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Palladium-catalyzed asymmetric migratory diarylation of unactivated directing-group-free internal alkenes

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Enantioselective dicarbofunctionalization of alkenes is a powerful strategy for constructing functionalized sp^3-rich molecules, yet it remains challenging for unactivated substrates lacking directing groups. While asymmetric multicomponent reactions catalyzed by d^{10} transition metals have advanced for activated alkenes, enantioselective multicomponent cross-coupling of unactivated alkenes, particularly enabling remote functionalization to stereoselectively generate the nonadjacent stereocenters, is still underdeveloped. Herein, we report a palladium-catalyzed asymmetric migratory dicarbofunctionalization of directing-group-free, trisubstituted unactivated alkenes. This method forges remote stereogenic centers, enabling both 1,3-diarylation and 1,4-diarylation with high enantioselectivity and diastereoselectivity. Mechanistic studies indicate a chain-walking process involving irreversible Pd-H migration, rationalizing the observed regiocontrol.

Olefins are indispensable feedstocks for bulk chemicals, bioactive molecules, and functional materials, making the development of highly selective alkene transformations a central pursuit in organic synthesis. Among these, the stereoselective conversion of planar alkenes into diverse, highly functionalized three-dimensional sp^3-hybridized molecules is particularly valuable. This is underscored by the well-established benefit of increased sp^3-character in organic molecules for the success of clinical drug candidates[1]. Since Sigman's foundational work[2–4], asymmetric multicomponent cross-coupling reactions of alkenes catalyzed by d^{10} transition metals–specifically, dicarbofunctionalization–have emerged as a powerful synthetic strategy[5–16]. This approach enables the simultaneous incorporation of two distinct carbon fragments across the π-bond, facilitating rapid assembly of molecular complexity (Fig. 1). Prior efforts focused predominantly on reactive alkenes, such as acrylates, enamides, or styrenes[2,17–30]. In this realm, these functional groups regulate regioselectivity, also enhance reactivity, thus enabling facile migratory insertion of carbon-metal bonds or carbon-radical addition. However, enantioselective migratory dicarbofunctionalization of activated alkenes still remains scarce; only two cases include Sigman's 1,1-diarylation of acrylates and our 1,3-diarylation of enamides[17,31,32] (Fig. 1a, top). Despite these impressive advances, stereoselective intermolecular dicarbofunctionalization of unactivated alkenes remains largely underdeveloped, yet is highly desirable in organic synthesis[13–16].

To accelerate the reactivity of unactivated alkenes, chelation-assisted strategies have been elegantly developed for chiral nickel-catalyzed 1,2-dicarbofunctionalization of unbiased alkenes[33–38] (Fig. 1a, bottom). Representative examples include the Chu group's enantioselective reductive 1,2-alkyl-alkenylation via five-membered nickellacycle formation[33,34], the Engle group's redox-neutral 1,2-diarylation, as well as Chen group's reductive 1,2-diarylation through stereoselective migratory insertion[35–37]. However, enantioselective dicarbofunctionalization of the simple unactivated alkenes persisted as a formidable unmet challenge–with only one isolated

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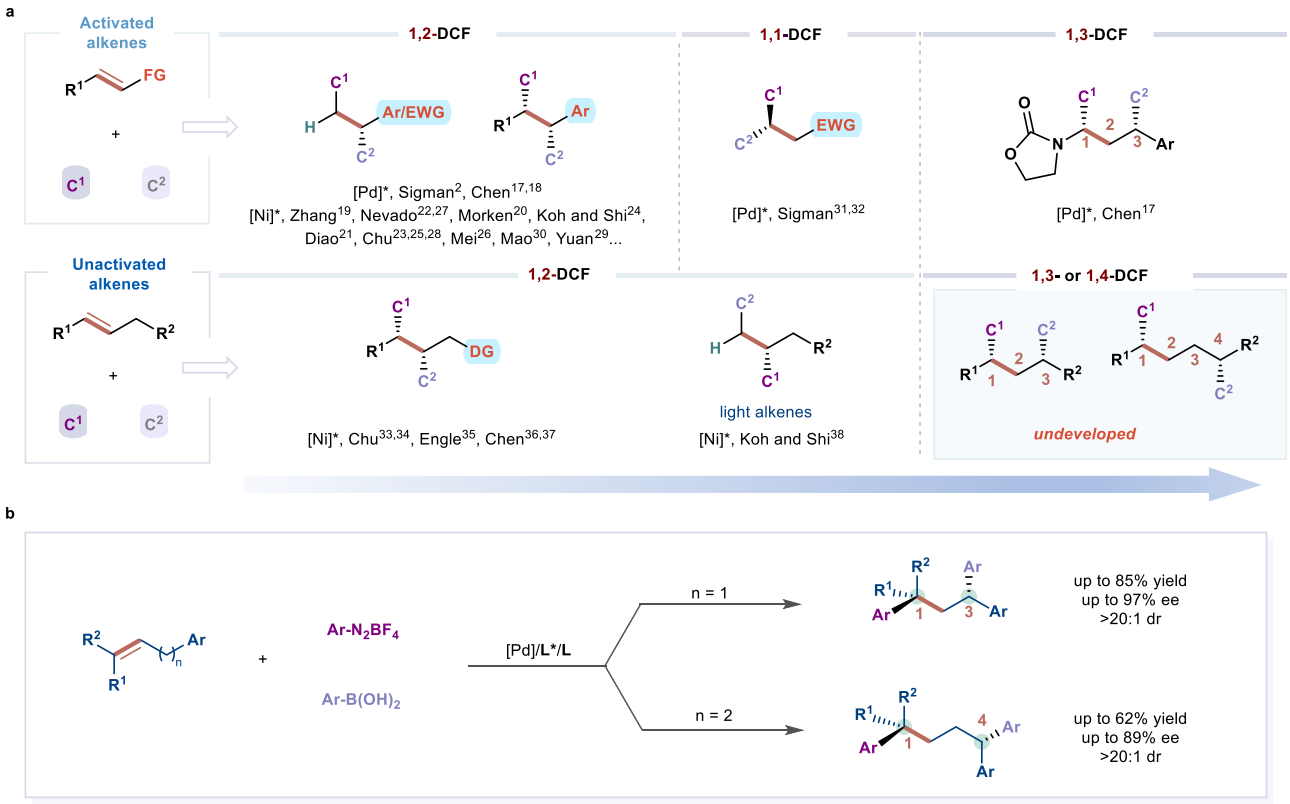

Fig. 1 | Overview of transition metal-catalyzed enantioselective intermolecular dicarbofunctionalization of alkenes. a Enantioselective Dicarbofunctionalization (DCF) of Acyclic Alkenes. **b** Enantioselective 1,3 and 1,4-Diarylation of Unactivated Trisubstituted Acyclic Alkenes (this work).

example that the collaborative work between Koh and Shi presented the asymmetric 1,2-dicarbofunctionalization of light alkenes enabled by bulky chiral N-heterocyclic carbene-ligated nickel catalysis[38]. Beyond these advances, remote functionalization of unactivated alkenes is a distinct challenge, where successful examples could enable unconventional C–C bond formation at distant sites[39–51]. Notably, while several racemic 1,3-dicarbofunctionalization via nickel catalysis have been independently reported by Giri[52,53], Zhao[54], Martin[55], and Shu group[56], the asymmetric versions remained elusive, representing a critical synthetic gap.

Based on our continued research interest in d^{10} transition metal-catalyzed asymmetric dicarbofunctionalization[17,18,57–64], we herein address these limitations by achieving the Pd-catalyzed asymmetric migratory dicarbofunctionalization of unactivated internal alkenes (Fig. 1b). This method accomplishes the enantioselective 1,3- and 1,4-dicarbofunctionalization of unactivated alkenes, forging remote stereogenic centers with high enantioselectivity; moreover, the broad reactivity without pre-installed directing group can overcome fundamental substrate constraints in alkene difunctionalization. This strategy enables expedient construction of 1,3- and 1,4-nonadjacent stereocenters with high enantioselectivity and diastereoselectivity, addressing a long-standing synthetic challenge in organic chemistry[65–70]. Mechanistic studies confirm a chain-walking process involving irreversible Pd-H migration, rationalizing the observed regiocontrol.

Results and discussion

Reaction optimization for diarylation of alkenes

Initial optimization of asymmetric remote dicarbofunctionalization employed non-activated trisubstituted alkene **1a**, aryl diazonium salt **2a**, and arylboronic acid **3a** as model substrates with 5.0 mol% $Pd(OAc)_2$, 10 mol% (*S*)-Cy-Box (**L1**) as chiral ligand, and 16 mol% diethyl fumarate as achiral ligand in presence of 1.0 equivalent Ag_2CO_3 (Table 1). Pleasingly, this ligand-swap strategy proved effective for palladium-catalyzed 1,3-diarylation, affording the desired product **4a** in 48% yield with 88% ee in DME (Table 1, entry 1). It should be noted that the addition of Ag_2CO_3 facilitates the transmetalation step[18]. Reactions in 1,4-dioxane showed comparable yield and marginally improved enantioselectivity (Table 1, entry 2), prompting further investigation of mixed DME/1,4-dioxane solvent ratios. Notably, a 1:3 DME/1,4-dioxane mixture delivered **4a** in 57% yield and 92% ee (Table 1, entries 3–5). Subsequent screening of various substituted chiral BiOx ligands (Table 1, entries 6–10) revealed minimal impact on yield and enantioselectivity, with the isopropyl-substituted BiOx ligand **L3** proving optimal, delivering **4a** in 62% yield and 93% ee (Table 1, entry 7). Given the importance of additives in promoting efficient cross-coupling by accelerating reductive elimination, several fumarate diesters with different substituents (isopropyl **A2**, isobutyl **A3**, tert-butyl **A4**, phenyl **A5**, methyl **A6**) were evaluated (Table 1, entries 11-15). Diphenyl fumarate (**A5**) successfully facilitated the reaction, maintaining a slightly higher yield and similar enantioselectivity. Further optimization of the palladium catalyst identified $[Pd(allyl)Cl]_2$ as optimal, furnishing **4a** in 79% isolated yield with 93% ee (Table 1, entry 16). The current three-component cross-coupling protocol was not suitable for aryl halides as electrophiles.

Substrate scope of unactivated trisubstituted alkenes

With optimized conditions established, we evaluated the scope of unactivated trisubstituted alkenes (Fig. 2). Symmetric alkenes bearing a benzyl substituent were systematically investigated. Both electron-withdrawing and electron-donating *para*-substituted phenyl groups at the terminal site afforded products **4b**–**4e** in moderate to good yields (61–72%) with excellent enantioselectivities (91–94% ee). The reaction tolerated a *meta*-fluoro-substituted phenyl counterpart, providing **4f** in 40% yield and 91% ee. *ortho*-Substituted alkenes proved particularly effective, yielding **4g** in 74% yield and 97% ee. Notably, an alkene

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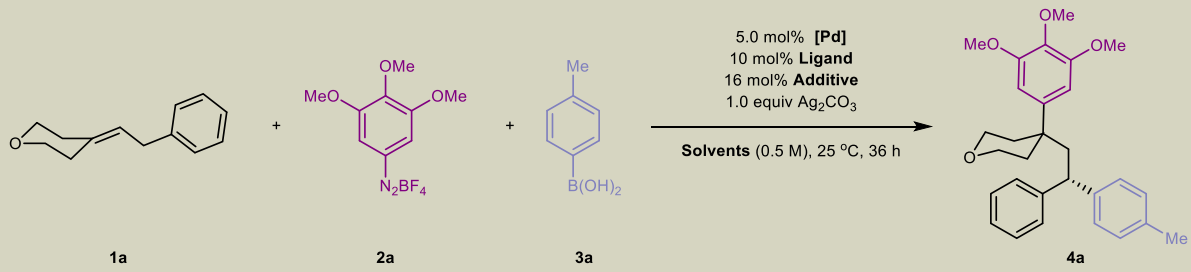
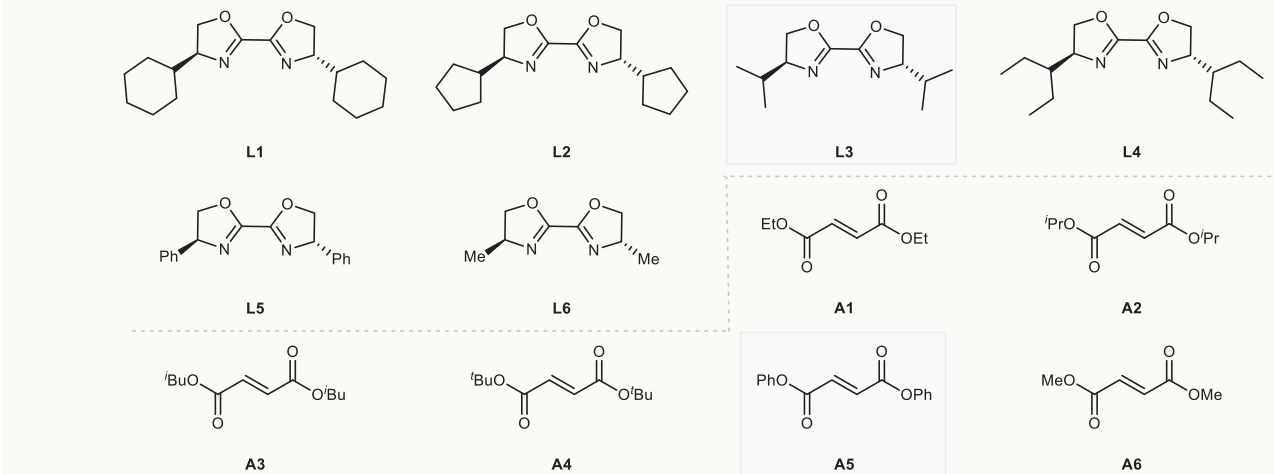
Table 1 | Reaction optimization



1a 2a 3a 4a

Entry	Solvents	Ligands	Additives	[Pd] sources	Yield of 4a (%)	Ee of 4a (%)
1	DME	L1	A1	$Pd(OAc)_2$	48	88
2	1,4-Dioxane	L1	A1	$Pd(OAc)_2$	48	92
3	DME/1,4-Dioxane (v/v = 3/1)	L1	A1	$Pd(OAc)_2$	67	84
4	DME/1,4-Dioxane (v/v = 1/1)	L1	A1	$Pd(OAc)_2$	56	84
5	DME/1,4-Dioxane (v/v = 1/3)	L1	A1	$Pd(OAc)_2$	57	92
6	DME/1,4-Dioxane (v/v = 1/3)	L2	A1	$Pd(OAc)_2$	55	88
7	DME/1,4-Dioxane (v/v = 1/3)	L3	A1	$Pd(OAc)_2$	62	93
8	DME/1,4-Dioxane (v/v = 1/3)	L4	A1	$Pd(OAc)_2$	53	88
9	DME/1,4-Dioxane (v/v = 1/3)	L5	A1	$Pd(OAc)_2$	56	87
10	DME/1,4-Dioxane (v/v = 1/3)	L6	A1	$Pd(OAc)_2$	52	90
11	DME/1,4-Dioxane (v/v = 1/3)	L3	A2	$Pd(OAc)_2$	63	93
12	DME/1,4-Dioxane (v/v = 1/3)	L3	A3	$Pd(OAc)_2$	62	93
13	DME/1,4-Dioxane (v/v = 1/3)	L3	A4	$Pd(OAc)_2$	54	93
14	DME/1,4-Dioxane (v/v = 1/3)	L3	A5	$Pd(OAc)_2$	65	93
15	DME/1,4-Dioxane (v/v = 1/3)	L3	A6	$Pd(OAc)_2$	57	91
16[b]	DME/1,4-Dioxane (v/v = 1/3)	L3	A5	$[Pd(allylCl)]_2$	79(79)[a]	93
17	DME/1,4-Dioxane (v/v = 1/3)	L3	A5	$Pd(dba)_2$	69	93
18[b]	DME/1,4-Dioxane (v/v = 1/3)	L3	A5	$[Pd(\pi\text{-cinnamyl})Cl]_2$	72	93



Reaction conditions: alkene **1a** (1.0 equiv, 0.10 mmol), aryl diazonium salt **2a** (2.0 equiv, 0.20 mmol), arylboronic acid **3a** (3.0 equiv, 0.30 mmol), [Pd] (5.0 mol %, 0.005 mmol), chiral ligand (10 mol %, 0.01 mmol), additive (16 mol %, 0.016 mmol), and Ag_2CO_3 (1.0 equiv, 0.10 mmol) in solvents (0.2 mL, 0.5 M) at 25 °C. The yields were determined by ^{1}H NMR using dibromomethane as an internal standard, and the ee values were determined by chiral HPLC. [a]Isolated yields within the parentheses. [b]2.5 mol % [Pd] was used.

bearing an acetal group was efficiently converted to the ketone-containing product **4h** (55%, 94% ee), demonstrating direct ketone formation and expanding synthetic utility. Intriguingly, an unactivated alkene bearing methyl and ethyl substituents delivered the 1,3-diarylation product **4i** bearing nonadjacent stereocenters in 44% isolated yield, 91% ee and >20:1 dr under minimally modified solvent conditions, highlighting the stereoselective Pd-H migration pathway. A trifluoromethyl-substituted alkene at the terminal position of a linear alkyl chain afforded **4j** (43%, 91% ee). Diverse aromatic substituents, including methoxy (**4k**) and benzodioxole (**4l**) provided products in moderate yields with good stereoselectivity. It should be noted that all 1,3-diarylation proceeded with high stereoselectivity, with no diastereomers observed in the reaction mixture. However, the migratory diarylation of a linear 1,2-disubstituted alkene analog afforded the

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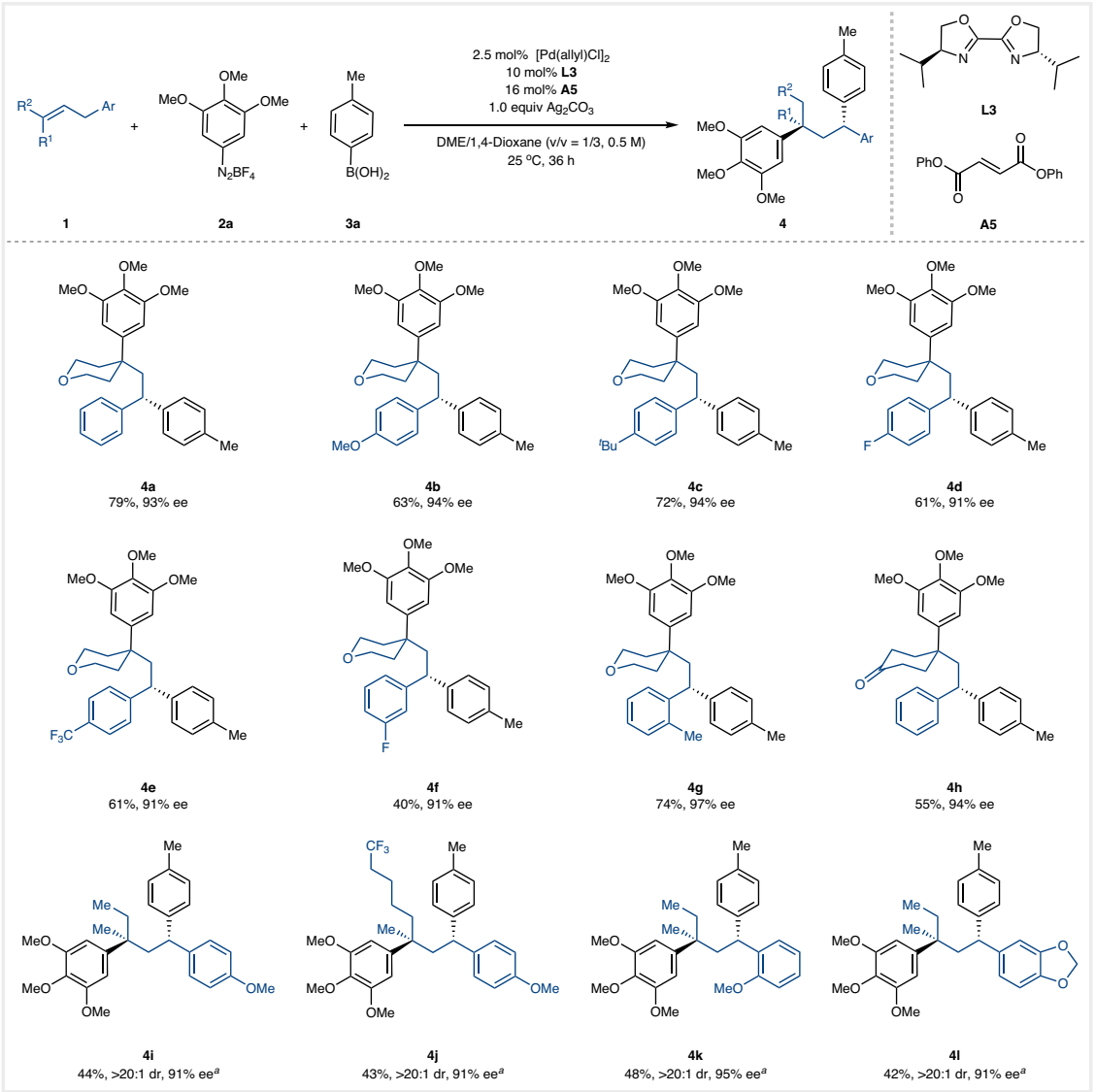

Fig. 2 | Substrate scope of unactivated trisubstituted alkenes. Reaction conditions: alkene **1** (1.0 equiv, 0.20 mmol), aryl diazonium salt **2a** (2.0 equiv, 0.40 mmol), arylboronic acid **3a** (3.0 equiv, 0.60 mmol), $[Pd(allyl)Cl]_2$ (2.5 mol %, 0.005 mmol), **L3** (10 mol %, 0.02 mmol), **A5** (16 mol %, 0.032 mmol), and Ag_2CO_3 (1.0 equiv, 0.20 mmol) in DME/1,4-Dioxane (0.4 mL (v/v = 1/3), 0.5 M) at 25 °C. Isolated yields were reported, and the ee values were determined by chiral HPLC. [a]DCM/1,4-Dioxane (0.4 mL (v/v = 1/3), 0.5 M) was used.

desired product only in very low yield, and the reaction failed entirely with fully substituted alkenes under the standard conditions. Further efforts will be devoted to addressing this limitation.

Substrate scope of aryldiazonium salts and arylboronic acids

Subsequently, we examined aryl diazonium salts and arylboronic acids, evaluating electronic effects and substituent positions (Fig. 3). *para*-Functionalized aryl diazonium salts afforded products **4m**–**4o** in 45–62% yield with 90–94% ee. Naphthalene-derived (**4p**) and benzodioxole-derived (**4q**) diazonium salts gave good yields and enantioselectivities. Diazonium salts bearing *meta*-substituents (–Cl, –OBn, –OEt; **4r**–**4t**) delivered products with excellent enantiocontrol (up to 94% ee). Arylboronic acids with diverse *para*-substituents (–^{t}Bu **4u**, –OMe **4v**, –TMS **4w**, –CF_3 **4x**) provided target products in high yields (up to 85%) with 94% ee. *meta*-Substituted arylboronic acids (**4y**–**4ab**) exhibited excellent enantioselectivities (up to 95% ee). Sterically encumbered biphenyl-2-ylboronic acid afforded **4ac** in 63% yield and 96% ee. Electron-withdrawing substituents on the boronic acid (**4ad**) did not diminish stereoselectivity. The configuration of **4ae** was unambiguously confirmed by X-ray crystallography, demonstrating stereoselective Pd-H chain walking process.

Beyond controlling stereoselectivity at the C-3 position, we investigated whether this migratory 1,n-diarylation strategy could extend to longer distances. Sigman and coworkers demonstrated that Pd–H species undergo stereoselective reinsertion into alkene intermediates in asymmetric remote Heck reactions[4], a similar reactivity pattern also observed in our prior Pd-catalyzed diastereoselective 1,1-diarylation of 1,1-arylethylenes[62]. Applying standard conditions to unactivated trisubstituted alkene bearing a phenethyl substituent **5** smoothly delivered the 1,4-diarylation product **6a** in 52% yield (Fig. 4). Notably, enantioselectivity decreased relative to the 1,3-diarylation (83% ee vs. 93% ee for **4a**). Further optimization of chiral ligands, solvents, and palladium catalysts failed to improve enantiocontrol. This result suggests partial dissociation of the Pd–H species from the alkene intermediate occurs during extended migration. The reaction tolerated diverse aryl boronic acids, affording products **6b**–**6i** in 44–62% yield while establishing a new stereocenter at the C-4 position with

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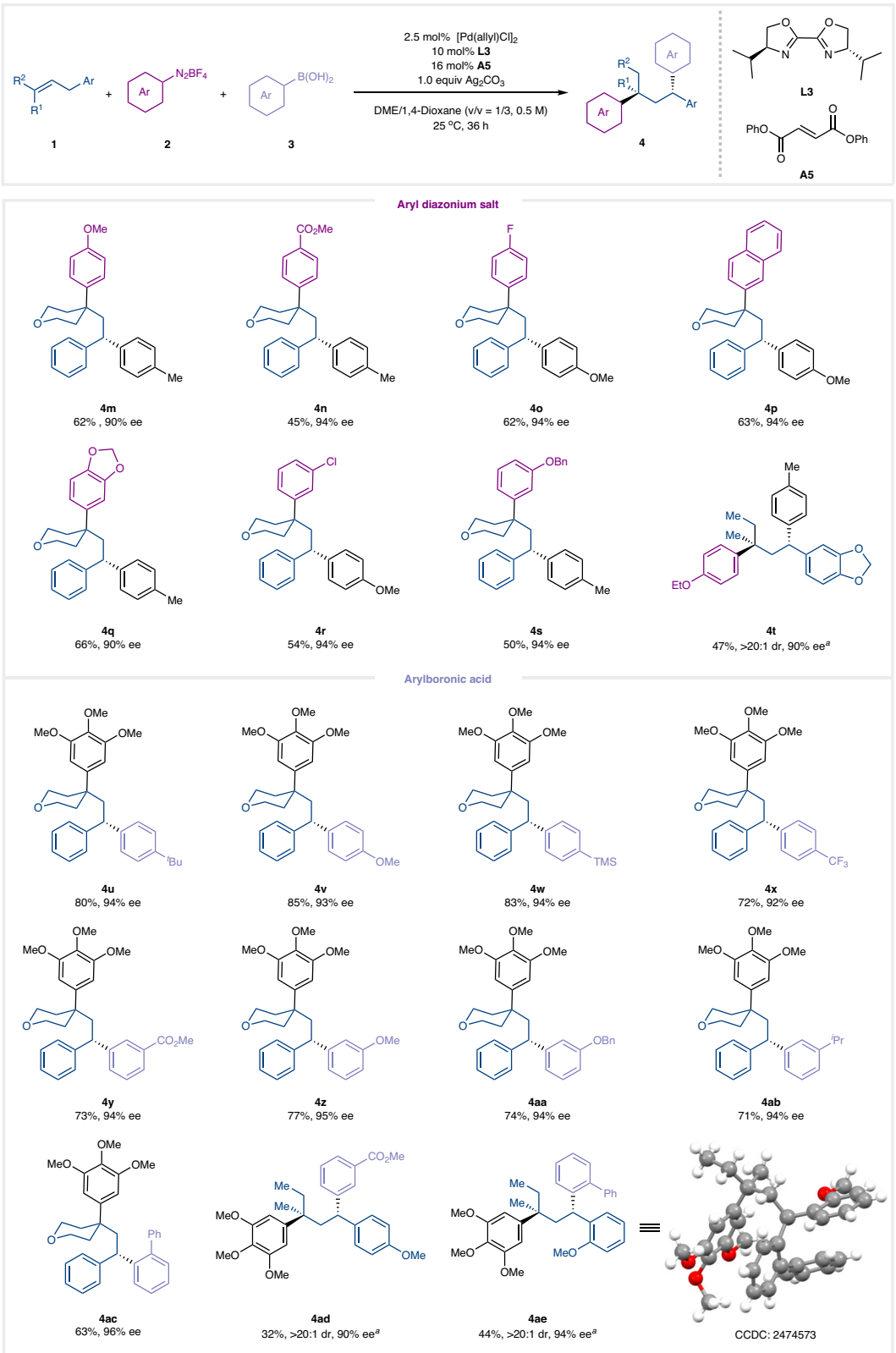

Fig. 3 | Substrate scope of aryl diazonium salts and arylboronic acids. Reaction conditions: alkene **1** (1.0 equiv, 0.20 mmol), aryl diazonium salt **2** (2.0 equiv, 0.40 mmol), arylboronic acid **3** (3.0 equiv, 0.60 mmol), $[Pd(allyl)Cl]_2$ (2.5 mol %, 0.005 mmol), **L3** (10 mol %, 0.02 mmol), **A5** (16 mol %, 0.032 mmol), and Ag_2CO_3 (1.0 equiv, 0.20 mmol) in DME/1,4-Dioxane (0.4 mL (v/v = 1/3), 0.5 M) at 25 °C. Isolated yields were reported and the ee values were determined by chiral HPLC. [a]DCM/1,4-Dioxane (0.4 mL (v/v = 1/3), 0.5 M) was used.

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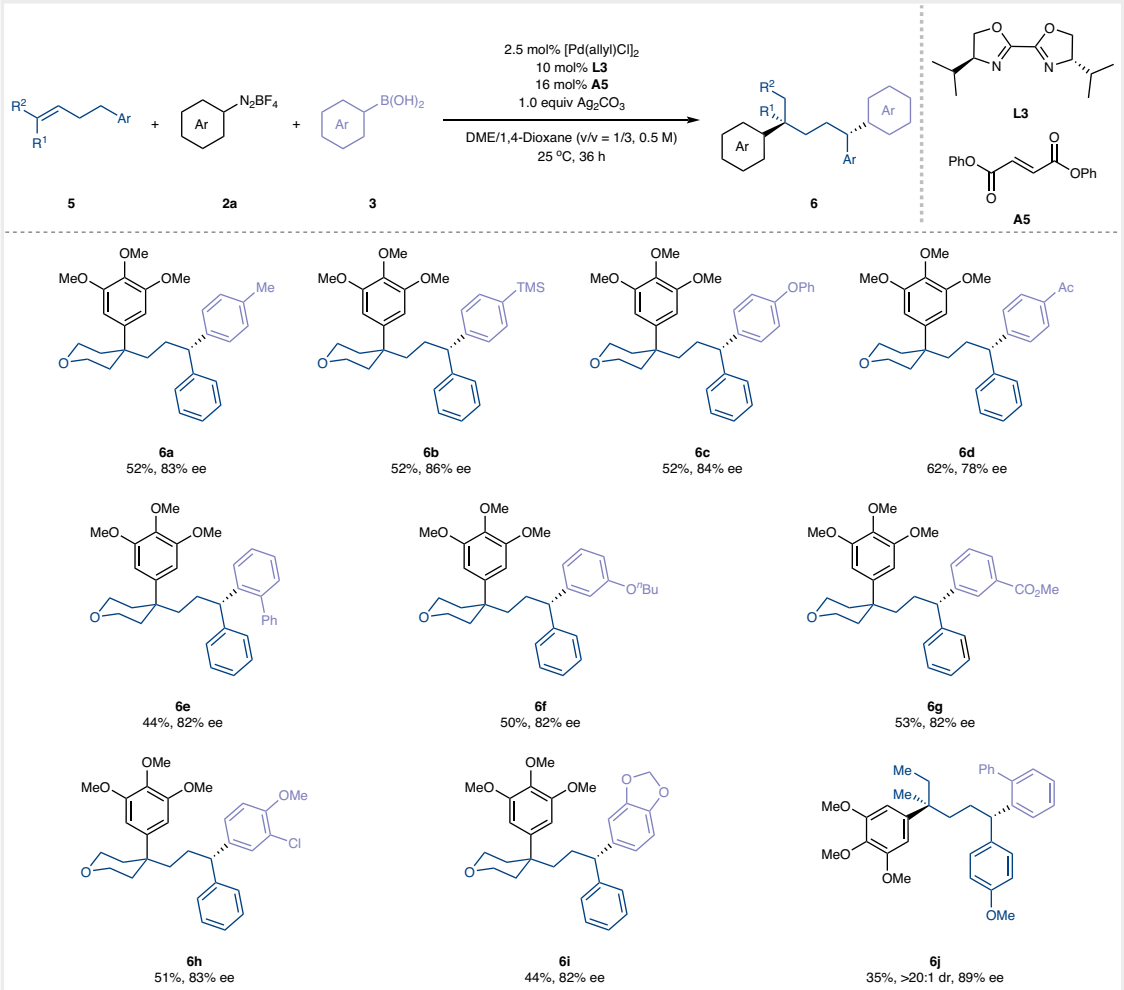

Fig. 4 | Palladium-catalyzed 1,4-diarylation of unactivated trisubstituted alkenes. Reaction conditions: alkene **5** (1.0 equiv, 0.20 mmol), aryl diazonium salt **2a** (2.0 equiv, 0.40 mmol), arylboronic acid **3** (3.0 equiv, 0.60 mmol), $[Pd(allyl)Cl]_2$ (2.5 mol %, 0.005 mmol), **L3** (10 mol %, 0.02 mmol), **A5** (16 mol %, 0.032 mmol), and Ag_2CO_3 (1.0 equiv, 0.20 mmol) in DME/1,4-Dioxane (0.4 mL (v/v = 1/3), 0.5 M) at 25 °C. Isolated yields were reported, and the ee values were determined by chiral HPLC.

78–86% ee. It was noteworthy that this 1,4-diarylation also proceeds smoothly for the unsymmetric trisubstituted alkenes, delivering the desired product **6j** with 89% ee and more than 20:1 dr. The presence of an aromatic ring at the alkene terminus is therefore critical for the observed 1,3- and 1,4-diarylation, an effect we attribute to the stabilization of a key benzylic palladium intermediate.

Mechanistic investigation

To further elucidate the impact of alkyl chain length on the stereoselective chain-walking process and the reversibility of Pd-H migration, preliminary mechanistic investigations were conducted (Fig. 5). While remote 1,n-diarylation of unactivated alkenes yielded products **8**, **10**, **12** in moderate isolated yields (45–57%), enantioselectivity declined significantly: 1,5-diarylation afforded product **8** in 26% ee, 1,6-diarylation yielded product **10** in 8% ee, and near-racemization occurred in 1,7-diarylation with only 4% ee (Fig. 5a). This erosion in enantioselectivity suggests insufficient weak interactions, such as potential coordination between phenyl ring at the terminal site of the unfunctionalized alkene intermediate with the palladium center during the long distance migration process such as 1,6- and 1,7-diarylations[71], leading to undesired Pd-H dissociation. While the undesired dissociation rate maybe slower than the re-insertion of Pd-H intermediate in the short-distance migration, such as 1,3-diarylation and 1,4-diarylation processes. Another possibility is a geometrically defined alkene intermediate cannot be formed when the stereogenic center is far from to the carbon-palladium site that undergoing the β-H elimination.

Deuterium-labeling experiments then probed the Pd-H chain-walking pathway: reaction of **5a-D** (dideuterated at the benzylic position) gave **6a-D** with >99% deuterium at C-3, and reaction of **7-D** (dideuterated at C-4) resulted in regioselective deuterium migration (>99%) from C-4 to C-3, with no labeling at C-1, C-2, or C-5 (Fig. 5b). These results collectively indicate that the chain-walking migration proceeds exclusively in a net forward direction toward the reaction site (eg. from C-4 to C-5 position), without detectable reversal. This regioselective, irreversible progression supports the proposed Pd–H insertion into the transient alkene intermediate, thereby preventing deuterium scrambling, while a behavior that stands in sharp contrast to the reversible chain-walking often observed in NiH-catalyzed cross-coupling chemistry[42]. Furthermore, a crossover experiment between deuterated **5a-D** and non-deuterated **5b** in the 1,4-diarylation yielded only **6a-D** and **6k**, with no crossover product, demonstrating that the Pd-H species remains tightly bound to the alkene chain during 1,4-migration, thereby preserving high enantioselectivity (Fig. 5c). Based on these findings and previous results[17,18], a plausible mechanism for the 1,3-diarylation is proposed (Fig. 5d). The reaction is initiated with

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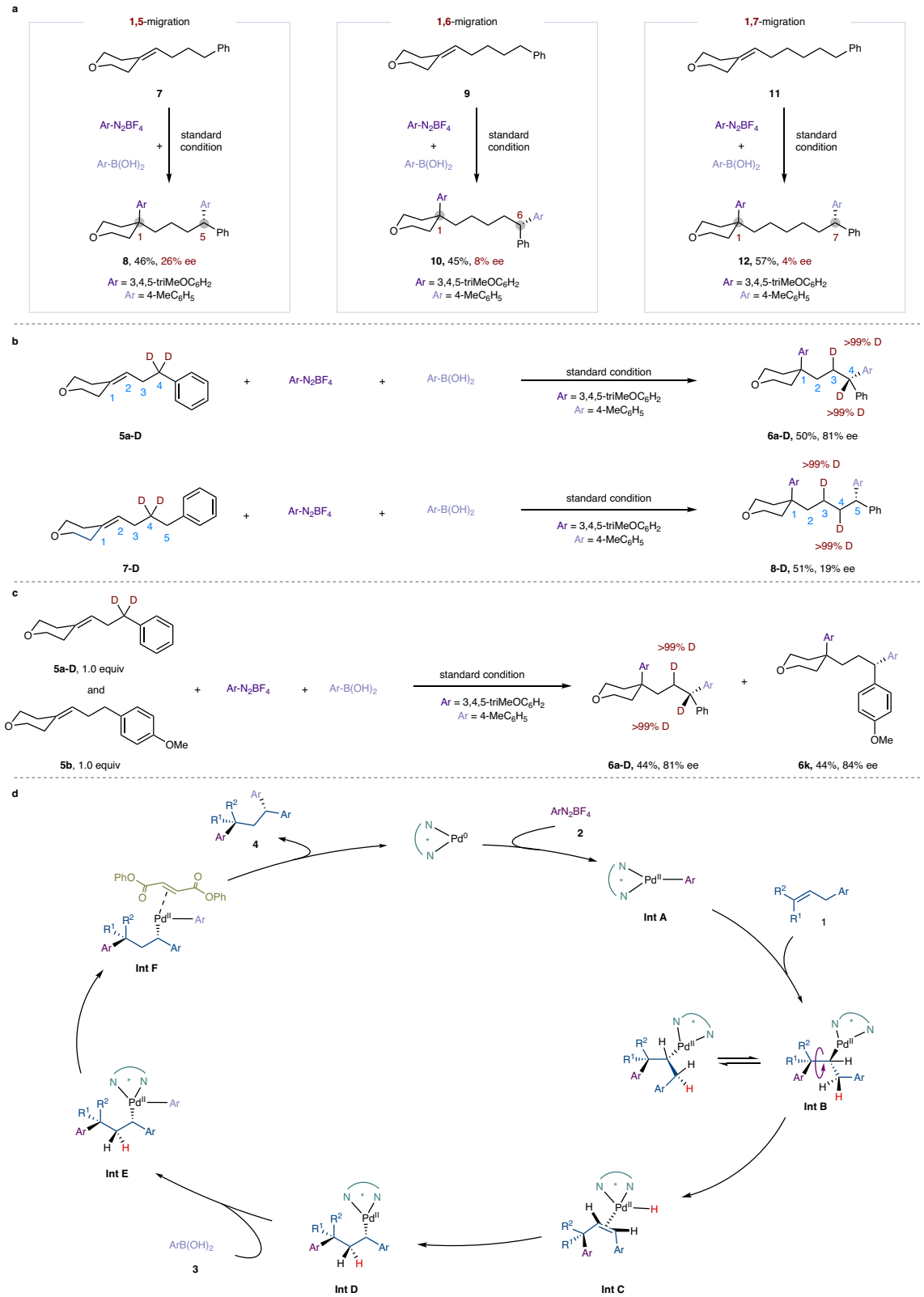

Fig. 5 | Mechanistic studies. a Effect of the alkyl chain length. **b** Deuterium-labeling experiment. **c** Cross-over experiment. **d** Proposed mechanism.

oxidative addition of Pd(0) catalyst with the aryl diazonium salts, forming intermediate **Int-A**. Stereoselective migratory insertion of **Int-A** across the alkene C=C bond yields **Int-B**. Syn β-hydride elimination from Int-B then produces **Int-C**[42]. The resulting Pd–H species undergoes chain-walking migration followed by stereoselective re-insertion into the alkene, affording the stabilized benzyl palladium species **Int-D**[72,73]. Subsequent transmetalation of **Int-D** with an arylboronic acid assisted by ligand exchange[18], followed by reductive elimination promoted by the electronically deficient diphenyl fumarate, delivers the desired migratory product **4** and regenerates the Pd(0) catalyst.

In conclusion, we have developed a palladium-catalyzed enantioselective migratory dicarbofunctionalization of unactivated internal alkenes. This method enables facile 1,3- and 1,4-diarylation by integrating aryl diazonium salts and arylboronic acids as coupling partners. Notably, 1,3- and 1,4-non-contiguous stereocenters are formed with high enantio- and diastereoselectivity. Mechanistic studies indicate the migration proceeds via irreversible Pd–H insertion. Current efforts focus on tackling the unactivated fully substituted alkenes asymmetric cross-coupling for accessing non-contiguous quaternary stereocenters.

Methods

General procedure for diarylation of alkenes

To a dried 8-mL vial was charged with $[Pd(allyl)Cl]_2$ (2.5 mol %), **L3** (10 mol %), **A5** (16 mol %), Ag_2CO_3 (1.0 equiv), aryl diazonium salts (2.0 equiv), arylboronic acids (3.0 equiv) and alkene (1.0 equiv). After evacuated and backfilled nitrogen three times, DME/1,4-Dioxane (v/v = 1/3, 0.5 M) or DCM/1,4-Dioxane (v/v = 1/3, 0.5 M) was added. The reaction was allowed to stirred at 25 °C for 36 ~ 48 h, and then the reaction was filtered with celite and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography to yield the diarylation product.

Data availability

All data to support the conclusions are available in the main text or the supplementary materials. The X-ray Crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Center (CCDC) under deposition numbers CCDC 2474573 (**4ae**) and 2475482 (**6a-D**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Data supporting the findings of this manuscript are also available from the corresponding author upon request.

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Author contributions

Y.C. conceived the projects. L.F., Y.X., H.G., and W.H. performed the experiments under the supervision of W.-H. Z., J.Q., and Y.C. Y.X. and Y.C. wrote the manuscript with the feedback of all other authors.

Competing interests

The authors declare no competing interests.

Additional information

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