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

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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 acroylamide *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]bicycles[6] 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 nifeviroc contains a trisubstituted pyrrolidine and shows an IC_{50} value of 2.9 nM against the CCR5 receptor, but the IC_{50} 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).

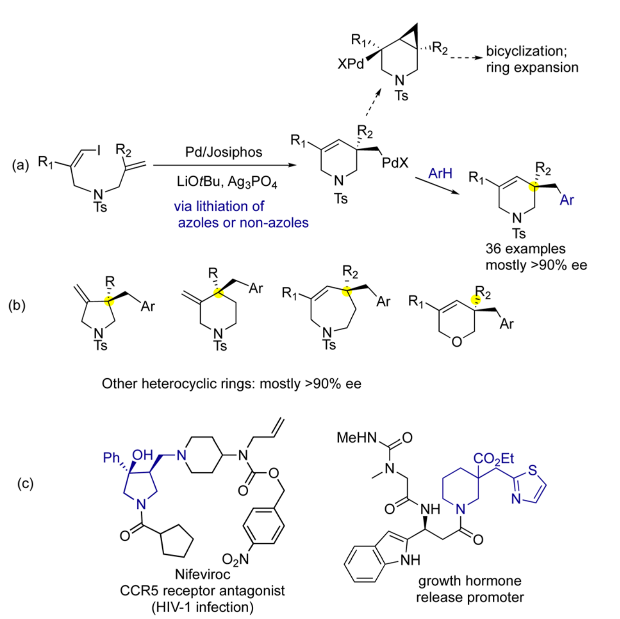

Fig. 1 (a) Domino arylation–heteroarylation of *N*-acroylamides for stereoselective synthesis of 3,3-disubstituted oxindoles. (b) Domino alkenylation–heteroarylation of olefins for asymmetric synthesis of azacycles of 5–7 ring sizes and 4,5-dihydropyran derivatives. (c) Examples of drugs containing piperidines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

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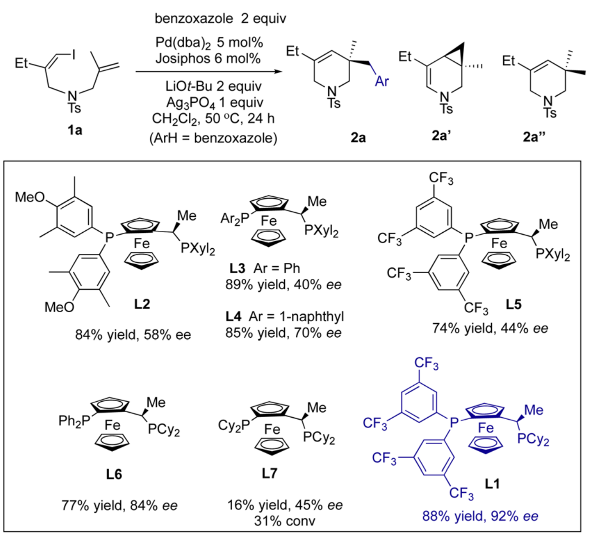
In a model study of iododiene **1a** and benzoxazole, we first explored a family of Josiphos ligands[12] to identify suitable ancillary ligands for palladium catalysts (see Scheme 1). In Pd^{II} complexes of Josiphos, switching from PAr_2 to PCy_2 (Ar = aryl; Cy = cyclohexyl) groups on the 1-ethyl sidearm 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 PCy_2 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 piperideine **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 PCy_2 sidearm gave consistently higher ees than the former. On the other hand, the complex of **L7** carrying two highly donating PCy_2 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.

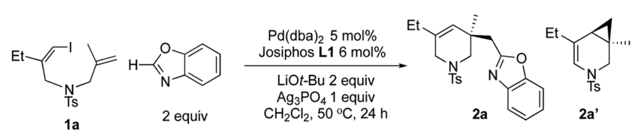
During condition optimization, we noticed that other reaction parameters were also important. The choice of metal alkoxides had a remarkable impact on the outcome. Without an added alkoxide, only 16% conversion of **1a** was detected without any formation of **2a** (Table 1, entry 2). LiOMe led to moderate yield and ee (entry 2); LiO*t*-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 NaO*t*-Bu or KO*t*-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, Ag_2CO_3, 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

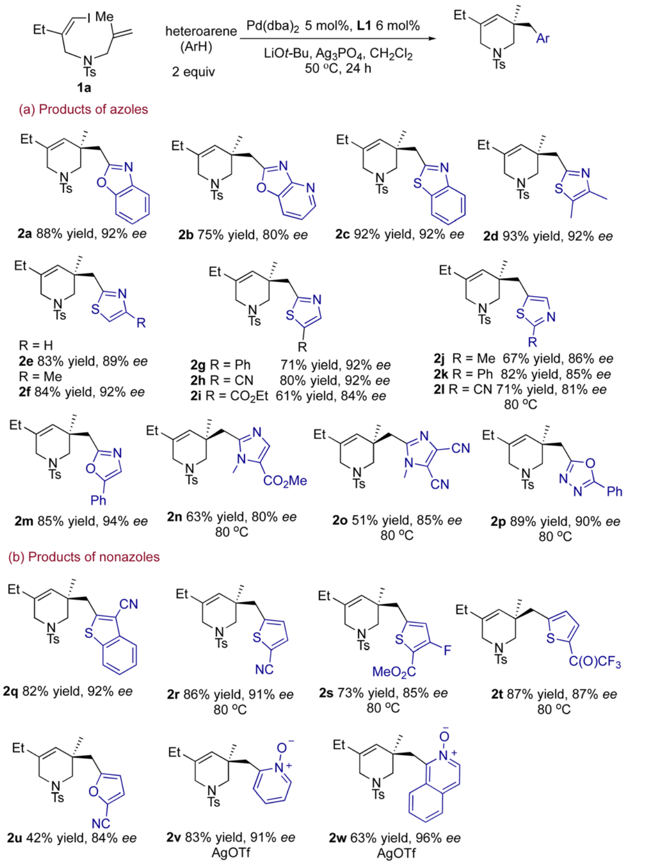


Scheme 1 Screening of Josiphos ligands on a model domino reaction of **1a** and benzoxazole (GC yields on a 0.05 mmol scale in 0.3 mL of CH_2Cl_2). dba = dibenzylideneacetone.

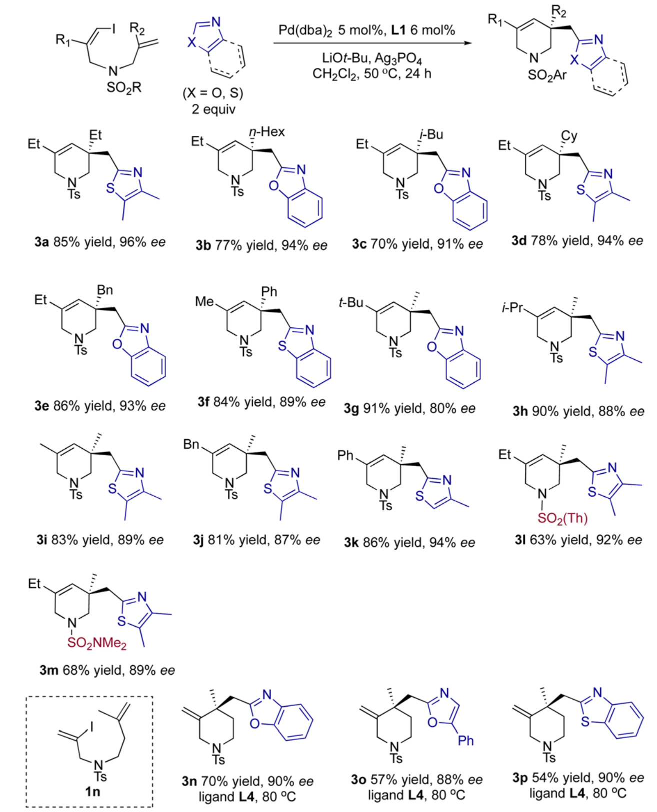
Table 1 The effect of reaction parameters on a model reaction of **1a** and benzoxazole under conditions using Josiphos **L1** (0.05 mmol scale in 0.3 mL of CH_2Cl_2. Calibrated GC conversion and yields and ees determined for pure samples). Ts = 4-toluenesulfonamide; dba = dibenzylideneacetone



Entry	Change of conditions	Conv. of **1a** (%)	Yield of **2a** (%)	Yield of **2a′** (%)
1	No change	100	88 (92% ee)	9
2	No LiO*t*-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	NaO*t*-Bu	33	12 (86% ee)	6
7	KO*t*-Bu	92	26 (85% ee)	5
8	No Ag_3PO_4	100	48 (81% ee)	<5
9	Ag_2CO_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 CH_2Cl_2).



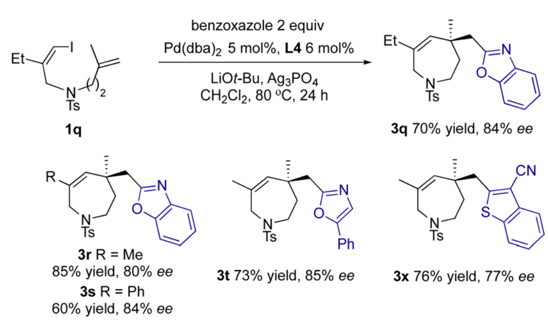
Scheme 3 Stereoselective formation of 6-membered piperideines and piperidines *via* domino couplings (isolated yields on a 0.1 mmol scale in 0.5 mL of CH_2Cl_2). Th = 2-thienyl.

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 Ag_3PO_4 to AgOTf increased the stereoselectivity to >90% ees.

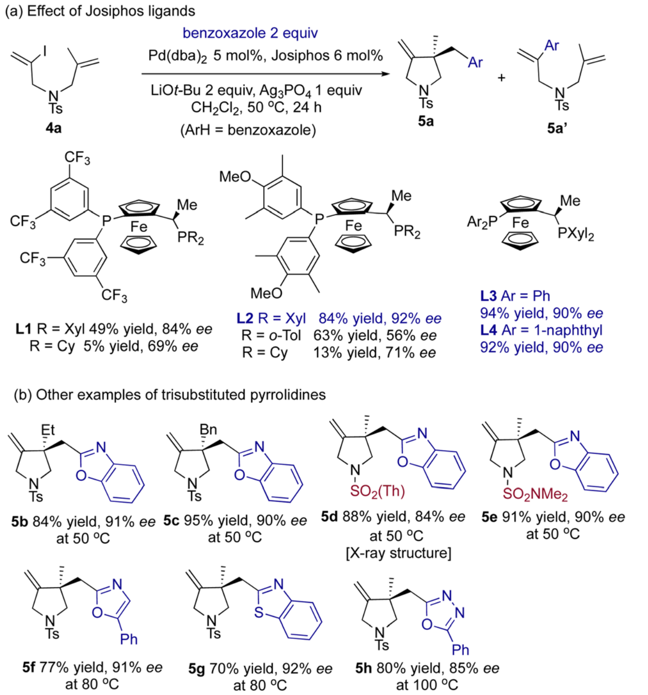
Next, we studied structural variations of (*Z*)-1-iodo-1,6-dienes in stereoselective formation of piperideines (Scheme 3). The alkenyl fragment can tolerate different C5-substituents (ethyl, *n*-hexyl, isobutyl, cyclohexyl, benzyl and phenyl) (**3a–f**), while the C3 substituents of the iodoalkenyl fragment 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-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 CH_2Cl_2).



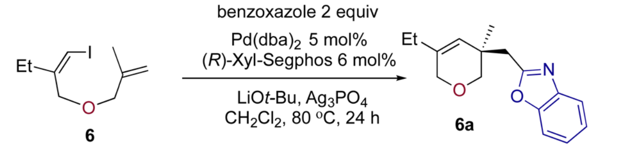
Scheme 5 Stereoselective formation of substituted pyrrolidines *via* domino couplings (isolated yields on a 0.1 mmol scale in 0.5 mL of CH_2Cl_2): (a) the effect of Josiphos ligands and (b) examples of pyrrolidines obtained under conditions using Josiphos **L2**. Th = 2-thienyl.

resulted. In this model reaction, Josiphos **L3** and **L4** also provided excellent yields and 90% ee (Scheme 5a). LiO*t*Bu 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.

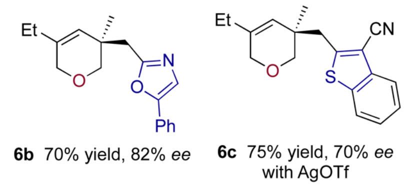
The enantioselective formation of pyrrolidines tolerated well structural variations in iododienes (Scheme 5b), for example, ethyl and benzyl groups on olefinic units (**5b–c**) and acid-labile 2-thienylsulfonamide and *N*,*N*-dimethylsulfamate linkers (**5d–e**). Azoles such as benzoxazole, benzothiazole and 1,3,4-oxadiazole coupled well (**5fi**). 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 (pK_a 31 in

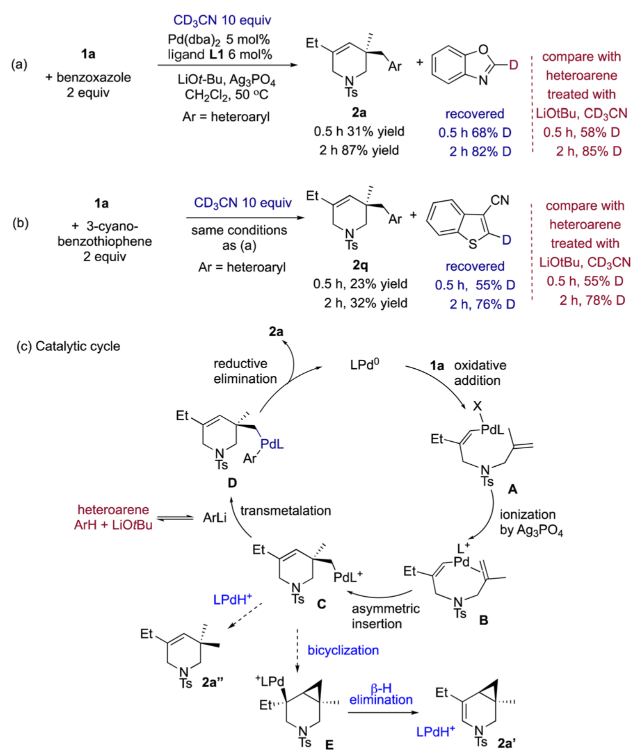


diphosphine	6a
Josiphos **L1**	67% yield, 53% *ee*
(*R*)-Xyl-BINAP	65% yield, 82% *ee*
(*R*)-Xyl-Segphos	80% yield, 95% *ee*



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 (pK_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



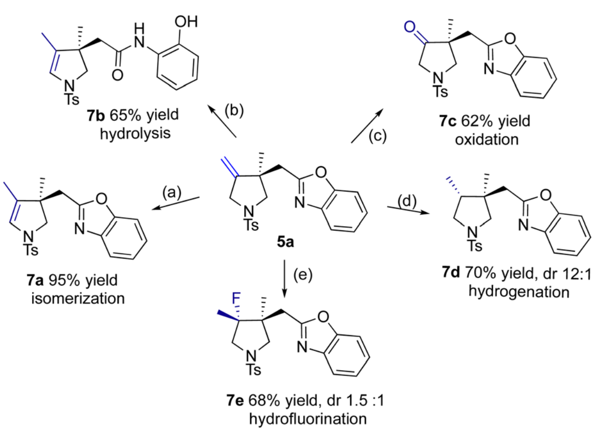
Scheme 7 Catalytic domino couplings of **1a** with (a) benzoxazole and (b) 3-cyanobenzothiophene in the presence of CD_3CN. (c) A putative catalytic cycle of domino coupling of model substrate **1a** and a heteroarene and the formation of side products (Ar = heteroaryl).

LiO*t*Bu 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 LiO*t*Bu and CD_3CN (<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) Ag_2CO_3 complexes ligated by biarylphosphines were reported by others to catalyze deuteration of azoles, indoles and thiophenes using D_2O or CH_3OD.[22] However, Ag_3PO_4 or Ag_2CO_3 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 CD_3CN and LiO*t*Bu 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 LiO*t*Bu 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 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 $Co_2(CO)_8$ 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 $KPPh_2$, however, resulted in olefinic isomerization with ring opening of benzoxazole (**7b**).[26] (c) Moreover, $RuCl_3$-catalyzed oxidative cleavage using $NaIO_4$ (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 conditions[28] produced a regioselectively Markovnikov adducts **7e** (as two distereomers 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 LiO*t*Bu. This mechanism is distinct from *n*CDM previously reported by Zhu *et al.* in catalytic arylation–heteroarylation.



Scheme 8 Product derivatization: (a) $Co_2(CO)_8$, mesitylene, 130 °C, 24 h; (b) $HPPh_2$, KOH, DMSO, 90 °C, 1 h; (c) cat. $RuCl_3$, $NaIO_4$, EtOAc/MeCN/H_2O 1 : 1 : 1, RT, 15 h; (d) 5% Pd/C, H_2 (balloon), MeOH, RT, 16 h; (e) $Fe(NO_3)_3\cdot 9H_2O$, $NaBH_4$, Selectfluor, MeCN/H_2O 1 : 1, 0 °C, 2 h.

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.

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