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Palladium/XuPhos-catalyzed enantioselective cascade Heck/intermolecular C(sp²)-H alkylation reaction†

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Palladium-catalyzed enantioselective domino Heck/intramolecular C–H functionalization reaction, as a valuable strategy for creating molecular diversity, has remained a prominent challenge. Here, we describe a Pd/XuPhos catalyst for asymmetric domino Heck/intermolecular C–H alkylation of unactivated alkenes with diverse polyfluoro- and heteroarenes in a highly chemo- and enantioselective manner. This process enables efficient synthesis of various dihydrobenzofurans, indolines and indanes, which are of interest in pharmaceutical research and other areas. Late-stage modifications of the core structures of natural products are also well showcased. Moreover, synthetic transformations create a valuable platform for preparing a series of functionalized molecules. Several control experiments for mechanistic study are conducted to pursue a further understanding of the reaction.

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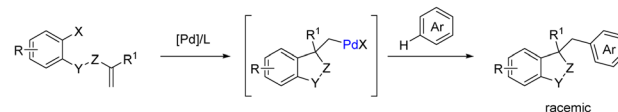
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Introduction

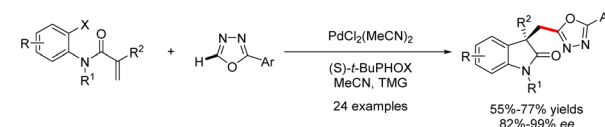
Palladium-catalyzed C–H bond functionalization, as a synthetically significant yet challenging bond-forming process, has been tremendously exploited to realize precision control of site-selectivity for fabricating densely functionalized molecules.^{1,2} Among others, palladium-catalyzed domino Heck/C–H functionalization reaction involving an σ -alkylpalladium intermediate represents one of the most powerful, step- and atom-economic tools to construct highly functionalized heterocyclics bearing quaternary carbon centers.^{3–9} Compared with Heck/intramolecular C–H functionalization,^{3–9} the intermolecular reactions are more challenging owing to the direct C–H functionalization side reactions. In 2009, the group of Fagnou reported a pioneering study on palladium-catalyzed domino Heck/intermolecular C–H alkylation reactions between aryl bromides with sulfur-containing heterocycles.¹⁰ Utilizing a similar strategy, Sharma and Van der Eycken demonstrated that acrylamides could react with 1,3,4-oxadiazoles to construct bis-heteroaryl frameworks under microwave irradiation.^{11,12} Later, the domino process was applied to the synthesis of alkylated polyfluoroarene

derivatives employing electron-deficient polyfluoroarenes as the direct arylation coupling partner, which was accomplished by Liang and Xu.¹³ Recently, Kuram *et al.* disclosed that 1,2,3-triazoles were also suitable coupling partners to obtain bisheterocycles bearing all-carbon quaternary centers.¹⁴ Despite continuous development in the Heck/C–H alkylation reaction (Scheme 1a), the exploration of its asymmetric variants is still dramatically limited. To the best of our knowledge, enantioselective domino Heck/intermolecular C–H bond functionalization was only established by Zhu and co-workers, efficiently creating various 3,3-disubstituted oxindoles and bisoxindoles (Scheme 1b).¹⁵ Thus, the identification of new catalysts for this interesting reaction is still highly in demand.

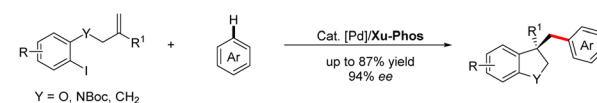
a) Pd-catalyzed domino Heck/intermolecular C-H alkylation reaction



b) Pd-catalyzed enantioselective domino Heck/intermolecular C-H alkylation reaction (Zhu)



c) Pd-catalyzed enantioselective domino Heck/intermolecular C-H alkylation reaction (This work)



Scheme 1 Previous work and this work on Pd-catalyzed domino Heck/intermolecular C–H alkylation reaction.

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In 2022, a remarkable example of highly enantioselective domino Heck/intramolecular C–H alkylation for the selective synthesis of chiral strained 5,4- and 5,5-spirocycles was accomplished by our group, employing our own developed **Sadphos** as the chiral ligand.⁸ Based on the success of the intramolecular variant and our ongoing interest on domino Heck reactions,^{8,16–19} we were intrigued to develop newly efficient catalyst systems to realize domino Heck/intermolecular C–H alkylation, which, if successful, would offer a highly efficient route for the construction of various privileged heterocycle skeletons existing in a number of natural products and drugs.^{20–23}

Herein, we establish a Pd/**XuPhos** system as an effective catalyst for the enantioselective cascade Heck/intermolecular C(sp²)–H alkylation reaction of unactivated alkenes with various polyfluoroarenes, providing expedient access to a wide spectrum of structurally diverse dihydrobenzofuran-, indoline- and indane-containing polyfluoroarene compounds (Scheme 1c). Moreover, the significance of this methodology is also underscored by easily converting products to other classes of functionalized molecules.

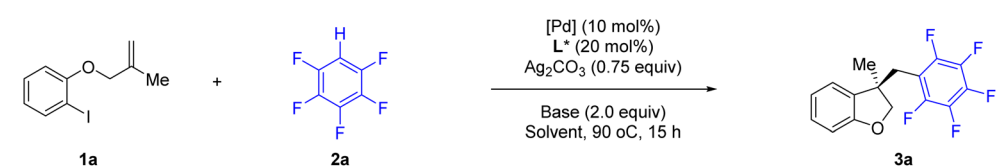
Results and discussion

We began our investigation using *o*-iodophenol-derived allyl ether **1a** and pentafluorobenzene **2a** as model substrates (Table 1 and Scheme 2). An exhaustive screening of various

types of monodentate and bidentate commercial ligands showed that ligands **L3** and **L5–7** failed to deliver the desired product **3a** (Scheme 2). Although ligand **L1–2** showed better enantioselectivity and ligand **L4** favored this transformation, both of them didn't obtain **3a** with satisfactory results. Then, we turned attention to our developed ligands, which have demonstrated potential performances in palladium-catalyzed asymmetric cascade Heck reactions. The examination of the **Sadphos** ligand kit indicated that only *N*-Me masked ligands could deliver the desired product, in which **Xu4** was the optimal choice, allowing the formation of **3a** in 60% yield with 52% ee. Further screening of different solvents indicated that Et₂O, ⁱPr₂O and MTBE resulted in higher ee (Table 1, entries 1–3). The use of DCM, DMF, CH₃CN and DCE as solvent increased neither yield nor ee (entries 4–7). Subsequently, we focused on the optimization of the metal salt and base (entries 8–16). When the metal salt and base were changed to Pd₂dba₃·CHCl₃ and Cs₂CO₃, respectively, the desired product **3a** was obtained in 83% yield with 90% ee (entry 16). To our delight, lowering the temperature to 80 °C provided **3a** with a slightly higher ee of 92% (entry 17). Finally, it was found that Ag₂CO₃ had also a considerable effect on the reactivity (entry 18).

Having established the optimized conditions, the scope of this reaction was examined by using various *o*-iodophenol-derived allyl ethers. Different linear and branched alkyl groups on the alkene moiety proceeded smoothly to furnish

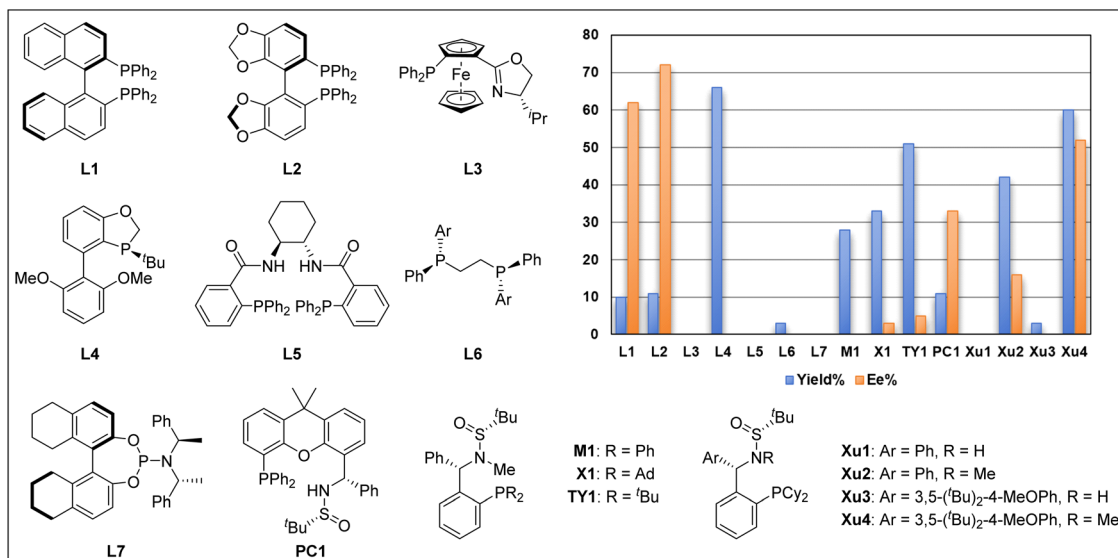
Table 1 Optimization of reaction conditions^a



Entry	[Pd]	Solvent	Base	Yield ^b (%)	Ee ^c (%)
1	Pd ₂ dba ₃	Et ₂ O	K ₂ CO ₃	66	76
2	Pd ₂ dba ₃	ⁱ Pr ₂ O	K ₂ CO ₃	80	84
3	Pd ₂ dba ₃	MTBE	K ₂ CO ₃	74	80
4	Pd ₂ dba ₃	DCM	K ₂ CO ₃	44	28
5	Pd ₂ dba ₃	DMF	K ₂ CO ₃	10	5
6	Pd ₂ dba ₃	CH ₃ CN	K ₂ CO ₃	45	49
7	Pd ₂ dba ₃	DCE	K ₂ CO ₃	48	35
8	Pd ₂ dba ₃ ·CHCl ₃	ⁱ Pr ₂ O	K ₂ CO ₃	82	88
9	Pd(η-allyl)Cl ₂	ⁱ Pr ₂ O	K ₂ CO ₃	78	75
10	Pd(OAc) ₂	ⁱ Pr ₂ O	K ₂ CO ₃	24	25
11	Pd(TFA) ₂	ⁱ Pr ₂ O	K ₂ CO ₃	60	32
12	Pd(acac) ₂	ⁱ Pr ₂ O	K ₂ CO ₃	15	3
13	Pd ₂ dba ₃ ·CHCl ₃	ⁱ Pr ₂ O	KOH	70	80
14	Pd ₂ dba ₃ ·CHCl ₃	ⁱ Pr ₂ O	KO ^t Bu	74	63
15	Pd ₂ dba ₃ ·CHCl ₃	ⁱ Pr ₂ O	CsOPiv	46	7
16	Pd ₂ dba ₃ ·CHCl ₃	ⁱ Pr ₂ O	Cs ₂ CO ₃	83	90
17 ^d	Pd ₂ dba ₃ ·CHCl ₃	ⁱ Pr ₂ O	Cs ₂ CO ₃	84	92
18 ^{d,e}	Pd ₂ dba ₃ ·CHCl ₃	ⁱ Pr ₂ O	Cs ₂ CO ₃	Trace	—

^a Unless otherwise noted, all reactions were performed with **1a** (0.1 mmol), **2a** (0.3 mmol), Ag₂CO₃ (0.075 mmol), base (0.2 mmol), 10 mol% [Pd] and 20 mol% ligand in 1.0 mL solvent at 90 °C for 15–48 h. ^b NMR yield with CH₂Br₂ as an internal standard. ^c Enantioselectivity was determined by chiral-phase HPLC. ^d 80 °C. ^e No Ag₂CO₃ added.





Scheme 2 Representative diphosphorus ligands examined in this work.

3b–3f in good yields with excellent enantioselectivities. Numerous allyl ethers bearing functional groups, such as trimethylsilyl (**1g**), methoxycarbonyl (**1h**), chloro (**1i** and **1j**) and fluoro (**1k**), were compatible with the reaction to form the corresponding products in satisfactory results. To our delight, substrates with various ether, thiol ether and N-heterocycles appended to the alkyl chain were suitable for the reaction to deliver the expected products **3l–3r** with 90–93% ee. Particularly noteworthy was the tolerance of the reaction conditions to the more structurally complex contexts. A variety of allyl ethers derived from the core structures of natural products were also suitable substrates, converting to the target products (**3s–3u**) in excellent yields with outstanding diastereoselectivities.

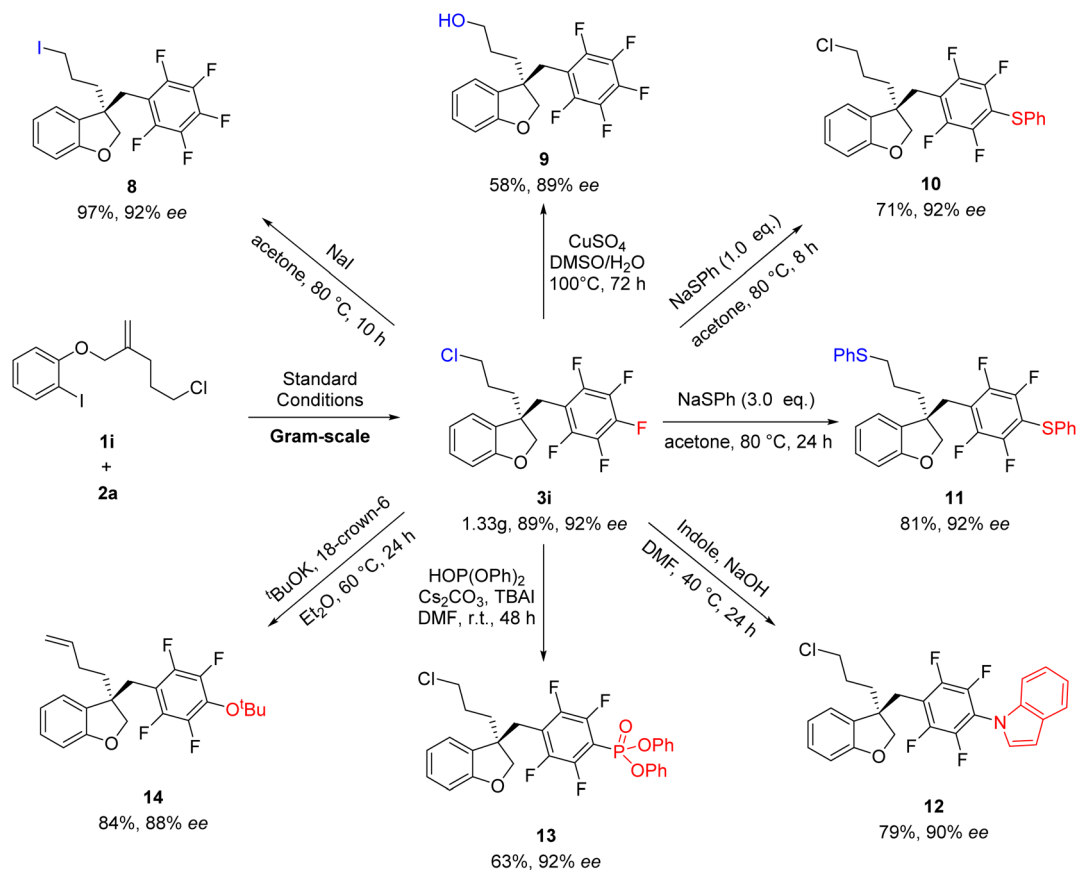
Subsequently, the effect of substituents on the benzene ring of the *o*-iodophenol moiety was investigated under the standard reaction conditions (Scheme 3). Substituting the phenyl ring with electron-donating and electron-withdrawing groups at C4 and C5 positions appeared to have limited effects on the results, and **5a–5d** were afforded in modest to good yields with excellent ee values. 3,3-Disubstituted indolines and indanes are frequently found in pharmaceuticals, natural alkaloids, and as fascinating building blocks in organic synthesis. Despite progress made in this field, the synthesis of these chiral compounds is still in high demand. Satisfactorily, the present asymmetric C–H functionalization of alkene reaction was also applicable to the substrates employing BocN and C as a tether, delivering the indoline **5e** and indanes **5f** with good yields and ee values.

To ascertain the scope of this method, a variety of poly-fluoroarenes were further investigated (Scheme 3). Both 1,2,4,5-tetrafluorobenzene and 2,3,5,6-tetrafluoropyridine smoothly underwent the C–H functionalization process and transformed to the corresponding products (**7a** and **7b**) in good yields with excellent ee values. For 2,3,5,6-tetrafluoroanisole derivatives, alkyl ethers (such as Me and *t*Bu) and aryl ethers (such as naphthyl and phenyl groups) were also well accommodated

under mild conditions, giving the desired products (**7c–7h**) in 82–90% yields with 87–93% ee. It is noteworthy that electron-donating groups (such as methyl and methoxy groups) and electron-withdrawing groups (such as trifluoromethyl group) on the phenyl ring were all well tolerated, furnishing the desired products (**7i–7k**) with good to excellent ee. Furthermore, changing the *O*-substituent to a *N*- and CH_2 -substituent on the tetrafluorobenzene ring could also smoothly drive the reaction to form products **7l–7n** with satisfactory results. The absolute configuration of the product was confirmed by the X-ray diffraction analysis of **7n**. Next, the scope of fluorobenzenes with fewer fluorine atoms was investigated. Unfortunately, decreasing the fluorine atoms could drive the reaction to form products with lower yield and ee (**7o–7p**), which might be related to the fact that more fluorine atoms can increase the pK_a value of substrates. We next investigated several heteroarene substrates. To our delight, oxadiazole **6q** and **6r**, thiophene **6s**, benzothiophene **6t** and benzofuran **6u** could react smoothly, affording the corresponding products (**7q–7u**) with high yields (52–76%) and excellent ees (90–92%).

To further demonstrate the reliability of this method, the reaction of **1i** and **2a** was conducted on a larger scale of 5 mmol, affording the desired products **3i** without loss of efficiency and the ee value (Scheme 4). Subsequently, synthetic transformations of **3i** were carried out. As shown in Scheme 5, the Cl group could be substituted by different nucleophilic reagents, thus leading to **8** and **9** in 97 and 58% yields, respectively. It's very interesting to find that the substitution of **3i** with different equivalents of NaSPh could produce **10** and **11**, respectively, in high yields. Notably, **3i** have two sites which can conduct nucleophilic substitution reaction. If stronger nucleophilic reagents were used, the direct functionalized of polyfluoroarenes could be selectively achieved to afford **12–14** in good yields. It was found that the C=C bond of **14** was generated through the elimination of the C–Cl bond in the presence of strong base *t*BuOK.





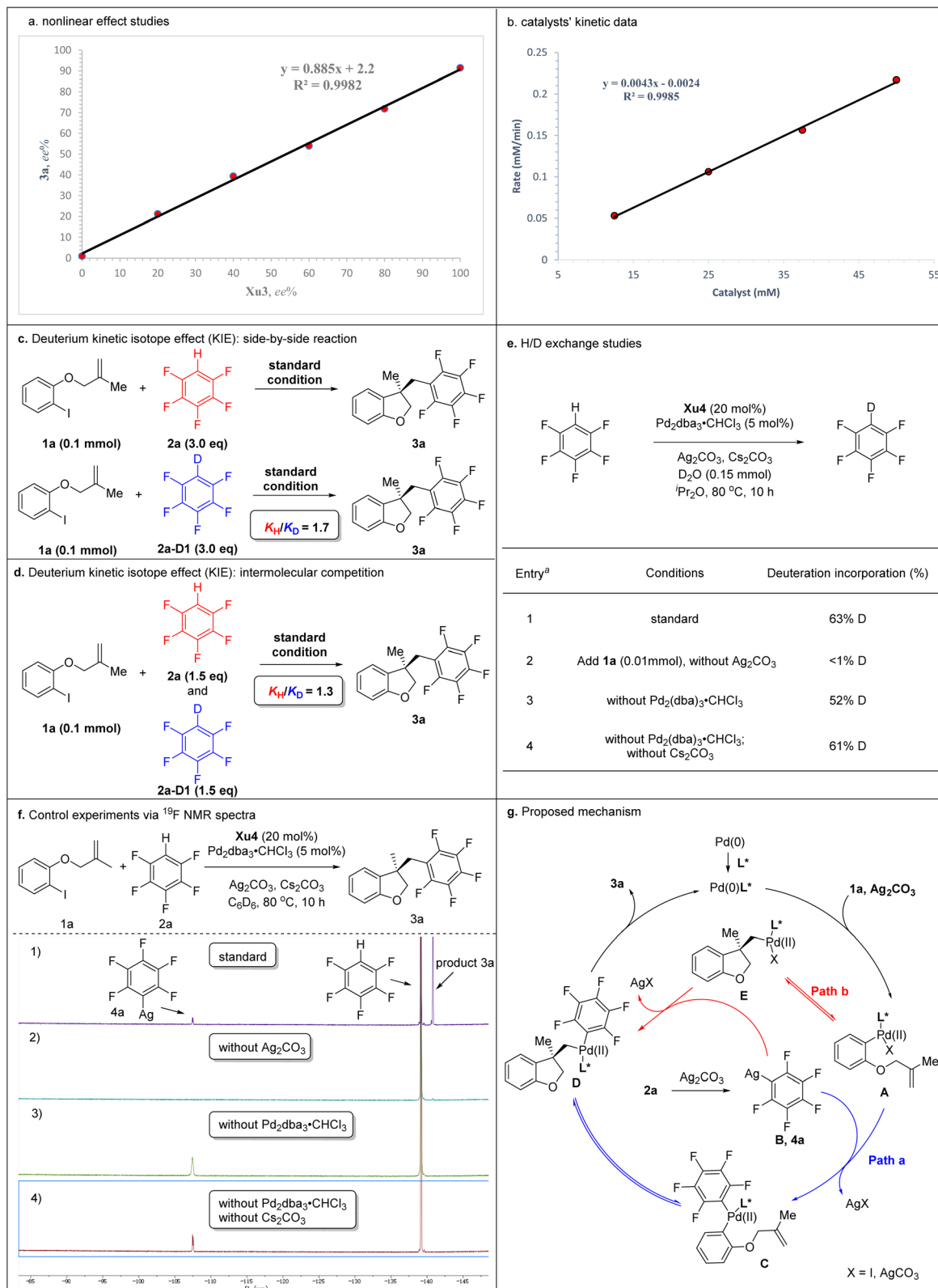
Scheme 4 The synthetic transformation of 3i.

To gain deep insight into the reaction mechanism, several control experiments were carried out (Schemes 5). Nonlinear effect studies on the enantiomeric composition of the chiral ligand **Xu3** and product **3a** (Scheme 5a) and initial rate experiments (Scheme 5b) indicated that there is a significant first-order dependence on the catalyst. We performed side-by-side experiments with pentafluorobenzene **2a** and deuterated pentafluorobenzene **2a-[D1]** to measure the initial reaction rate, respectively. The side-by-side experiments provided a K_H/K_D value of 1.7 (Scheme 5c). The intermolecular competition reaction of **2a** and **2a-[D1]** in the same pot showed a K_H/K_D value of 1.3 calculated from the consumption of **2a** and **2a-[D1]** (Scheme 5d). We also carried out H/D exchange experiments between C_6F_5H and D_2O (5.0 equiv.). Analysis by 2H NMR spectroscopy showed 63% deuterium incorporation under standard conditions (Scheme 5e, entry 1). These results indicated that the C–H activation might not be the rate-determining step in this process. Moreover, adding **1a** (0.1 mmol) to the reaction, <1% deuterium incorporation was detected in the absence of Ag_2CO_3 (Scheme 5e, entry 2). 52% and 61% deuterium incorporation was detected under standard conditions without $Pd_2dba_3 \cdot CHCl_3$ or without $Pd_2dba_3 \cdot CHCl_3$ and Cs_2CO_3 , respectively (Scheme 5e, entries 3 and 4). These results suggested that Ag_2CO_3 was essential to activate the pentafluorobenzene. We further monitored the reaction

via ^{19}F NMR spectroscopy. After 10 h, compound **4a** was detected based on a diagnostic signal at approximately -107.4 ppm, which matches the C_6F_5Ag species chemical shift in the literature (Scheme 5f, entry 1).²⁴ In addition, this same intermediate was also formed under standard conditions without $Pd_2dba_3 \cdot CHCl_3$ or without $Pd_2dba_3 \cdot CHCl_3$ and Cs_2CO_3 (Scheme 5f, entries 3 and 4), which indicated that Ag_2CO_3 could activate the pentafluorobenzene to afford the C_6F_5Ag species.

Two possible mechanisms were depicted as shown in Scheme 5g. Oxidative addition of Pd(0) with **1a** afforded aryl-palladium species **A**, followed by transmetalation with intermediate **B** which was generated by the reaction of **2a** with Ag_2CO_3 , resulting in the formation of complex **C**. The subsequent intramolecular Heck-type reaction of intermediate **C** provided chiral species **D**, which could undergo reductive elimination to produce product **3a** and regenerate the Pd(0) catalyst. Alternatively, the intramolecular Heck-type reaction of intermediate **A** occurred firstly to generate intermediate **E**. Then, complex **E** underwent transmetalation with intermediate **B** to afford chiral species **D**. Finally, reductive elimination of **D** gave **3a** and regenerated the Pd(0) catalyst. Notably, the mechanism involving the transformation of $ArPd(II)L^*$ species into positively charged $ArPd(II)L^*$ species in the presence of silver salt could not be ruled out.





Scheme 5 Mechanistic studies and proposed mechanism.



Conclusions

In summary, with the use of diverse polyfluoro- and heteroarenes as direct arylation coupling partners, Pd/XuPhos complexes are shown to be effective catalysts for asymmetric domino Heck/intermolecular C–H alkylation of unactivated alkenes, in which, a variety of dihydrobenzofuran, indoline and indane compounds are obtained in high performance. Easily accessible substrates, mild conditions, good functional group tolerance and various synthetically transformations of the products make this protocol highly attractive. Additionally, mechanistic studies indicate that C–H activation might not be the rate-determining step in this process. We anticipate that this methodology will inspire the discovery of more novel catalyst systems for handling these valuable and challenging asymmetric transformations.

Data availability

All data have been provided in the main text and ESI.†

Author contributions

C. F., Q.-P. W. and B. X. carried out the experimental and data-analysis work. Z.-M. Z. and J. Z. designed the reaction, directed the project, and wrote the paper with the assistance of B. X.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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