

Cite this: *Chem. Sci.*, 2023, 14, 3010

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

Received 30th December 2022
Accepted 16th February 2023

DOI: 10.1039/d2sc07117g

rsc.li/chemical-science

Catalytic enantioselective alkenylation–heteroarylation of olefins: stereoselective syntheses of 5–7 membered azacycles and oxacycles†

Zhaoming Ma,^a Lantian Sun^b and Jianrong Steve Zhou^{id} ^{*a}

Catalytic enantioselective domino alkenylation–heteroarylation of nonconjugated iododienes proceeded with excellent stereoselectivity and broad scope of substrates. The reaction enables stereoselective syntheses of substituted azacycles such as piperidine, pyrrolidine, azepine and dihydropyrans carrying new quaternary stereocenters. Mechanistically, C–H bonds of heterocycles were activated by lithium alkoxides *via* reversible deprotonation, rather than conventional palladium(II)-assisted metalation processes. Many types of heteroarenes can be used, including not only azoles (such as thiazoles, oxazoles, imidazoles and oxadiazoles), but also nonazoles (thiophene, furan and azine *N*-oxides).

There is a resurgence of research interest in developing enantioselective domino coupling reactions initiated by Heck-type arylation of pendant alkenes.¹ For example, Zhu *et al.*² reported a stereoselective synthesis of stereodefined 3,3-disubstituted oxindoles *via* domino couplings of acrylamide *ortho*-triflates. The heteroarenes were limited to azoles having acidified C–H bonds such as benzothiazole, benzoxazole and 1,3,4-oxadiazole;³ they were activated *via* a palladium-based mechanism of nonconcerted metalation–deprotonation.⁴ However, analogous stereoselective domino couplings of alkenyl electrophiles proved to be much more difficult,⁵ due to side reactions such as Heck-type bicyclization onto the alkenyl groups after insertion to form [3.1.0]bicycles⁶ or subsequent ring expansion (see Fig. 1a).⁷

We report herein a general method for catalytic domino alkenylation–heteroarylation to readily access 5–7 membered azacycles, as well as oxacyclic dihydropyran derivatives (see Fig. 1a and b).⁸ These saturated azacycles, pyrrolidines and piperidines are among the most frequently used rings in medicines, including both heterocycles and carbocycles (Fig. 1b).⁹ For example, anti-HIV agent nifedipine contains a trisubstituted pyrrolidine and shows an IC₅₀ value of 2.9 nM

against the CCR5 receptor, but the IC₅₀ value of its enantiomer was only 380 nM.¹⁰ The new reaction provides azacycles carrying quaternary stereocenters at C3 or C4 positions which are difficult to prepare from other catalytic reactions.¹¹ It also enabled asymmetric ring closure to form oxacyclic dihydropyrans (Fig. 1b).

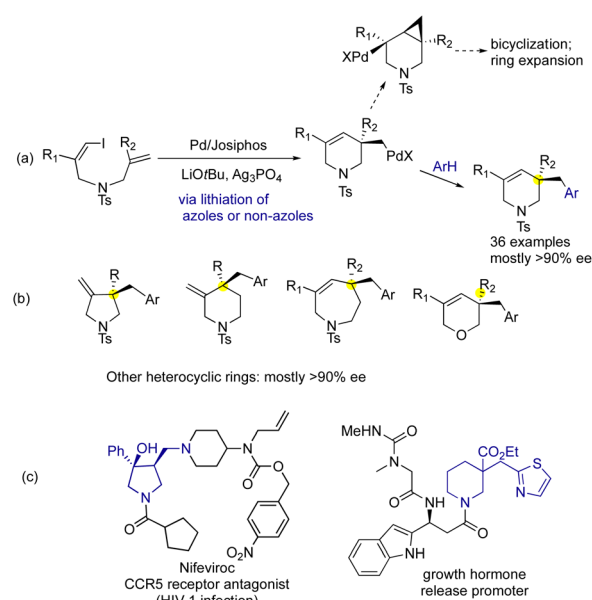


Fig. 1 (a) Domino arylation–heteroarylation of *N*-acrylamides for stereoselective synthesis of 3,3-disubstituted oxindoles. (b) Domino alkenylation–heteroarylation of olefins for asymmetric synthesis of azacycles of 5–7 ring sizes and 4,5-dihydropyran derivatives. (c) Examples of drugs containing piperidines and pyrrolidines.

^aState Key Laboratory of Chemical Oncogenomics, Guangdong Provincial Key Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, Room F312, 2199 Lishui Road, Nanshan District, Shenzhen 518055, China. E-mail: jrzhou@pku.edu.cn

^bDepartment of Chemistry, Hong Kong Baptist University, 224 Waterloo Road, Kowloon Tong, Hong Kong, China

† Electronic supplementary information (ESI) available: Experimental procedures, characterization of isolated products and CIF files of crystallographic data. CCDC 2152684 (5d). For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d2sc07117g>

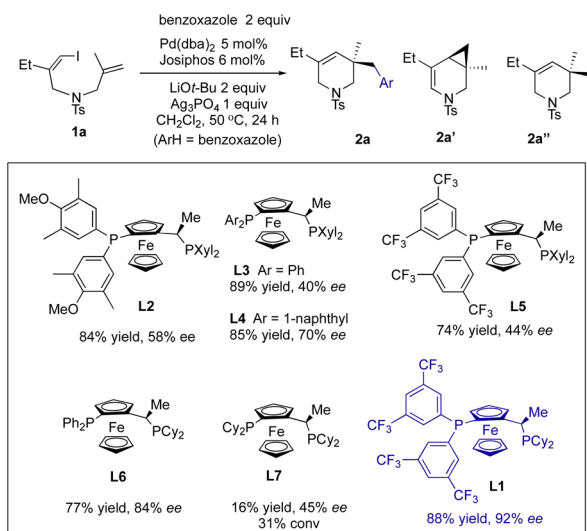
In a model study of iododiene **1a** and benzoxazole, we first explored a family of Josiphos ligands¹² to identify suitable ancillary ligands for palladium catalysts (see Scheme 1). In Pd^{II} complexes of Josiphos, switching from PAr₂ to PCy₂ (Ar = aryl; Cy = cyclohexyl) groups on the 1-ethyl sidearm is accompanied by not only electronic perturbation, but also a substantial conformational change in chelate rings formed by palladium and Josiphos, so as to avoid close contact of large PCy₂ rings with the ferrocene ring.¹³ Consequently, all four *P*-substituents will undergo a substantial conformational change; hence a significant change occurs in the chiral environment surrounding the palladium centers.

The modularity and tunability of both steric and electronic properties of Josiphos ligands are very rewarding. This allowed us to quickly identify Josiphos **L1** (ref. 14) which provides desired piperidine **2a** in 88% yield and 92% ee, along with a small amount of an oxidative dimer of benzoxazole. If benzoxazole was omitted, the reaction pathway sidetracked to Heck bicyclization (41% **2a'** in 87% ee) and reductive Heck cyclization (27% **2a''**). The Heck bicyclization leading to **2a'** also eliminated PdH species, which can undergo ligand exchange with alkyl palladium complex **C** to form **2a''** via C–H reductive elimination (see Scheme 7c below). The Heck bicyclization has no parallelism in domino coupling reactions of aryl electrophiles (see Fig. 1a). Josiphos analogues **L2–L4** carrying two diarylphosphines only afforded moderate 40–70% ees. In comparison, the Josiphos series having a strongly donating PCy₂ sidearm gave consistently higher ees than the former. On the other hand, the complex of **L7** carrying two highly donating PCy₂ donors showed poor catalytic activity and afforded a low level of stereoselectivity. It is well known that in cationic Heck-type reactions, the key step of alkene insertion is accelerated by weakly donating ligands and retarded by strongly donating phosphines.¹⁵ Axially chiral biphosphines were also tested; for

example, axially chiral BINAP and Segphos furnished 58% ee and 81% ee, respectively.

During condition optimization, we noticed that other reaction parameters were also important. The choice of metal alkoxides had a remarkable impact on the outcome. Without an added alkoxide, only 16% conversion of **1a** was detected without any formation of **2a** (Table 1, entry 2). LiOMe led to moderate yield and ee (entry 2); LiOt-Bu, NaOMe or KOMe proved to be the best bases in terms of both chemical yields and ees (entries 4 and 5); the more basic alkoxides NaOt-Bu or KOt-Bu gave poor yields of **2a** probably due to fast deprotonation and ring opening of 2-metalated benzoxazole (entries 6 and 7).¹⁶ The use of silver phosphate was essential, without which the model reaction gave a complex mixture containing **2a** in 48% yield and 81% ee (entry 8). Other silver salts, Ag₂CO₃, AgOAc or AgOTf can also provide **2a** in 60–85% yields and ~90% ees (entries 9–11). The result suggests that these silver salts may act as halide abstractors to create a coordination site for enantiofacial olefin insertion.

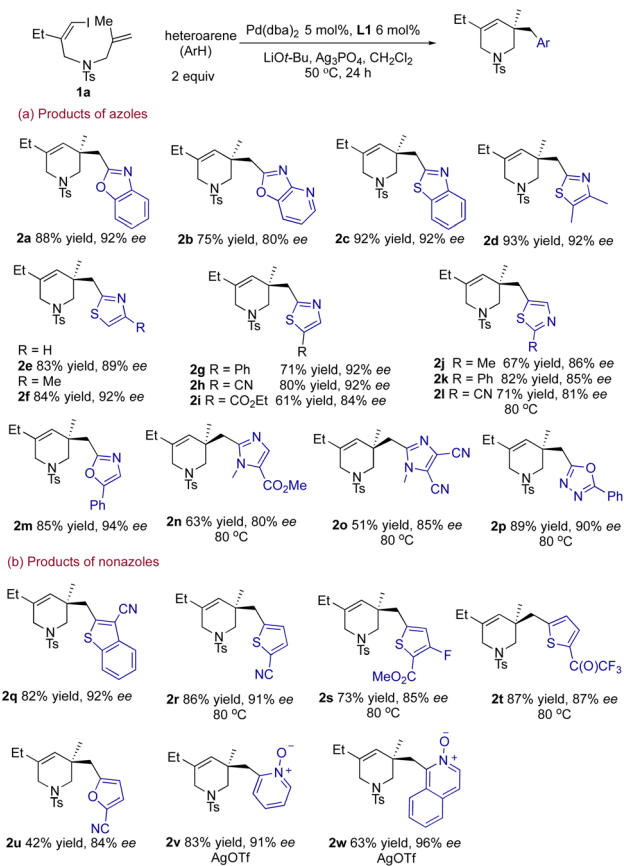
The Pd catalyst of Josiphos **L1** can be applied to domino couplings of iododialkene **1a** with many classes of heteroarenes (Scheme 2). We were gratified to find that the combination of lithium *t*-butoxide and silver phosphate enabled efficient activation of azoles including (benzo)thiazole, (benzo)oxazole, imidazoles and oxadiazole, but also nonazoles such as (benzo)thiophene,¹⁷ furan and azine *N*-oxides. In reactions of thiazoles (**2h–i**), polar groups, esters and nitrile were well tolerated. Notably, the C–H activation of C2-substituted thiazoles (**2j–l**) occurred regioselectively at C5 positions next to the sulfur atom. In the reactions of imidazoles (**2n–o**), (benzo)thiophenes (**2q–t**) and furan (**2u**), electron-withdrawing groups (*e.g.*, ester, nitrile and trifluoroacetyl) were important to the activation and



Scheme 1 Screening of Josiphos ligands on a model domino reaction of **1a** and benzoxazole (GC yields on a 0.05 mmol scale in 0.3 mL of CH₂Cl₂). dba = dibenzylideneacetone.

Table 1 The effect of reaction parameters on a model reaction of **1a** and benzoxazole under conditions using Josiphos **L1** (0.05 mmol scale in 0.3 mL of CH₂Cl₂). Calibrated GC conversion and yields and ees determined for pure samples). Ts = 4-toluenesulfonamide; dba = dibenzylideneacetone

Entry	Change of conditions	Conv. of 1a (%)	Yield of 2a' (%)	
			Yield of 2a (%)	(%)
1	No change	100	88 (92% ee)	9
2	No LiOt-Bu	16	0	0
3	LiOMe	100	63 (58% ee)	12
4	NaOMe	100	89 (90% ee)	0
5	KOMe	100	73 (92% ee)	0
6	NaOt-Bu	33	12 (86% ee)	6
7	KOt-Bu	92	26 (85% ee)	5
8	No Ag ₃ PO ₄	100	48 (81% ee)	<5
9	Ag ₂ CO ₃	100	75 (92% ee)	12
10	AgOAc	100	59 (94% ee)	12
11	AgOTf	100	84 (90% ee)	8

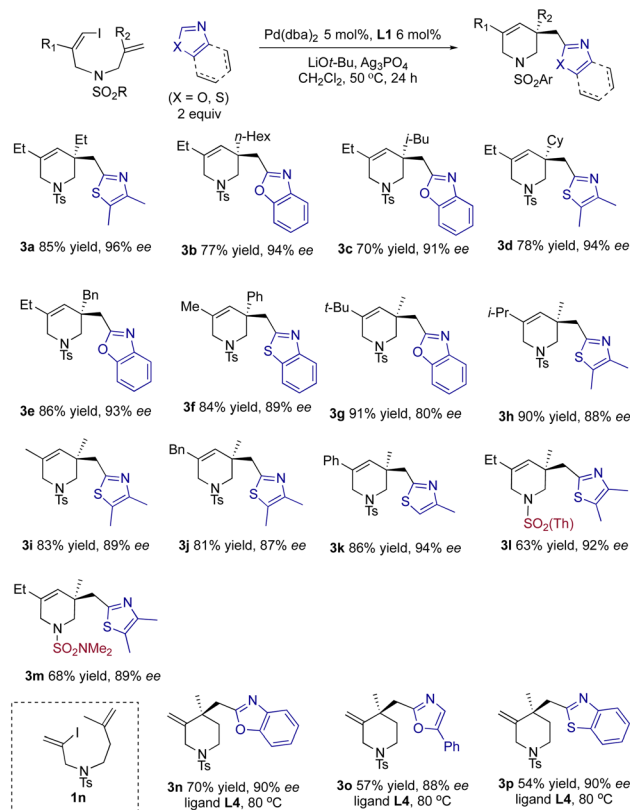


Scheme 2 Examples of azoles and non-azoles in enantioselective formation of piperidines (isolated yields from a 0.1 mmol scale in 0.5 mL of CH₂Cl₂).

couplings of these heteroarenes. Notably, both pyridine and isoquinoline *N*-oxides were regioselectively activated at C2 positions to give products **2v–w** in ~70% ees under the standard conditions using **L1**. Switching from Ag₃PO₄ to AgOTf increased the stereoselectivity to >90% ees.

Next, we studied structural variations of (*Z*)-1-iodo-1,6-dienes in stereoselective formation of piperideines (Scheme 3). The alkenyl fragment can tolerate different C5-substituents (ethyl, *n*-hexyl, isobutyl, cyclohexyl, benzyl and phenyl) (**3a–f**), while the C3 substituents of the iodoalkenyl fragment can be *t*-butyl, *i*-propyl, methyl, benzyl and phenyl (**3g–k**). Moreover, the *N*-tosylamide linker can be substituted by 2-thienylsulfonamide and *N,N*-dimethylsulfamate (**3l–m**). We also attempted to prepare piperidines carrying quaternary stereocenters at C4 positions, by using 2-iodo-1,7-diene **1n**. At first, its reaction with benzoxazole failed to produce product **3n** in a reasonable quantity. After switching from ligand **L1** to **L4** possessing a large di(1-naphthyl)phosphine sidearm, we succeeded in producing piperidines **3n–p** from benzoxazole, oxazole and benzothiazole in satisfactory yields and with ~90% ee (Scheme 3).

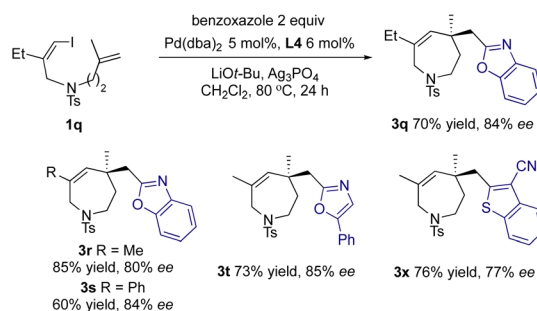
Seven-membered azepane derivatives are important motifs in medicines,¹⁸ but catalytic asymmetric syntheses for these azacycles are still limited to date.¹⁹ Thus, the Pd catalyst of Josiphos **L4** also promoted domino coupling of (*Z*)-1-iodo-1,7-



Scheme 3 Stereoselective formation of 6-membered piperideines and piperidines via domino couplings (isolated yields on a 0.1 mmol scale in 0.5 mL of CH₂Cl₂). Th = 2-thienyl.

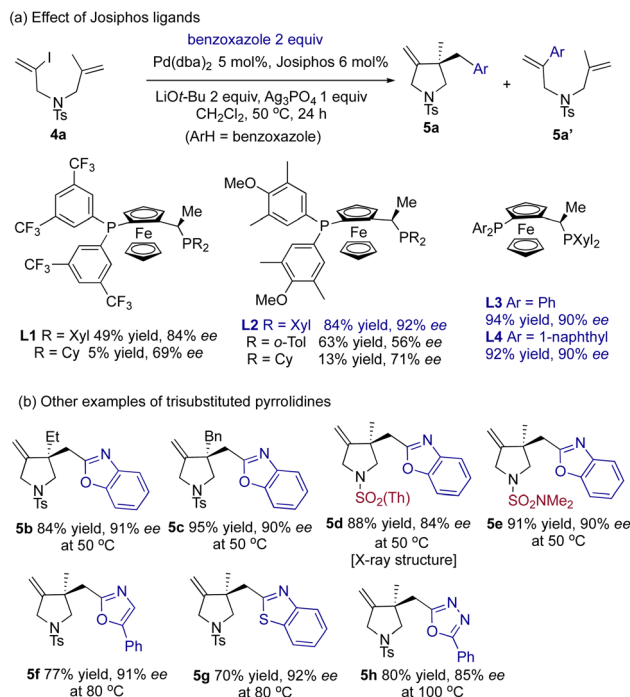
diene **1q** with benzothiazole via a rare 7-*exo-trig* cyclization (Scheme 4).²⁰ Asymmetric formation of tetrahydroazepine **3q** was achieved in 70% yield and 84% ee (or 92 : 8 er). In contrast, the Pd/**L1** catalyst failed to produce a significant amount of product **3q**. The domino couplings using **L4** proceeded well with 5-phenyloxazole and 3-cyanobenzothiophene, too (**3t–3x**).

Furthermore, we successfully used the new method for stereoselective construction of trisubstituted pyrrolidines. Thus, a reaction of 2-iodo-1,6-diene **4a** with benzoxazole generated **5a** in 49% yield and 84% ee. After switching ligand **L1** to Josiphos **L2**, a satisfactory result of 84% yield and 92% ee



Scheme 4 Stereoselective formation of tetrahydroazepines via domino couplings of **1q** (isolated yields on a 0.1 mmol scale in 0.5 mL of CH₂Cl₂).





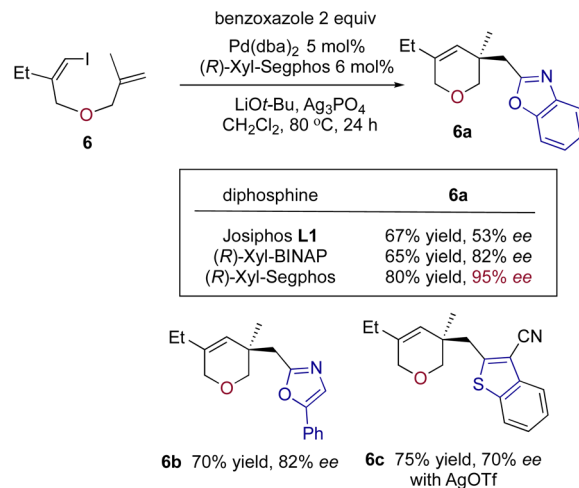
Scheme 5 Stereoselective formation of substituted pyrrolidines via domino couplings (isolated yields on a 0.1 mmol scale in 0.5 mL of CH_2Cl_2): (a) the effect of Josiphos ligands and (b) examples of pyrrolidines obtained under conditions using Josiphos L2. Th = 2-thienyl.

resulted. In this model reaction, Josiphos L3 and L4 also provided excellent yields and 90% ee (Scheme 5a). LiOtBu was important, without which only 26% conversion of 4a was detected, without any production of 5a. Additionally, when Ag_3PO_4 was omitted, the reaction afforded 5a in 31% yield and 71% ee, together with some premature coupling (26% yield of 5a'), hinting that the silver salt played a crucial role in halide abstraction to create a "vacant" site for enantiofacial olefin insertion.

The enantioselective formation of pyrrolidines tolerated well structural variations in iododienes (Scheme 5b), for example, ethyl and benzyl groups on olefinic units (5b–c) and acid-labile 2-thienylsulfonamide and *N,N*-dimethylsulfamate linkers (5d–e). Azoles such as benzoxazole, benzothiazole and 1,3,4-oxadiazole coupled well (5f). Single crystals of 5d were obtained *via* vapor diffusion of hexane into a solution in DCM. X-ray crystallography thus established its absolute configuration to be 3*R*.†

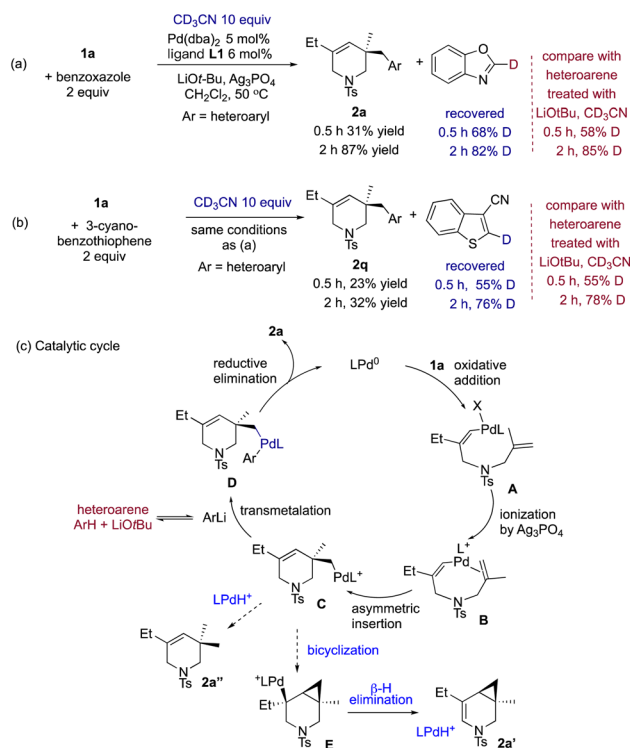
We also attempted to prepare oxacycle 6a *via* a domino coupling of iodo-1,6-diene 6 (Scheme 6). Initially, we found that the Pd/L1 catalyst only provided 6a in a moderate yield and 53% ee, but after changing the ancillary ligand to (*R*)-xyl-Segphos, the result was readily improved to 80% yield and 95% ee. Thus, the Pd/xyl-Segphos catalyst efficiently enabled stereoselective formation of other oxacycles 6b–c from 5-phenyloxazole and 3-cyanobenzothiophene. The six-membered oxacycles are present in some medicines as core structures.²¹

To gain insights into the activation of heteroarenes under catalytic conditions, we added 10 equiv. of CD_3CN ($\text{p}K_a$ 31 in



Scheme 6 The effect of diphosphines on the formation of 6a and some examples of oxacycles obtained from domino couplings catalyzed by Pd/xyl-Segphos (isolated yields on a 0.1 mmol scale in 0.5 mL of CH_2Cl_2).

DMSO) to catalytic domino couplings of 1a with benzoxazole and 3-cyanobenzothiophene. Several observations were made. (a) 1a and benzoxazole ($\text{p}K_a$ 25 in DMSO) reacted efficiently and almost full conversion was reached to give 86% yield of 2a after 2 h, while the recovered benzoxazole was 82% deuterated at the C2 position (see Scheme 7a). Treatment of benzoxazole with



Scheme 7 Catalytic domino couplings of 1a with (a) benzoxazole and (b) 3-cyanobenzothiophene in the presence of CD_3CN . (c) A putative catalytic cycle of domino coupling of model substrate 1a and a heteroarene and the formation of side products (Ar = heteroaryl).



LiOtBu alone resulted in a comparable level of deuteration (85% after 2 h). A similar phenomenon was seen with deuteration of 3-cyanobenzothiophene (see Scheme 7b). (b) Parent thiophene and benzothiophene failed to participate in domino coupling; they did not undergo deuteration by LiOtBu and CD₃CN (<5%), either. Therefore, the electron-withdrawing groups are important for acidifying C–H bonds of (benzo)thiophenes and furan to allow reversible deprotonation to occur (e.g., **2q–u** in Scheme 2). (c) Ag₂CO₃ complexes ligated by biarylphosphines were reported by others to catalyze deuteration of azoles, indoles and thiophenes using D₂O or CH₃OD.²² However, Ag₃PO₄ or Ag₂CO₃ together with Josiphos **L1** only effected very low levels of deuteration in DCM after 2 h (2% and 11% for two heteroarenes). Thus, silver(i) heteroaryl complexes are probably not responsible for the activation and coupling of heteroarenes under our conditions. (d) Palladium(ii) complexes were known to activate azoles and nonazoles *via* several different mechanisms, such as concerted metalation–deprotonation (CMD)²³ nonconcerted metalation–deprotonation^{4a,b} and electrophilic CMD,²⁴ depending on the nature of (hetero)arenes, ancillary ligands and conditions (such as bases and solvents). However, the extent of deuteration of the heteroarenes recovered from the two catalytic whole reactions (see Scheme 7) agreed well with those from control reactions with CD₃CN and LiOtBu in DCM. Thus, palladium(ii) complexes did not play a significant role in activation of heteroarenes under our catalytic conditions. Thus, we concluded that the deuteration results point to a mechanistic scenario in which LiOtBu promoted reversible formation of lithiated heteroarenes.

In a productive catalytic cycle (see Scheme 7c), silver phosphate or carbonate abstracted the halide ion from oxidative-addition complex **A** to produce cationic alkenyl complex **B**. It quickly underwent asymmetric olefin insertion to form alkyl palladium species **C** which, in turn, was intercepted by a lithio heteroarene. Final C–C reductive elimination of species **D** completed the catalytic cycle of domino coupling. The lithiation, we believe, may be the rate-limiting step, at least in

reactions of furans, thiophenes and benzothiophenes. When complex **C** was not trapped by an organometallic reagent, it was sidetracked to bicyclization forming side product **2a'**. The Heck bicyclization forming **2a'** also eliminated PdH species, which can undergo ligand exchange with alkyl palladium complex **C** and subsequent C–H reductive elimination to form **2a''** (see Scheme 7c below).

As a showcase of synthetic utility, product **5a** was readily converted to other compounds *via* transformations of its olefinic group (see Scheme 8). (a) Stirring **5a** with Co₂(CO)₈ in refluxing xylene led to olefin isomerization to a more stable isomer, 2-pyrroline **7a** *via* an allyl cobalt hydride species.²⁵ (b) Treatment with *in situ* formed KPPH₂, however, resulted in olefinic isomerization with ring opening of benzoxazole (**7b**).²⁶ (c) Moreover, RuCl₃-catalyzed oxidative cleavage using NaIO₄ (ref. 27) provided ketone **7c** under mild conditions. (d) Catalytic hydrogenation over Pd/C occurred facioselectively to give **7d** in a dr of 12 : 1, using the benzoxazole ring as a directing group. The configuration of *cis*-3,4-dimethyl pyrrolidine was established with NOESY analysis. (e) Iron-catalyzed radical hydrofluorination of **5a** under Boger's conditions²⁸ produced a regioselectively Markovnikov adducts **7e** (as two diastereomers in a ratio of 1.5 : 1).

In conclusion, we report enantioselective domino alkenylation–heteroarylation reactions in excellent enantioselectivity. The reactions produced 5–7 membered azacycles (pyrrolidine, piperidine and tetrahydroazepine) containing new quaternary stereocenters, which are not easily accessible from other methods. We found that many types of heteroarenes, both azoles and nonazoles, are suitable substrates, including (benzo)thiazole, (benzo)oxazole, imidazole, oxadiazole, (benzo)thiophene, furan and azine *N*-oxides. Mechanistically, deuteration experiments indicated that both azoles and nonazoles were activated by regioselective, reversible lithiation by LiOtBu. This mechanism is distinct from *n*CDM previously reported by Zhu *et al.* in catalytic arylation–heteroarylation.

Data availability

Experimental and NMR data (both in pdf) have been included.

Author contributions

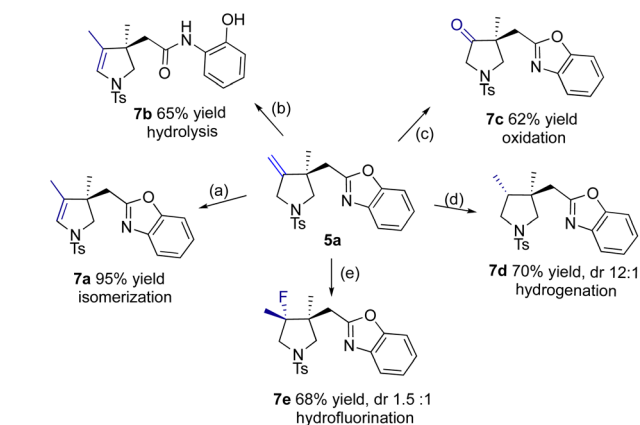
ZM conducted all catalytic experiments and compound characterization and LS conducted derivatization reactions described in Scheme 8. JSZ drafted the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We acknowledge financial support from the National Natural Science Foundation of China (22271007), Peking University Shenzhen Graduate School, State Key Laboratory of Chemical Oncogenomics, Guangdong Provincial Key Laboratory of



Scheme 8 Product derivatization: (a) Co₂(CO)₈, mesitylene, 130 °C, 24 h; (b) HPPH₂, KOH, DMSO, 90 °C, 1 h; (c) cat. RuCl₃, NaIO₄, EtOAc/MeCN/H₂O 1 : 1 : 1, RT, 15 h; (d) 5% Pd/C, H₂ (balloon), MeOH, RT, 16 h; (e) Fe(NO₃)₃·9H₂O, NaBH₄, Selectfluor, MeCN/H₂O 1 : 1, 0 °C, 2 h.



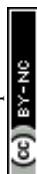
Chemical Genomics and Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs for JSZ. Hao Xie at PKUSZ conducted X-ray diffraction and data collection.

Notes and references

- (a) H. A. Döndaş, M. d. G. Retamosa and J. M. Sansano, Recent Development in Palladium-Catalyzed Domino Reactions: Access to Materials and Biologically Important Carbo- and Heterocycles, *Organometallics*, 2019, **38**, 1828; (b) Y. Ping, Y. Li, J. Zhu and W. Kong, Construction of Quaternary Stereocenters by Palladium-Catalyzed Carbopalladation-Initiated Cascade Reactions, *Angew. Chem., Int. Ed.*, 2019, **58**, 1562; (c) W. Li and J. Zhang, Recent advances in Pd-catalyzed asymmetric addition reactions, in *Adv. Organomet. Chem.*, ed. P. J. Pérez, Academic Press, 2020, ch. 6, vol. 74, p. 325; (d) R.-X. Liang and Y.-X. Jia, Aromatic π -Components for Enantioselective Heck Reactions and Heck/Anion-Capture Domino Sequences, *Acc. Chem. Res.*, 2022, **55**, 734; (e) Q. Pan, Y. Ping and W. Kong, Nickel-Catalyzed Ligand-Controlled Selective Reductive Cyclization/Cross-Couplings, *Acc. Chem. Res.*, 2023, DOI: [10.1021/acs.accounts.2c00771](https://doi.org/10.1021/acs.accounts.2c00771); (f) H. Pellissier, Recent Developments in Enantioselective Domino Reactions. Part B: First Row Metal Catalysts, *Adv. Synth. Catal.*, 2023, DOI: [10.1002/adsc.202300002](https://doi.org/10.1002/adsc.202300002); (g) H. Pellissier, Recent Developments in Enantioselective Domino Reactions. Part A: Noble Metal Catalysts, *Adv. Synth. Catal.*, 2023, DOI: [10.1002/adsc.202201284](https://doi.org/10.1002/adsc.202201284).
- (a) W. Kong, Q. Wang and J. Zhu, Palladium-Catalyzed Enantioselective Domino Heck/Intermolecular C–H Bond Functionalization: Development and Application to the Synthesis of (+)-Esermethole, *J. Am. Chem. Soc.*, 2015, **137**, 16028; (b) X. Bao, Q. Wang and J. Zhu, Palladium-Catalyzed Enantioselective Narasaka–Heck Reaction/Direct C–H Alkylation of Arenes: Iminoarylation of Alkenes, *Angew. Chem., Int. Ed.*, 2017, **56**, 9577; (c) S. Tong, A. Limouni, Q. Wang, M.-X. Wang and J. Zhu, Catalytic Enantioselective Double Carbopalladation/C–H Functionalization with Statistical Amplification of Product Enantiopurity: A Convertible Linker Approach, *Angew. Chem., Int. Ed.*, 2017, **56**, 14192.
- (a) O. René, D. Lapointe and K. Fagnou, Domino Palladium-Catalyzed Heck-Intermolecular Direct Arylation Reactions, *Org. Lett.*, 2009, **11**, 4560; (b) N. Zeidan, T. Beisel, R. Ross and M. Lautens, Palladium-Catalyzed Arylation/Heteroarylation of Indoles: Access to 2,3-Functionalized Indolines, *Org. Lett.*, 2018, **20**, 7332.
- (a) J. M. Joo, B. B. Touré and D. Sames, C–H Bonds as Ubiquitous Functionality: A General Approach to Complex Arylated Imidazoles via Regioselective Sequential Arylation of All Three C–H Bonds and Regioselective *N*-Alkylation Enabled by SEM-Group Transposition, *J. Org. Chem.*, 2010, **75**, 4911; (b) V. Gandon and C. Hoarau, Concerted vs Nonconcerted Metalation–Deprotonation in Orthogonal Direct C–H Arylation of Heterocycles with Halides: A Computational Study, *J. Org. Chem.*, 2021, **86**, 1769; (c) S. Teng and J. S. Zhou, Metal-catalyzed asymmetric heteroarylation of alkenes: diverse activation mechanisms, *Chem. Soc. Rev.*, 2022, **51**, 1592.
- (a) X. Chen, J. Zhao, M. Dong, N. Yang, J. Wang, Y. Zhang, K. Liu and X. Tong, Pd(0)-Catalyzed Asymmetric Carbohalogenation: H-Bonding-Driven C(sp³)-Halogen Reductive Elimination under Mild Conditions, *J. Am. Chem. Soc.*, 2021, **143**, 1924; (b) J.-B. Qiao, Y.-Q. Zhang, Q.-W. Yao, Z.-Z. Zhao, X. Peng and X.-Z. Shu, Enantioselective Reductive Divinylation of Unactivated Alkenes by Nickel-Catalyzed Cyclization Coupling Reaction, *J. Am. Chem. Soc.*, 2021, **143**, 12961; (c) L. Qi, M. Dong, J. Qian, S. Yu and X. Tong, Pd⁰-Catalyzed Asymmetric Carbonitration Reaction Featuring an H-Bonding-Driven Alkyl–PdII–ONO₂ Reductive Elimination, *Angew. Chem., Int. Ed.*, 2023, **62**, e202215397.
- (a) Y. Zhang and E.-i. Negishi, Metal-promoted cyclization. 25. Palladium-catalyzed cascade carbometalation of alkynes and alkenes as an efficient route to cyclic and polycyclic structures, *J. Am. Chem. Soc.*, 1989, **111**, 3454; (b) R. Grigg, U. Sakee, V. Sridharan, S. Sukirthalingam and R. Thangavelauthum, Palladium catalysed bis- and tris-cyclisations furnishing fused cyclopropyl carbo/heterocycles, *Tetrahedron*, 2006, **62**, 9523; (c) W. Liu and X. Tong, Pd(0)-Catalyzed Cyclizative Carboboration of *n*-Iodo-1,6-diene (*n* = 1 or 2): Access to Structurally Complex Allylboronates and Alkylboronates, *Org. Lett.*, 2019, **21**, 9396.
- (a) Z. Owczarczyk, F. Lamaty, E. J. Vawter and E. Negishi, Apparent endo-mode cyclic carbopalladation with inversion of alkene configuration via exo-mode cyclization-cyclopropanation rearrangement, *J. Am. Chem. Soc.*, 1992, **114**, 10091; (b) C.-W. Lee, K. S. Oh, K. S. Kim and K. H. Ahn, Suppressed β -Hydride Elimination in Palladium-Catalyzed Cascade Cyclization–Coupling Reactions: An Efficient Synthesis of 3-Arylmethylpyrrolidines, *Org. Lett.*, 2000, **2**, 1213; (c) K. H. Kim, S. H. Kim, H. J. Lee and J. N. Kim, Palladium-Catalyzed Domino Cyclization (5-exo/3-exo), Ring-Expansion by Palladium Rearrangement, and Aromatization: An Expedient Synthesis of 4-Arylnicotinates from Morita–Baylis–Hillman Adducts, *Adv. Synth. Catal.*, 2013, **355**, 1977.
- P. Bhutani, G. Joshi, N. Raja, N. Bachhav, P. K. Rajanna, H. Bhutani, A. T. Paul and R. Kumar, U.S. FDA Approved Drugs from 2015–June 2020: A Perspective, *J. Med. Chem.*, 2021, **64**, 2339.
- (a) M. Aldeghi, S. Malhotra, D. L. Selwood and A. W. E. Chan, Two- and Three-dimensional Rings in Drugs, *Chem. Biol. Drug Des.*, 2014, **83**, 450; (b) R. D. Taylor, M. MacCoss and A. D. G. Lawson, Rings in Drugs, *J. Med. Chem.*, 2014, **57**, 5845; (c) E. Vitaku, D. T. Smith and J. T. Njardarson, Analysis of the Structural Diversity, Substitution Patterns, and Frequency of Nitrogen Heterocycles among U.S. FDA Approved Pharmaceuticals, *J. Med. Chem.*, 2014, **57**, 10257.
- D. Ma, S. Yu, B. Li, L. Chen, R. Chen, K. Yu, L. Zhang, Z. Chen, D. Zhong, Z. Gong, R. Wang, H. Jiang and G. Pei, Synthesis and Biological Evaluation of 1,3,3,4-



- Tetrasubstituted Pyrrolidine CCR5 Receptor Antagonists. Discovery of a Potent and Orally Bioavailable Anti-HIV Agent, *ChemMedChem*, 2007, **2**, 187.
- 11 G. Liu, W. Fu, X. Mu, T. Wu, M. Nie, K. Li, X. Xu and W. Tang, Pyrrolidines and piperidines bearing chiral tertiary alcohols by nickel-catalyzed enantioselective reductive cyclization of *N*-alkynones, *Commun. Chem.*, 2018, **1**, 90.
 - 12 (a) H.-U. Blaser, W. Brieden, B. Pugin, F. Spindler, M. Studer and A. Togni, Solvias Josiphos Ligands: From Discovery to Technical Applications, *Top. Catal.*, 2002, **19**, 3; (b) H. U. Blaser, B. Pugin, F. Spindler, E. Mejía and A. Togni, Josiphos Ligands: From Discovery to Technical Applications, in *Privileged Chiral Ligands and Catalysts*, ed. Q.-L. Zhou, Wiley-VCH, Weinheim, 2011.
 - 13 J. S. Zhou, Phosphorus Ligands, in *Comprehensive Coordination Chemistry III*, ed. E. C. Constable, G. Parkin and L. Que Jr, Elsevier, Oxford, 2021, p. 32.
 - 14 In a preliminary antineoplastic study, compound **2a** showed an IC₅₀ value of 0.1 μ M against HeLa cells.
 - 15 (a) *The Mizoroki–Heck Reaction*, ed. M. Oestreich, Wiley, New York, 2009; (b) J. Hu, Y. Lu, Y. Li and J. Zhou, Highly Active Catalysts of Bisphosphine Oxides for Asymmetric Heck Reaction, *Chem. Commun.*, 2013, **49**, 9425; (c) C. Wu and J. Zhou, Asymmetric Intermolecular Heck Reaction of Aryl Halides, *J. Am. Chem. Soc.*, 2014, **136**, 650; (d) S. Teng and J. S. Zhou, C–C Bond Formation Through Heck-Like Reactions, in *Comprehensive Organometallic Chemistry IV*, ed. G. Parkin, K. Meyer and D. O'hare, Elsevier, Oxford, 2022, p. 2.
 - 16 (a) G. W. Rewcastle and A. R. Katritzky, Generation and Reactions of sp²-Carbanionic Centers in the Vicinity of Heterocyclic Nitrogen Atoms, in *Adv. Heterocycl. Chem.*, ed. A. R. Katritzky, Academic Press, 1993, vol. 56, p. 155; (b) E. Crowe, F. Hossner and M. J. Hughes, 2-Metallated Oxazoles; pKa Dependent Deuterations, NMR Studies and Palladium Catalysed Coupling, *Tetrahedron*, 1995, **51**, 8889; (c) C. Hilf, F. Bosold, K. Harms, M. Marsch and G. Boche, The Equilibrium Between 2-Lithium-Oxazole-(Thiazole, -Imidazole) Derivatives and Their Acyclic Isomers – A Structural Investigation, *Chem. Ber.*, 1997, **130**, 1213.
 - 17 (a) C. Lei, X. Jin and J. Zhou, Palladium-Catalyzed Heteroarylation and Concomitant ortho-Alkylation of Aryl Iodides, *Angew. Chem., Int. Ed.*, 2015, **54**, 13397; (b) X. Wu, C. Lei, G. Yue and J. Zhou, Palladium-Catalyzed Direct Cyclopropylation of Heterocycles, *Angew. Chem., Int. Ed.*, 2015, **54**, 9601.
 - 18 G.-F. Zha, K. P. Rakesh, H. M. Manukumar, C. S. Shantharam and S. Long, Pharmaceutical significance of azepane based motifs for drug discovery: a critical review, *Eur. J. Med. Chem.*, 2019, **162**, 465.
 - 19 (a) S. J. Lee and P. Beak, Asymmetric Synthesis of 4,5,6- and 3,4,5,6-Substituted Azepanes by a Highly Diastereoselective and Enantioselective Lithiation–Conjugate Addition Sequence, *J. Am. Chem. Soc.*, 2006, **128**, 2178; (b) J.-J. Feng, T.-Y. Lin, C.-Z. Zhu, H. Wang, H.-H. Wu and J. Zhang, The Divergent Synthesis of Nitrogen Heterocycles by Rhodium(I)-Catalyzed Intermolecular Cycloadditions of Vinyl Aziridines and Alkynes, *J. Am. Chem. Soc.*, 2016, **138**, 2178; (c) C.-Z. Zhu, J.-J. Feng and J. Zhang, Rhodium(I)-Catalyzed Intermolecular Aza-[4+3] Cycloaddition of Vinyl Aziridines and Dienes: Atom-Economical Synthesis of Enantiomerically Enriched Functionalized Azepines, *Angew. Chem., Int. Ed.*, 2017, **56**, 1351; (d) G.-W. Wang and J. F. Bower, Modular Access to Azepines by Directed Carbonylative C–C Bond Activation of Aminocyclopropanes, *J. Am. Chem. Soc.*, 2018, **140**, 2743; (e) W. Zawodny, S. L. Montgomery, J. R. Marshall, J. D. Finnigan, N. J. Turner and J. Clayden, Chemoenzymatic Synthesis of Substituted Azepanes by Sequential Biocatalytic Reduction and Organolithium-Mediated Rearrangement, *J. Am. Chem. Soc.*, 2018, **140**, 17872; (f) T. Yang, X. Guo, Q. Yin and X. Zhang, Intramolecular asymmetric reductive amination: synthesis of enantioenriched dibenz[c,e]azepines, *Chem. Sci.*, 2019, **10**, 2473; (g) Y. Mao, Y. Gao and Z. Miao, Research Progress on the Asymmetric Cyclization Synthesis of Seven-Membered Rings via Transition Metal Catalysis, *Chin. J. Org. Chem.*, 2022, **42**, 1904; (h) M. Dong, L. Qi, J. Qian, S. Yu and X. Tong, Pd(0)-Catalyzed Asymmetric 7-Endo Hydroacyloxylation Cyclization of 1,6-Enyne Enabled by an Anion Ligand-Directed Strategy, *J. Am. Chem. Soc.*, 2023, **145**(3), 1973.
 - 20 (a) J. K. Ray, S. Paul, P. Ray, R. Singha, D. Y. Rao, S. Nandi and A. Anoop, Pd-catalyzed intramolecular sequential Heck cyclization and oxidation reactions: a facile pathway for the synthesis of substituted cycloheptenone evaluated using computational studies, *New J. Chem.*, 2017, **41**, 278; (b) H. Hu, Y. Peng, T. Yu, S. Cheng, S. Luo and Q. Zhu, Palladium-Catalyzed Enantioselective 7-exo-Trig Carbopalladation/Carbonylation: Cascade Reactions To Achieve Atropisomeric Dibenzol[b,d]azepin-6-ones, *Org. Lett.*, 2021, **23**, 3636.
 - 21 M. D. Delost, D. T. Smith, B. J. Anderson and J. T. Njardarson, From Oxiranes to Oligomers: Architectures of U.S. FDA Approved Pharmaceuticals Containing Oxygen Heterocycles, *J. Med. Chem.*, 2018, **61**, 10996.
 - 22 (a) E.-C. Li, G.-Q. Hu, Y.-X. Zhu, H.-H. Zhang, K. Shen, X.-C. Hang, C. Zhang and W. Huang, Ag₂CO₃-Catalyzed H/D Exchange of Five-Membered Heteroarenes at Ambient Temperature, *Org. Lett.*, 2019, **21**, 6745; (b) A. Tlahuext-Aca and J. F. Hartwig, Site-Selective Silver-Catalyzed C–H Bond Deuteration of Five-Membered Aromatic Heterocycles and Pharmaceuticals, *ACS Catal.*, 2021, **11**, 1119.
 - 23 (a) S. I. Gorelsky, D. Lapointe and K. Fagnou, Analysis of the Concerted Metalation-Deprotonation Mechanism in Palladium-Catalyzed Direct Arylation Across a Broad Range of Aromatic Substrates, *J. Am. Chem. Soc.*, 2008, **130**, 10848; (b) D. Lapointe and K. Fagnou, Overview of the Mechanistic Work on the Concerted Metallation–Deprotonation Pathway, *Chem. Lett.*, 2010, **39**, 1118; (c) N. A. Strotman, H. R. Chobanian, Y. Guo, J. He and J. E. Wilson, Highly Regioselective Palladium-Catalyzed Direct Arylation of Oxazole at C-2 or C-5 with Aryl



- Bromides, Chlorides, and Triflates, *Org. Lett.*, 2010, **12**, 3578; (d) D. L. Davies, S. A. Macgregor and C. L. McMullin, Computational Studies of Carboxylate-Assisted C–H Activation and Functionalization at Group 8–10 Transition Metal Centers, *Chem. Rev.*, 2017, **117**, 8649.
- 24 (a) L. Wang and B. P. Carrow, Oligothiophene Synthesis by a General C–H Activation Mechanism: Electrophilic Concerted Metalation–Deprotonation (eCMD), *ACS Catal.*, 2019, **9**, 6821; (b) B. P. Carrow, J. Sampson and L. Wang, Base-Assisted C–H Bond Cleavage in Cross-Coupling: Recent Insights into Mechanism, Speciation, and Cooperativity, *Isr. J. Chem.*, 2020, **60**, 230.
- 25 L. V. R. Bonaga and M. Krafft, When the Pauson-Khand and Pauson-Khand type reactions go awry: a plethora of unexpected results, *Tetrahedron*, 2004, **60**, 9795.
- 26 C. Li, Y. Huang, S. Cao, Y. Luo, Y. Zhang and G. Yang, A robust and facile method for desulfonation to amines, *Org. Chem. Front.*, 2021, **8**, 6182.
- 27 (a) D. Yang and C. Zhang, Ruthenium-Catalyzed Oxidative Cleavage of Olefins to Aldehydes, *J. Org. Chem.*, 2001, **66**, 4814; (b) D. F. Fernández, M. Gulías, J. L. Mascareñas and F. López, Iridium(I)-Catalyzed Intramolecular Hydrocarbonation of Alkenes: Efficient Access to Cyclic Systems Bearing Quaternary Stereocenters, *Angew. Chem., Int. Ed.*, 2017, **56**, 9541.
- 28 T. J. Barker and D. L. Boger, Fe(III)/NaBH₄-Mediated Free Radical Hydrofluorination of Unactivated Alkenes, *J. Am. Chem. Soc.*, 2012, **134**, 13588.

