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

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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.[1] Despite significant advancement in the development of metal catalysts and directing groups, there remained some limitations: (1) sterically demanding internal olefins[2] 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[3] 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[2a–g] 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 $Pd^{II}X_2$ active species could cleave the specific C–H bonds.[4a] Ackermann demonstrated Co(III)-catalyzed imidate enabled C–H amidation and annulation cascade with well-tolerated heterocycles.[4b–d] Glorius reported Ru-catalyzed C–H annulation with propargyl alcohol carbonates and an array of N-heterocycles.[4e] 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).[4f]

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

Herein, by judicious choice of X-type directing groups, imidate esters, we developed the Ru(II)-catalyzed oxidative Heck reaction[7,8] of heterocycles with internal olefins, using the $Na_2CO_3 \cdot H_2O_2$ 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 imidate ester **1a**[9,10] and internal olefin **2a** as the model substrates. Optimization of reaction conditions revealed that with $Ru[(p\text{-cymene})Cl_2]_2$ and $AgNTf_2$ as the catalyst, NaOAc as the base, $Na_2CO_3 \cdot 1.5H_2O_2$ as the practical and inexpensive

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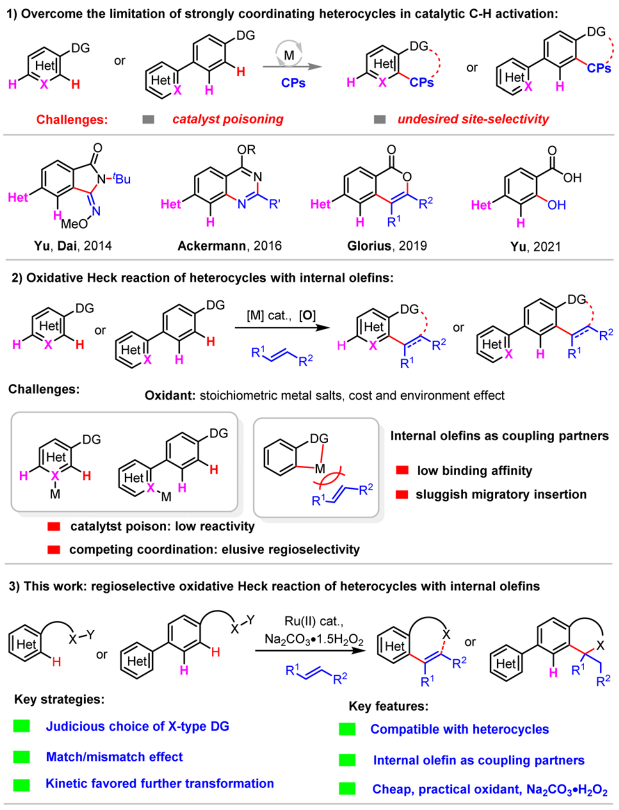


Scheme 1 Regioselective oxidative Heck reaction with internal olefins that tolerated strongly coordinating heterocycles.

oxidant, and biomass-derived GVL (γ-valerolactone) as the sustainable solvent, the desired olefin **3a** was obtained in good yield (Table 1, entry 1). The Rh(III) 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 $AgSbF_6$ could also serve as a halide scavenger to facilitate the generation of cationic Ru(II) catalytically active species (entries 4–6).

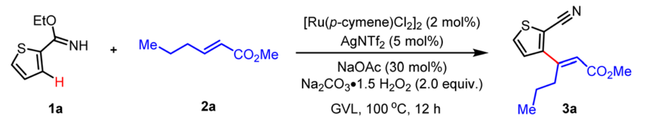
The utilization of acid, including HOAc, HOPiv or acetate salts such as NaOTFA or NaOPiv instead of NaOAc gave no improvement in the yield of **3a** (entries 7–9). The Cu(II) salt and Ag(I) oxidant effectively promoted the reaction with moderate yields, while DTBP prohibited the reactivity. It is noteworthy that $Na_2CO_3 \cdot 1.5H_2O_2$ 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[7] (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 carboxylic acid (**1-D**), and other X-type ligands such as N–OPiv amide (**1-E**) or $NMe_2$ (**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($sp^3$)-H position, affording α-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.

Table 1 Oxidative Heck reaction of heterocycles with internal olefins[a]

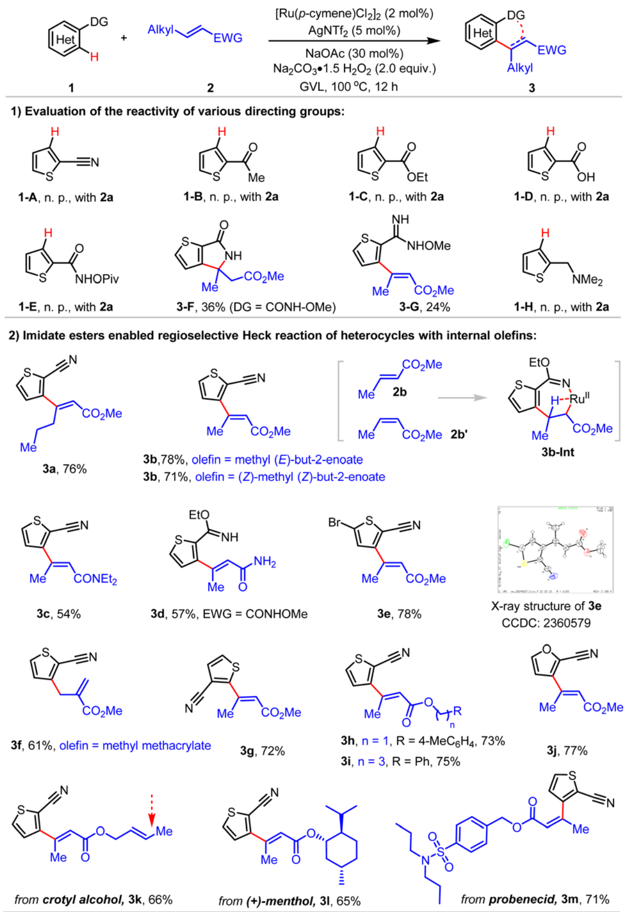


| Entry | Variation of standard conditions | Yield[b] (%) |
|---|---|---|
| 1 | Standard conditions | 76 |
| 2 | $Pd(OAc)_2$, $NiCl_2$ or $[IrCp^*Cl_2]_2$ as the catalyst | n.r. |
| 3 | $[RhCp^*Cl_2]_2$ as the catalyst | 73 |
| 4 | $AgSbF_6$ instead of $AgNTf_2$ | 65 |
| 5 | Without $[Ru(p\text{-cymene})Cl_2]_2$ | n.r. |
| 6 | Without $AgNTf_2$ | 27 |
| 7 | Without NaOAc | Trace |
| 8 | HOAc, PivOH instead of NaOAc | 30, 38 |
| 9 | NaOTFA, NaOPiv instead of NaOAc | 56, 67 |
| 10 | Without $Na_2CO_3 \cdot 1.5H_2O_2$ | 24 |
| 11 | AgOAc, DTBP or $Cu(OAc)_2$ as the oxidant | 68, trace, 66 |
| 12 | DCE, acetone, $^t$BuOH, EA as the solvent | 72, 34, 53, 22 |
| 13 | 30 °C, 60 °C or 80 °C | Trace, trace, 46 |
| 14 | 1-$AdCO_2H$ (0.5 equiv.), EtOH | <10 |

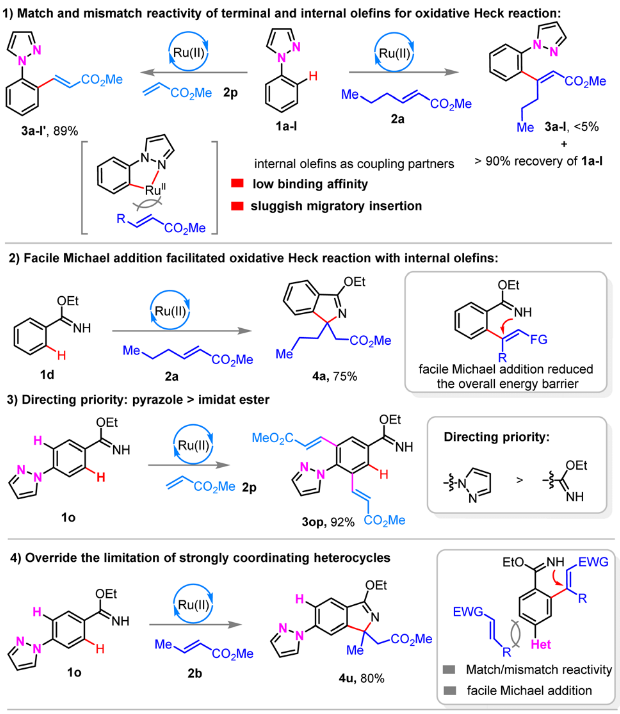
[a] Standard conditions: **1a** (0.10 mmol), **2a** (0.20 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (2 mol%), $AgNTf_2$ (5 mol%), NaOAc (30 mol%), $Na_2CO_3 \cdot H_2O_2$ (2.0 equiv.), GVL (1.0 mL), 100 °C, 12 h. [b] Isolated yield.

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.



Scheme 3 Preliminary mechanistic studies.

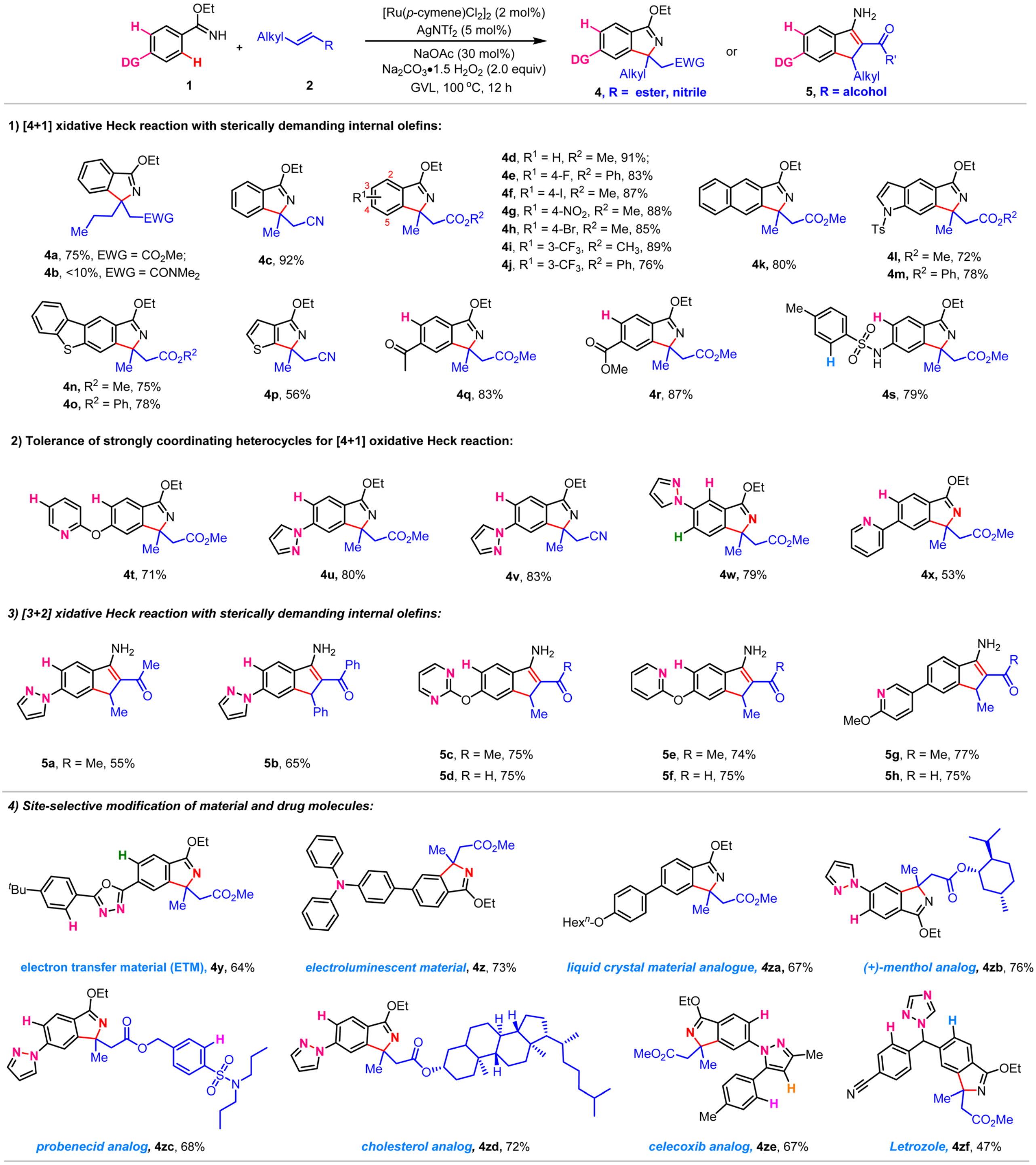
product **4a** in a high yield (Scheme 3(2)). Moreover, the oxidative Heck reaction of pyrazole substituted acrylamide ester **1o** with terminal olefin **2m** gave olefination product **3op** exclusively, indicating that the directing priority is that pyrazole is superior to imidate ester (Scheme 3(3)). 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'[4e] 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 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



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[11] 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 indenes contained carbonyl and amine functionalities, which could serve as a synthetic handle for the synthesis of heterocycles (please see the ESI† for further discussion).

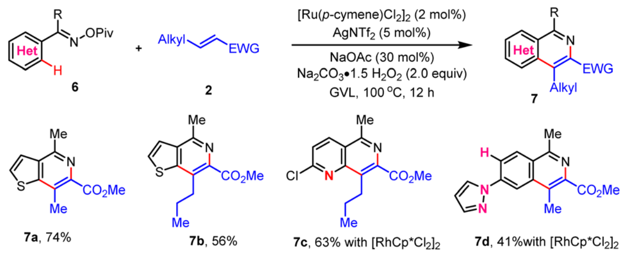
The oxime enabled Heck reaction has been demonstrated for the construction of heterocycles, while the use of heterocycles and sterically demanding internal olefin partners remained elusive to achieve regioselectivity and efficiency.[12] Herein, we found that N–OPiv oxime esters could well assist the 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),[12g] 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).

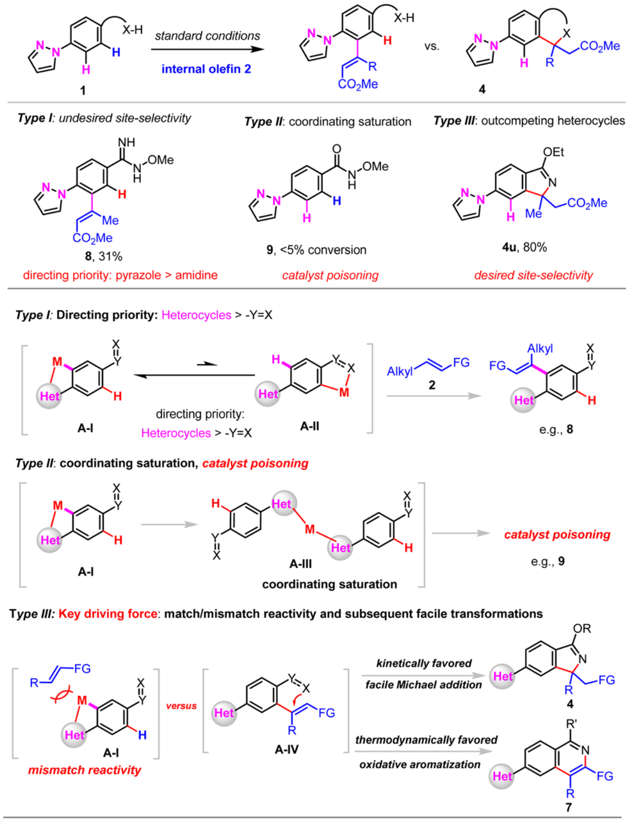
According to the experimental observations and related references, three typical reaction types might be involved in directed C–H functionalization of heterocycles. For type I reactivity, competing coordination of directing groups (DG) and heterocycles to the metal catalyst revealed that heterocycles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

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 small molecules) to reduce the overall energy barrier, C–H functionalization that overrides the limitation of strongly coordinating heterocycles might be achieved.[15]



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

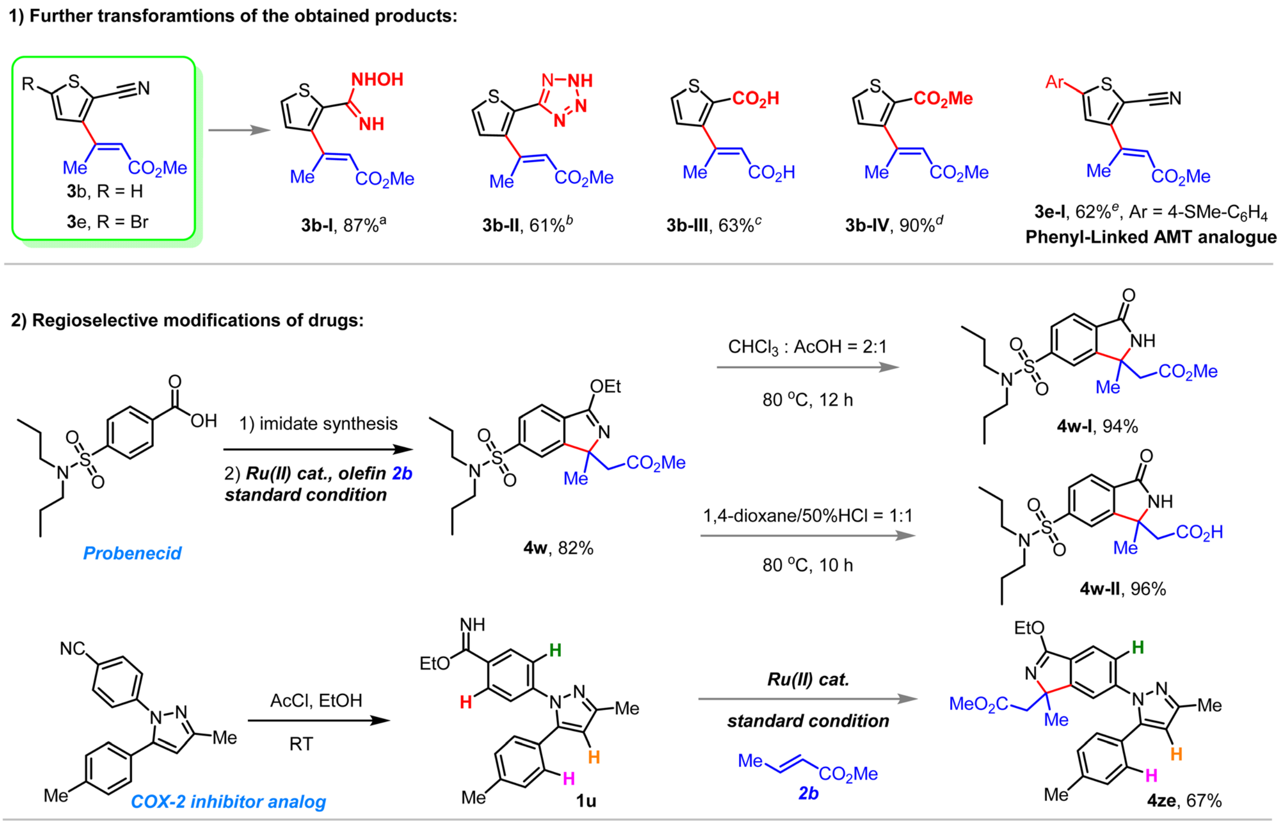


Scheme 6 Mechanistic studies.

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 7 Synthetic transformations. Conditions: (a) **3b** (0.1 mmol), NaOAc (2.0 equiv.), $NH_2OH\cdot HCl$ (2.0 equiv.), $MeOH/H_2O$ (1.0 mL/1.0 mL), 90 °C, 2 h; (b) **3b** (0.1 mmol), $NaN_3$ (4.0 equiv.), $NH_4Cl$ (2.0 equiv.), DMF (1.0 mL), $N_2$, 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), $K_2CO_3$ (2.0 equiv.), MeI (2.0 equiv.), THF (1.0 mL), 40 °C, 5 h; (e) **3e** (0.10 mmol), $Pd(PPh_3)_4$ (0.005 mmol), $K_2CO_3$ (0.4 mmol), Ar–B(OH)$_2$ (0.12 mmol), EtOH/$H_2O$/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 imidate 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

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