal olefins in the presence of strongly coordinating heterocycles.

Further investigation of electron-unbiased allylic alcohols as the coupling partners<sup>11</sup> disclosed that imidate esters enabled the [3 + 2] oxidative Heck reaction regioselectively. Notably, strongly coordinating heterocycles, including pyrazole (5a and 5b), pyridine (5g and 5h) and oxygen-bridged pyridine (5c and 5d), and oxygen-bridged pyrimidine (5e and 5f) were compatible for this regioselective oxidative Heck reaction with internal olefins, furnishing indenes together with the release of ethanol





and water. The obtained diverse indenenes contained carbonyl and amine functionalities, which could serve as a synthetic handle for the synthesis of heterocycles (please see the ESI† for further discussion).

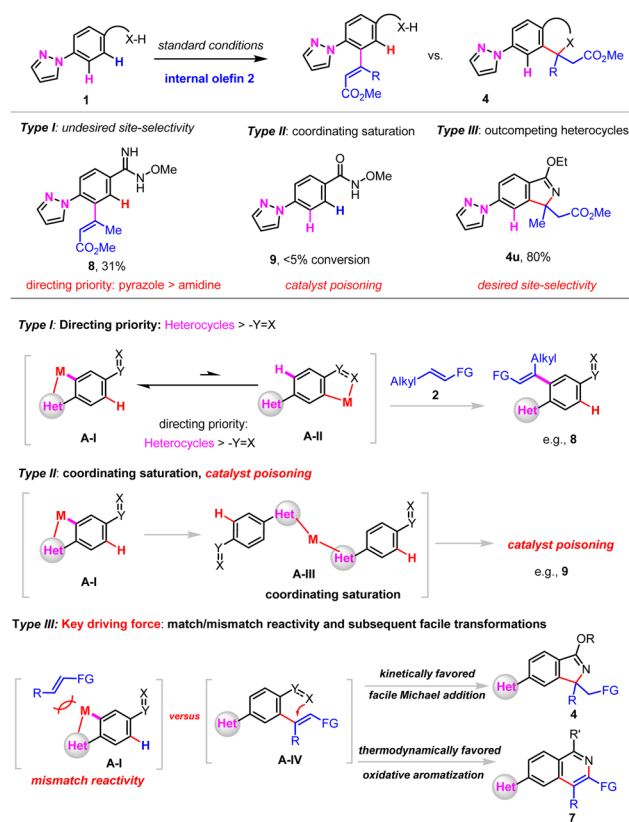
The oxime enabled Heck reaction has been demonstrated for the construction of heterocycles, while the use of heterocycles and sterically demanding internal olefin partners remained elusive to achieve regioselectivity and efficiency.<sup>12</sup> Herein, we found that N-OPiv oxime esters could well assist the oxidative Heck reaction with sterically demanding internal olefins, affording fused heterocycles (Scheme 5), including thieno[3,2-*c*]pyridines (**7a** and **7b**). Notably, 1,6-naphthyridines (**7c**) could be readily accessed, which exhibited superior performance in organic light-emitting diodes (OLEDs),<sup>12g</sup> while typical procedures suffered from limited substrate availability and harsh conditions. Moreover, this N-OPiv oxime enabled regioselective Heck reaction could also tolerate pyrazole (**7d**). It was speculated that the mismatch reactivity of pyrazole to the sterically demanding internal olefins and the oxidative Heck reaction followed by aromatization serve as key driving forces to the observed reactivity and regioselectivity.

Extensive exploration of the reactivity of various X-type nitrogen directing groups revealed that the oxidative Heck reaction of *N*-methoxy benzimidamide **1a-I** took place at the *ortho* position to pyrazole, which indicated that pyrazole showed directing priority to N-OMe benzimidamide. As for pyrazole substituted N-OMe amide **1a-II** might be responsible for the coordinative saturation of pyrazole to the metal catalyst, thus leading to catalyst poisoning (Scheme 6).

According to the experimental observations and related references, three typical reaction types might be involved in directed C-H functionalization of heterocycles. For type I reactivity, competing coordination of directing groups (DG) and heterocycles to the metal catalyst revealed that heterocycles showed directing priority to the DG, and undesired regioselectivity was often obtained, *e.g.*, **8** (Scheme 6(1)).<sup>13,14</sup>

For type II reactivity, the strongly coordinating heterocycles led to coordinating saturation and catalyst poisoning, and thus, recovery of the starting materials, *e.g.*, **9**.

For type III reactivity, by judicious choice of X-type directing groups and exploring the match/mismatch effect (*e.g.*, steric effect, low affinity of internal olefins for the oxidative Heck reaction in this work), as well as facile subsequent transformations (*e.g.*, kinetically favoured facile Michael addition, or thermodynamically favoured aromatization with the release of



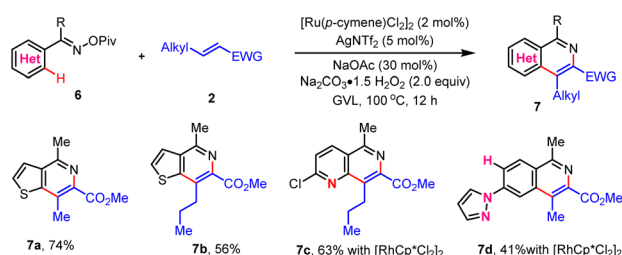
Scheme 6 Mechanistic studies.

small molecules) to reduce the overall energy barrier, C-H functionalization that overrides the limitation of strongly coordinating heterocycles might be achieved.<sup>15</sup>

The native functionality-enabled oxidative Heck reaction of heterocycles with internal olefins remains underexplored; so while considering the versatile nitrile functionality, we thus conducted selective modification of the obtained products (Scheme 7). Nitrile in the product **3b** was a versatile handle to an array of functionalities, including *N*-hydroxy carboximidamide (**3b-I**), tetrazole (**3b-II**), carboxylic acid (**3b-III**) and ester (**3b-IV**), which thus complement this directing strategy enabled oxidative Heck reaction of heterocycles with internal olefins (Scheme 7(1)).

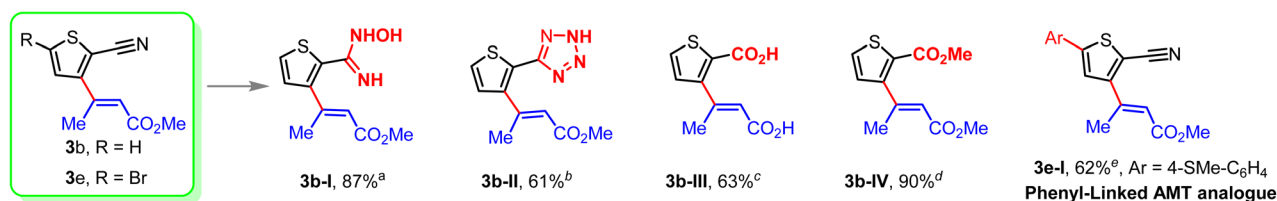
Moreover, Suzuki coupling of thiophene **3e** proceeded to give phenyl-linked AMT analogue **3e-I**, which further demonstrated the synthetic applications of this oxidative Heck reaction of heterocycles (please see the ESI† for details on the further synthetic applications).

Site-specific functionalization of drugs was also performed (Scheme 7(2)), *e.g.* the probenecid analogue (**4w**) could be further transformed to the corresponding isoindolin-1-ones (**4w-I** and **4w-II**). Significantly, site-selective modification of the celecoxib analogue that contained diverse directing groups, using this internal olefin participated oxidative Heck reaction, proceeded smoothly that overrides the traditional directing priority (**4ze**). This transformation provided valuable insight into the precise modification of complex molecules that contained multiple reactive C-H bonds.

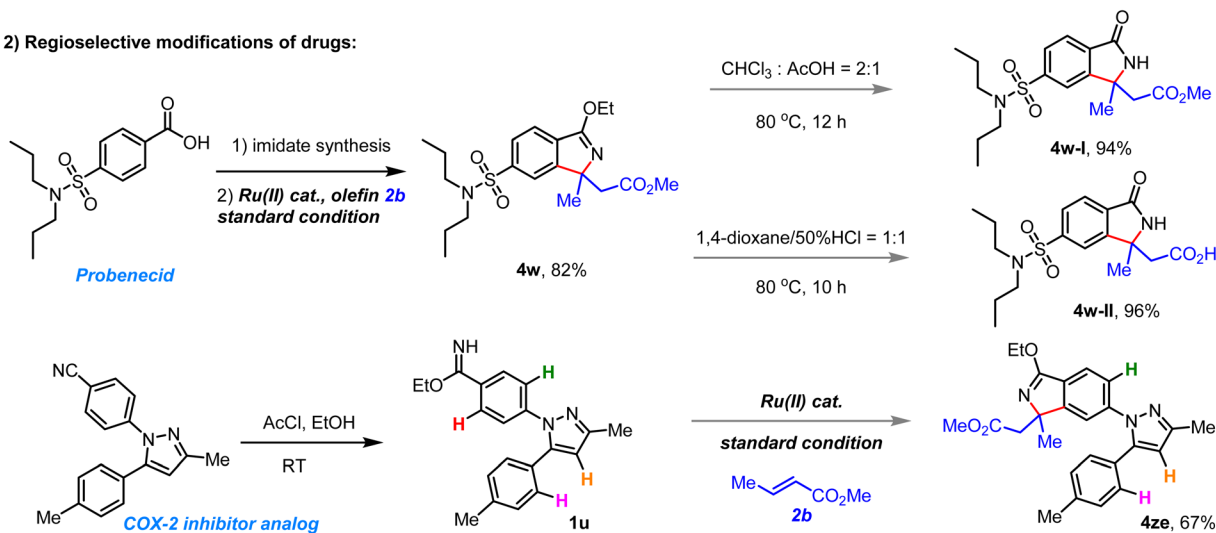


Scheme 5 N-OPiv oxime enabled oxidative Heck reaction of heterocycles with sterically demanding internal olefins.

## 1) Further transformations of the obtained products:



## 2) Regioselective modifications of drugs:



Scheme 7 Synthetic transformations. Conditions: (a) **3b** (0.1 mmol), NaOAc (2.0 equiv.), NH<sub>2</sub>OH·HCl (2.0 equiv.), MeOH/H<sub>2</sub>O (1.0 mL/1.0 mL), 90 °C, 2 h; (b) **3b** (0.1 mmol), NaN<sub>3</sub> (4.0 equiv.), NH<sub>4</sub>Cl (2.0 equiv.), DMF (1.0 mL), N<sub>2</sub>, 120 °C, 24 h; (c) **3b** (0.1 mmol), NaOH aqueous solution (3 equiv., 3 M), 80 °C, 15 h; (d) **3b-V** (0.05 mmol), K<sub>2</sub>CO<sub>3</sub> (2.0 equiv.), MeI (2.0 equiv.), THF (1.0 mL), 40 °C, 5 h; (e) **3e** (0.10 mmol), Pd(PPh<sub>3</sub>)<sub>4</sub> (0.005 mmol), K<sub>2</sub>CO<sub>3</sub> (0.4 mmol), Ar-B(OH)<sub>2</sub> (0.12 mmol), EtOH/H<sub>2</sub>O/toluene = (0.3 mL/0.4 mL/1.0 mL), 95 °C, 12 h.

## Conclusions

In summary, by judicious choice of X-type N-directing groups, we developed imide ester enabled regio- and stereo-selective oxidative Heck reactions with internal olefins that tolerated strongly coordinating heterocycles. The match/mismatch effect and subsequent kinetically or thermodynamically favourable transformations served as key driving forces to achieve promising efficiency and regioselectivity. Synthetic applications were demonstrated by rapid construction of molecular libraries of heterocycle-containing drugs and materials, and modification of functional molecules that contained diverse functionalities with unconventional regioselectivity. Further exploration of the synthetic potential of this site-selective C–H functionalization that overrides the strongly coordinating heterocycles towards materials and drugs is underway.

## Data availability

The data supporting this article have been included as part of the ESI.†

## Author contributions

X. Li conceived and directed the project. C. Chen and Q. Zhang performed the experiments, analysed the results and

contributed equally to this work. All authors discussed the results and commented on the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We are grateful for the financial support from the National Natural Science Foundation of China (22071034). We appreciate Prof. Zhe Wang at Guangdong University of Technology, Yu-Feng Liang at Shandong University, and Dr Zihang Qiu for the revision of this manuscript. We also thank the Instrumental Analysis Center of Guangdong University of Technology for their support.

## Notes and references

- (a) R. F. Heck, Palladium-Catalyzed Reactions of Organic Halides with Olefins, *Acc. Chem. Res.*, 1979, **12**, 146–151; (b) C. Jia, T. Kitamura and Y. Fujiwara, Catalytic Functionalization of Arenes and Alkanes via C–H Bond Activation, *Acc. Chem. Res.*, 2001, **34**, 633–639; (c) *The Mizoroki-Heck Reaction*, ed. M. Oestreich, Wiley, Chichester, 2009; (d) B. Dounay and L. E. Overman, *The Asymmetric*



Intramolecular Heck Reaction in Natural Product Total Synthesis, *Chem. Rev.*, 2003, **103**, 2945–2964.

- 2 For selected examples on the directed oxidative Heck reaction with internal olefins: (a) D. Leow, G. Li, T.-S. Mei and J.-Q. Yu, Activation of Remote *meta*-C–H Bonds Assisted by an End-on Template, *Nature*, 2012, **486**, 518–522; (b) G. Yang, P. Lindovska, D. Zhu, J. Kim, P. Wang, R.-Y. Tang, M. Movassaghi and J.-Q. Yu, Pd(II)-Catalyzed *meta*-C–H Olefination, Arylation, and Acetoxylation of Indolines Using a U-Shaped Template, *J. Am. Chem. Soc.*, 2014, **136**, 10807–10813; (c) J. Xu, J. Chen, F. Gao, S. Xie, X. Xu, Z. Jin and J.-Q. Yu, Sequential Functionalization of *meta*-C–H and *ipso*-C–O Bonds of Phenols, *J. Am. Chem. Soc.*, 2019, **141**, 1903–1907; (d) H. Park and J.-Q. Yu, Palladium-Catalyzed [3 + 2] Cycloaddition *via* Twofold 1,3-C(sp<sup>3</sup>)-H Activation, *J. Am. Chem. Soc.*, 2020, **142**, 16552–16556; (e) P. Zhang, Z. Jiang, Z. Fan, G. Li, Q. Ma, J. Huang, J. Tang, X. Xu, J.-Q. Yu and Z. Jin, Macrocyclization *via* Remote *meta*-Selective C–H Olefination Using a Practical Indolyl Template, *Chem. Sci.*, 2023, **14**, 8279–8287; (f) S. Bag, T. Patra, A. Modak, A. Deb, S. Maity, U. Dutta, A. Dey, R. Kancherla, A. Maji, A. Hazra, M. Bera and D. Maiti, Remote *para*-C–H Functionalization of Arenes by a D-Shaped Biphenyl Template-Based Assembly, *J. Am. Chem. Soc.*, 2015, **137**, 11888–11891; (g) Z. Yu, Q. Liu, Q. Li, Z. Huang, Y. Yang and J. You, Remote Editing of Stacked Aromatic Assemblies for Heteroannular C–H Functionalization by a Palladium Switch between Aromatic Rings, *Angew. Chem., Int. Ed.*, 2022, **61**, e202212079P.
- 3 For selected examples on the aerobic oxidative Heck reaction with terminal olefins: (a) Y.-H. Zhang, B.-F. Shi and J.-Q. Yu, Pd(II)-Catalyzed Olefination of Electron-Deficient Arenes Using 2,6-Dialkylpyridine Ligands, *J. Am. Chem. Soc.*, 2009, **131**, 5072–5074; (b) K. M. Engle, D.-H. Wang and J.-Q. Yu, Ligand-Accelerated C–H Activation Reactions: Evidence for a Switch of Mechanism, *J. Am. Chem. Soc.*, 2010, **132**, 14137–14153; (c) K. M. Engle, D.-H. Wang and J.-Q. Yu, Constructing Multiply Substituted Arenes Using Sequential Palladium(II)-Catalyzed C–H Olefination, *Angew. Chem., Int. Ed.*, 2010, **49**, 6169–6173; (d) M. Piotrowicz and J. Zakrzewski, Aerobic Dehydrogenative Heck Reaction of Ferrocene with a Pd(OAc)<sub>2</sub>/4,5-Diazafluoren-9-one Catalyst, *Organometallics*, 2013, **32**, 5709–5712; (e) M. Piotrowicz, J. Zakrzewski, R. Metivier, A. Brosseau, A. Makal and K. Wozniak, Aerobic Palladium(II)-Catalyzed Dehydrogenative Heck Reaction in the Synthesis of Pyrenyl Fluorophores. A Photophysical Study of  $\beta$ -Pyrenyl Acrylates in Solution and in the Solid State, *J. Org. Chem.*, 2015, **80**, 2573–2581; (f) B. Liu, H.-Z. Jiang and B.-F. Shi, Palladium-Catalyzed Oxidative Olefination of Phenols Bearing Removable Directing Groups under Molecular Oxygen, *J. Org. Chem.*, 2014, **79**, 1521–1526; (g) X. Cong, H. Tang, C. Wu and X. Zeng, Role of Mono-N-protected Amino Acid Ligands in Palladium(II)-Catalyzed Dehydrogenative Heck Reactions of Electron-Deficient (Hetero)arenes: Experimental and Computational Studies, *Organometallics*, 2013, **32**, 6565–6575; (h) Q. Huang, X. Zhang, L. Qiu, J. Wu, H. Xiao, X. Zhang and S. Lin, Palladium-Catalyzed Olefination and Arylation of Polyfluoroarenes Using Molecular Oxygen as the Sole Oxidant, *Adv. Synth. Catal.*, 2015, **357**, 3753–3757; (i) Y.-H. Xu, Y. K. Chok and T.-P. Loh, Synthesis and Characterization of a Cyclic Vinylpalladium(II) Complex: Vinylpalladium Species as the Possible Intermediate in the Catalytic Direct Olefination Reaction of Enamide, *Chem. Sci.*, 2011, **2**, 1822–1825.
- 4 (a) Y.-J. Liu, H. Xu, W.-J. Kong, M. Shang, H.-X. Dai and J.-Q. Yu, Overcoming the Limitations of Directed C–H Functionalizations of Heterocycles, *Nature*, 2014, **515**, 389–393; (b) H. Wang, M. M. Lorion and L. Ackermann, Overcoming the Limitations of C–H Activation with Strongly Coordinating N-Heterocycles by Cobalt Catalysis, *Angew. Chem., Int. Ed.*, 2016, **55**, 10386–10390; (c) M. Shang, M.-M. Wang, T. G. Saint-Denis, M.-H. Li, H.-X. Dai and J.-Q. Yu, Copper-Mediated Late-Stage Functionalization of Heterocycle-Containing Molecules, *Angew. Chem., Int. Ed.*, 2017, **56**, 5317–5321; (d) L.-L. Xu, X. Wang, B. Ma, M.-X. Yin, H.-X. Lin, H.-X. Dai and J.-Q. Yu, Copper Mediated C–H Amination with Oximes: en route to Primary Anilines, *Chem. Sci.*, 2018, **9**, 5160–5164; (e) Q. Lu, S. Mondal, S. Cembellin, S. Grefies and F. Glorius, Site-selective C–H Activation and Regiospecific Annulation Using Propargylic Carbonates, *Chem. Sci.*, 2019, **10**, 6560–6564; (f) Z. Li, Z. Wang, N. Chekshin, S. Qian, J. X. Qiao, P. T. Cheng, K.-S. Yeung, W. R. Ewing and J.-Q. Yu, A Tautomeric Ligand Enables Directed C–H Hydroxylation with Molecular Oxygen, *Science*, 2021, **372**, 1452–1457.
- 5 For the oxidative Heck reaction of strongly coordinating heterocycles with terminal olefins: (a) M. Ye, G.-L. Gao and J.-Q. Yu, Ligand-Promoted C-3 Selective C–H Olefination of Pyridines with Pd Catalysts, *J. Am. Chem. Soc.*, 2011, **133**, 6964–6967; (b) H.-X. Dai, A. F. Stepan, M. S. Plummer, Y.-H. Zhang and J.-Q. Yu, Divergent C–H Functionalizations Directed by Sulfonamide Pharmacophores: Late-Stage Diversification as a Tool for Drug Discovery, *J. Am. Chem. Soc.*, 2011, **133**, 7222–7228.
- 6 For selected reviews: (a) W. Ma, P. Gandeepan, J. Li and L. Ackermann, Recent advances in positional-selective alkenylations: removable guidance for twofold C–H activation, *Org. Chem. Front.*, 2017, **4**, 1435–1467; (b) U. Dhawa, N. Kaplaneris and L. Ackermann, Green strategies for transition metal-catalyzed C–H activation in molecular syntheses, *Org. Chem. Front.*, 2021, **8**, 4886–4913; (c) R. C. Samanta, T. H. Meyer, I. Siewert and L. Ackermann, Renewable resources for sustainable metallaelectro-catalysed C–H activation, *Chem. Sci.*, 2020, **11**, 8657–8670; (d) X. Shang and Z.-Q. Liu, *Chem. Soc. Rev.*, 2013, **42**, 3253; (e) K. Wang, F. Hu, Y. Zhang and J. Wang, *Sci. China: Chem.*, 2015, **58**, 1252; (f) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814; (g) B. Liu, L. Yang, P. Li, F. Wang and X. Li, *Org. Chem. Front.*, 2021, **8**, 1085–1101; (h) J. Zhang, X. Lu, C. Shen, L. Xu, L. Ding and G. Zhong, *Chem. Soc. Rev.*, 2013, **32**, 6565–6575; (i) Q. Huang, X. Zhang, L. Qiu, J. Wu, H. Xiao, X. Zhang and S. Lin, Palladium-Catalyzed Olefination and Arylation of Polyfluoroarenes Using Molecular Oxygen as the Sole Oxidant, *Adv. Synth. Catal.*, 2015, **357**, 3753–3757; (j) Y.-H. Xu, Y. K. Chok and T.-P. Loh, Synthesis and Characterization of a Cyclic Vinylpalladium(II) Complex: Vinylpalladium Species as the Possible Intermediate in the Catalytic Direct Olefination Reaction of Enamide, *Chem. Sci.*, 2011, **2**, 1822–1825.



- 2021, **50**, 3263–3314; (i) W. Ali, G. Prakash and D. Maiti, *Chem. Sci.*, 2021, **12**, 2735–2759.
- 7 For selected reviews: (a) S. De. Sarkar, W. S. Liu, I. Kozhushkov and L. Ackermann, Weakly Coordinating Directing Groups for Ruthenium(II)-Catalyzed C–H Activation, *Adv. Synth. Catal.*, 2014, **356**, 1461–1479; (b) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, Ruthenium(II)-Catalyzed C–H Bond Activation and Functionalization, *Chem. Rev.*, 2012, **112**, 5879–5918; (c) L. Ackermann and R. Vicente, Ruthenium-Catalyzed Direct Arylations through C–H Bond Cleavages, *Top. Curr. Chem.*, 2010, **292**, 211–229.
- 8 For selected Ru-catalyzed oxidative Heck reactions: (a) H. Weissman, X. Song and D. Milstein, Ru-Catalyzed Oxidative Coupling of Arenes with Olefins Using O<sub>2</sub>, *J. Am. Chem. Soc.*, 2001, **123**, 337–338; (b) E. J. Farrington, J. M. Brown, C. F. J. Barnard and E. Rowsell, Ruthenium-Catalyzed Oxidative Heck Reactions, *Angew. Chem., Int. Ed.*, 2002, **41**, 169–171; (c) K.-H. Kwon, D. W. Lee and C. S. Yi, Chelate-Assisted Oxidative Coupling Reaction of Arylamides and Unactivated Alkenes: Mechanistic Evidence for Vinyl C–H Bond Activation Promoted by an Electrophilic Ruthenium Hydride Catalyst, *Organometallics*, 2010, **29**, 5748–5750; (d) L. Ackermann and J. Pospech, Ruthenium-Catalyzed Oxidative C–H Bond Alkenylations in Water: Expedient Synthesis of Annulated Lactones, *Org. Lett.*, 2011, **13**, 4153–4155; (e) R. Manikandana and M. Jeganmohan, Recent Advances in the Ruthenium(II)-Catalyzed Chelation-Assisted C–H Olefination of Substituted Aromatics, Alkenes and Heteroaromatics with Alkenes via the Deprotonation pathway, *Chem. Commun.*, 2017, **53**, 8931–8947; (f) B. Li, K. Devaraj, C. Darcel and P. Dixneuf, Ruthenium(II) Catalysed Synthesis of Unsaturated Oxazolines via Arene C–H Bond Alkenylation, *Green Chem.*, 2012, **14**, 2706–2709; (g) S. I. Kozhushkov and L. Ackermann, Ruthenium-Catalyzed Direct Oxidative Alkenylation of Arenes through Twofold C–H Bond Functionalization, *Chem. Sci.*, 2013, **4**, 886–896; (h) C. N. Shambhavi and M. Jeganmohan, Ruthenium(II)-Catalyzed Redox-Neutral C–H Alkylation of Arylamides with Unactivated Olefins, *Org. Lett.*, 2021, **23**, 4849–4854; (i) A. Bechtoldt, M. E. Baumert, L. Vaccaro and L. Ackermann, Ruthenium(II) Oxidase Catalysis for C–H Alkenylations in Biomass-derived  $\gamma$ -valerolactone, *Green Chem.*, 2018, **20**, 398–402; (j) A. Bechtoldt, C. Tirlor, K. Raghuvanshi, S. Warratz, C. Kornhaass and L. Ackermann, Ruthenium Oxidase Catalysis for Site-Selective C–H Alkenylations with Ambient O<sub>2</sub> as the Sole Oxidant, *Angew. Chem., Int. Ed.*, 2016, **55**, 264–267; (k) X. Li, X. Hu, Z. Liu, J. Yang, B. Mei, Y. Dong and G. Liu, Ruthenium-Catalyzed Selectively Oxidative C–H Alkenylation of N-Acylated Aryl Sulfonamides by Using Molecular Oxygen as an Oxidant, *J. Org. Chem.*, 2020, **85**, 5916–5926; (l) A. S. Trita, A. Biafora, M. P. Drapeau, P. Weber and L. J. Gooßen, Regiospecific *ortho*-C–H Alkylation of Benzoic Acids, *Angew. Chem., Int. Ed.*, 2018, **57**, 14580–14584.
- 9 (a) X. Li, J. Rao, W. Ouyang, Q. Chen, N. Cai, Y.-J. Lu and Y. Huo, Sequential C–H and C–C Bond Cleavage: Divergent Constructions of Fused N-Heterocycles via Tunable Cascade, *ACS Catal.*, 2019, **9**, 8749–8756; (b) W. Ouyang, X. Cai, X. Chen, J. Wang, J. Rao, Y. Gao, Y. Huo, Q. Chen and X. Li, Sequential C–H Activation Enabled Expedient Delivery of Polyfunctional Arenes, *Chem. Commun.*, 2021, **57**, 8075–8078; (c) B. Liu, W. Ouyang, J. Nie, Y. Gao, K. Feng, Y. Huo, Q. Chen and X. Li, Weak Coordinated Nitrogen Functionality Enabled Regioselective C–H Alkynylation via Pd(II)/Mono-N-Protected Amino Acid Catalysis, *Chem. Commun.*, 2020, **56**, 11255–11258; (d) B. Liu, J. Rao, W. Liu, Y. Gao, Y. Huo, Q. Chen and X. Li, Ligand-Assisted Olefin-Switched Divergent Oxidative Heck Cascade with Molecular Oxygen Enabled by Self-Assembled Imines, *Org. Chem. Front.*, 2023, **10**, 2128–2137.
- 10 For selected examples: (a) D.-G. Yu, M. Suri and F. Glorius, Rh<sup>III</sup>/Cu<sup>II</sup>-Cocatalyzed Synthesis of 1*H*-Indazoles through C–H Amidation and N–N Bond Formation, *J. Am. Chem. Soc.*, 2013, **135**, 8802–8805; (b) X. Yang, X. Jin and C. Wang, Manganese-Catalyzed *ortho*-C–H Alkenylation of Aromatic N–H Imidates with Alkynes: Versatile Access to Mono-Alkenylated Aromatic Nitriles, *Adv. Synth. Catal.*, 2016, **358**, 2436–2442; (c) X. Wang and N. Jiao, Rh- and Cu-cocatalyzed aerobic oxidative approach to quinazolines via [4+ 2] C–H annulation with alkyl azides, *Org. Lett.*, 2016, **18**, 2150–2153; (d) N. Lv, Z. Chen, Y. Liu, Z. Liu and Y. Zhang, Synthesis of Functionalized Indenones via Rh-Catalyzed C–H Activation Cascade Reaction, *Org. Lett.*, 2017, **19**, 2588–2591; (e) X. Wu, H. Xiong, S. Sun and J. Cheng, Rhodium-Catalyzed Relay Carbenoid Functionalization of Aromatic C–H Bonds toward Fused Heteroarenes, *Org. Lett.*, 2018, **20**, 1396–1399; (f) X. Wang, A. Lerchen and F. Glorius, A comparative investigation: group 9 Cp\*M(III)-catalyzed Formal [4+ 2] Cycloaddition as an Atom-Economic Approach to Quinazolines, *Org. Lett.*, 2016, **18**, 2090–2093; (g) B. Jiang, S. Wu, J. Zeng and X. Yang, Controllable Rh(III)-Catalyzed C–H Arylation and Dealcoholization: Access to Biphenyl-2-carbonitriles and Biphenyl-2-carbimides, *Org. Lett.*, 2018, **20**, 6573–6577; (h) S. Yu, G. Tang, Y. Li, X. Zhou, Y. Lan and X. Li, Anthranil: An Aminating Reagent Leading to Bifunctionality for Both C(sp<sup>3</sup>)-H and C(sp<sup>2</sup>)-H under Rhodium(III) Catalysis, *Angew. Chem., Int. Ed.*, 2016, **55**, 8696–8700; (i) W.-J. Kong, L. H. Finger, A. M. Messinis, R. Kuniyil, J. C. A. Oliveira and L. Ackermann, Flow Rhodaelectro-Catalyzed Alkyne Annulations by Versatile C–H Activation: Mechanistic Support for Rhodium(III/IV), *J. Am. Chem. Soc.*, 2019, **141**, 17198–17206.
- 11 For selected examples on the oxidative Heck reaction of C-H bonds with allylic alcohols: (a) L. Huang, Q. Wang, J. Qi, X. Wu, K. Huang and H. Jiang, Rh(III)-Catalyzed *ortho*-Oxidative Alkylation of Unactivated Arenes with Allylic Alcohols, *Chem. Sci.*, 2013, **4**, 2665–2669; (b) J. Qi, L. Huang, Z. Wang and H. Jiang, Ruthenium- and Rhodium-Catalyzed Oxidative Alkylation of C–H Bonds: Efficient Access to  $\beta$ -Aryl Ketones, *Org. Biomol. Chem.*,





- 2013, **11**, 8009–8013; (c) Z. Shi, M. Bouladakis-Arapinis and F. Glorius, Rh(III)-Catalyzed Dehydrogenative Alkylation of (Hetero)arenes with Allylic Alcohols, Allowing Aldol Condensation to Indenes, *Chem. Commun.*, 2013, **49**, 6489–6491.
- 12 For selected reviews and examples: (a) H. Huang, X. Ji, W. Wu and H. Jiang, Transition Metal-Catalyzed C–H Functionalization of N-Oxyamine Internal Oxidants, *Chem. Soc. Rev.*, 2015, **44**, 1155–1171; (b) F. W. Patureau and F. Glorius, Oxidizing Directing Groups Enable Efficient and Innovative C–H Activation Reactions, *Angew. Chem., Int. Ed.*, 2011, **50**, 1977–1979; (c) J. M. Neely and T. Rovis, Rh(III)-Catalyzed Regioselective Synthesis of Pyridines from Alkenes and  $\alpha$ ,  $\beta$ -Unsaturated Oxime Esters, *J. Am. Chem. Soc.*, 2013, **135**, 66–69; (d) J. M. Neely and T. Rovis, Rh(III)-Catalyzed Decarboxylative Coupling of Acrylic Acids with Unsaturated Oxime Esters: Carboxylic Acids Serve as Traceless Activators, *J. Am. Chem. Soc.*, 2014, **136**, 2735–2738; (e) F. Romanov-Michailidis, K. F. Sedillo, J. M. Neely and T. Rovis, Expedient Access to 2,3-Dihydropyridines from Unsaturated Oximes by Rh(III)-Catalyzed C–H Activation, *J. Am. Chem. Soc.*, 2015, **137**, 8892–8895; (f) S. Lee, N. Semakul and T. Rovis, Direct Regio- and Diastereoselective Synthesis of  $\delta$ -Lactams from Acrylamides and Unactivated Alkenes Initiated by Rh<sup>III</sup>-Catalyzed C–H Activation, *Angew. Chem., Int. Ed.*, 2020, **59**, 4965–4969; (g) A. Luo, Y. Bao, X. Liu, J. Liu, W. Han, G. Yang, Y. Yang, Z. Bin and J. You, Unlocking Structurally Nontraditional Naphthyridine-Based Electron-Transporting Materials with C–H Activation–Annulation, *J. Am. Chem. Soc.*, 2024, **146**, 6240–6251.
- 13 (a) K. M. Engle, T.-S. Mei, M. Wasa and J.-Q. Yu, Weak Coordination as Powerful Means for Developing Broadly Useful C–H Functionalization Reactions, *Acc. Chem. Res.*, 2012, **45**, 788–802; (b) Y.-F. Yang, X. Hong, J.-Q. Yu and K. N. Houk, Experimental-Computational Synergy for Selective Pd(II)-Catalyzed C–H Activations of Aryl and Alkyl Groups, *Acc. Chem. Res.*, 2017, **50**, 2853–2860; (c) Q. Shao, K. Wu, Z. Zhuang, S. Qian and J.-Q. Yu, From Pd(OAc)<sub>2</sub> to Chiral Catalysts: The Discovery and Development of Bifunctional Mono-N-Protected Amino Acid Ligands for Diverse C–H Functionalization Reactions, *Acc. Chem. Res.*, 2020, **53**, 833–851.
- 14 (a) S. R. Neufeldt and M. S. Sanford, Controlling Site Selectivity in Palladium-Catalyzed C–H Bond Functionalization, *Acc. Chem. Res.*, 2012, **45**, 936–946; (b) Z. Huang and G. Dong, Site-Selectivity Control in Organic Reactions: A Quest To Differentiate Reactivity among the Same Kind of Functional Groups, *Acc. Chem. Res.*, 2017, **50**, 465–471; (c) J. F. Hartwig and M. A. Larsen, Undirected, Homogeneous C–H Bond Functionalization: Challenges and Opportunities, *ACS Cent. Sci.*, 2016, **2**, 281–292; (d) T. Brückl, R. D. Baxter, Y. Ishihara and P. S. Baran, Innate and Guided C–H Functionalization Logic, *Acc. Chem. Res.*, 2012, **45**, 826–839; (e) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, Palladium-Catalyzed Transformations of Alkyl C–H Bonds, *Chem. Rev.*, 2017, **117**, 8754–8786; (f) G. Shan, X. Yang, L. Ma and Y. Rao, Pd-Catalyzed C–H Oxygenation with TFA/TFAA: Expedient Access to Oxygen-Containing Heterocycles and Late-Stage Drug Modification, *Angew. Chem., Int. Ed.*, 2012, **51**, 13070–13074; (g) D. Lapointe, T. Markiewicz, C. J. Whipp, A. Toderian and K. Fagnou, Predictable and Site-Selective Functionalization of Poly(hetero)arene Compounds by Palladium Catalysis, *J. Org. Chem.*, 2011, **76**, 749–759; (h) L. V. Desai, K. J. Stowers and M. S. Sanford, Insights into Directing Group Ability in Palladium-Catalyzed C–H Bond Functionalization, *J. Am. Chem. Soc.*, 2008, **130**, 13285–13293.
- 15 K. Wu, N. Lam, D. A. Strassfeld, Z. Fan, J. X. Qiao, T. Liu, D. Stamos and J.-Q. Yu, Palladium (II)-Catalyzed C–H Activation with Bifunctional Ligands: From Curiosity to Industrialization, *Angew. Chem., Int. Ed.*, 2024, e202400509.

