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Palladium-catalyzed remote internal C(sp^3)−H bond chlorination of alkenes

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C(sp^3)−Cl bonds are present in numerous biologically active molecules and can also be used as a site for diversification by substitution or cross-coupling reactions. Herein, we report a remote internal site-selective C(sp^3)−H bond chlorination of alkenes through sequential alkene isomerization and hydrochlorination, enabling the synthesis of both benzylic and tertiary chlorides with excellent site-selectivity. This transformation offers exciting possibilities for the late-stage chlorination of derivatives of natural products and pharmaceuticals. We also demonstrate the regioconvergent synthesis of a single alkyl chloride from unrefined mixtures of isomeric alkenes, which can be extracted directly from petrochemical sources.

Alkyl chlorides are ubiquitous in nature and are found in nearly every class of biomolecules, ranging from alkaloids to terpenoids to steroids[1,2]. The chloro group serves as a crucial functional regulator in a variety of fields, including pharmaceuticals, materials, functional molecules, and natural products (Fig. 1a)[3–7]. Moreover, alkyl chlorides are widely employed as highly versatile synthetic building blocks in organic synthesis[8–10]. Therefore, significant efforts have been devoted to exploring diverse methodologies for their efficient synthesis[11–13].

Given the abundance and easy accessibility of alkene feedstocks, hydrochlorination of alkenes−including catalytic hydrochlorination[14–20] and hydrochlorination using HCl surrogates[21–27] or gaseous HCl[28–39]−represents one of the most straightforward and attractive approaches for synthesizing alkyl chlorides. Typically, hydrogen and chlorine atoms tend to add directly across the C=C bond (Fig. 1b, left). While the remote hydrochlorination of alkenes, which places a hydrogen on the alkene and a chlorine group distal to the alkene, offers promising opportunities for site-selectively chlorinating C(sp^3)−H bonds to synthesize structurally diverse alkyl chlorides, it still faces formidable challenges and remains largely unexplored (Fig. 1b, right). Recently, Liu and coworkers achieved a remarkable breakthrough in remote migratory hydrochlorination of alkenes, enabling the selective chlorination of terminal C(sp^3)−H bonds (Fig. 1c)[40]. The exceptional chemo- and site-selectivity is achieved through the use of a well-designed pyridine-oxazoline ligand containing a hydroxyl group. This hydroxyl group can form a hydrogen bond with the oxygen atom of

N-chlorosuccinimide (NCS), thereby accelerating the oxidation of stable linear alkyl Pd^{II} species by NCS to produce primary alkyl chlorides. Herein, in our continuing research interests in alkene hydrofunctionalizations[41–43], we report a Pd-catalyzed internally distant C(sp^3)−H bond chlorination through migratory hydrochlorination of alkenes (Fig. 1d). Most previous research on Pd-catalyzed chlorination of C(sp^3)−H bonds has predominantly used nitrogen-containing functional groups as directing groups, such as sulfoximine[44], amide derived from 8-aminoquinoline[45–47], and pyridine[48,49]. Recently, Yu and coworkers advanced this field by developing a Pd(II)-catalyzed β-C(sp^3)−H chlorination of carboxylic acids, where the carboxyl group serves as the directing group[50].

Despite significant progress in the transition-metal-catalyzed internal C(sp^3)−H bond functionalizations of alkenes through chain walking, achieving internal C(sp^3)−H bond chlorination remains an elusive goal[51–58]. One major challenge is the difficulty of forming C−Cl bonds via thermodynamically unfavorable reductive elimination from organometallic complexes, as the reverse process, oxidative addition, is more facile. This difficulty is further exacerbated when thermodynamically stable styrene derivatives can be formed through competitive β-hydrogen elimination[59–61]. Inspired by the C(sp^3)−H bond functionalizations of alkenes via high-valent palladium intermediates[62–64], we speculated that this challenging internal site-selective chlorination could be addressed by using appropriate oxidants and ancillary ligands. Iterative hydropalladation and β-H

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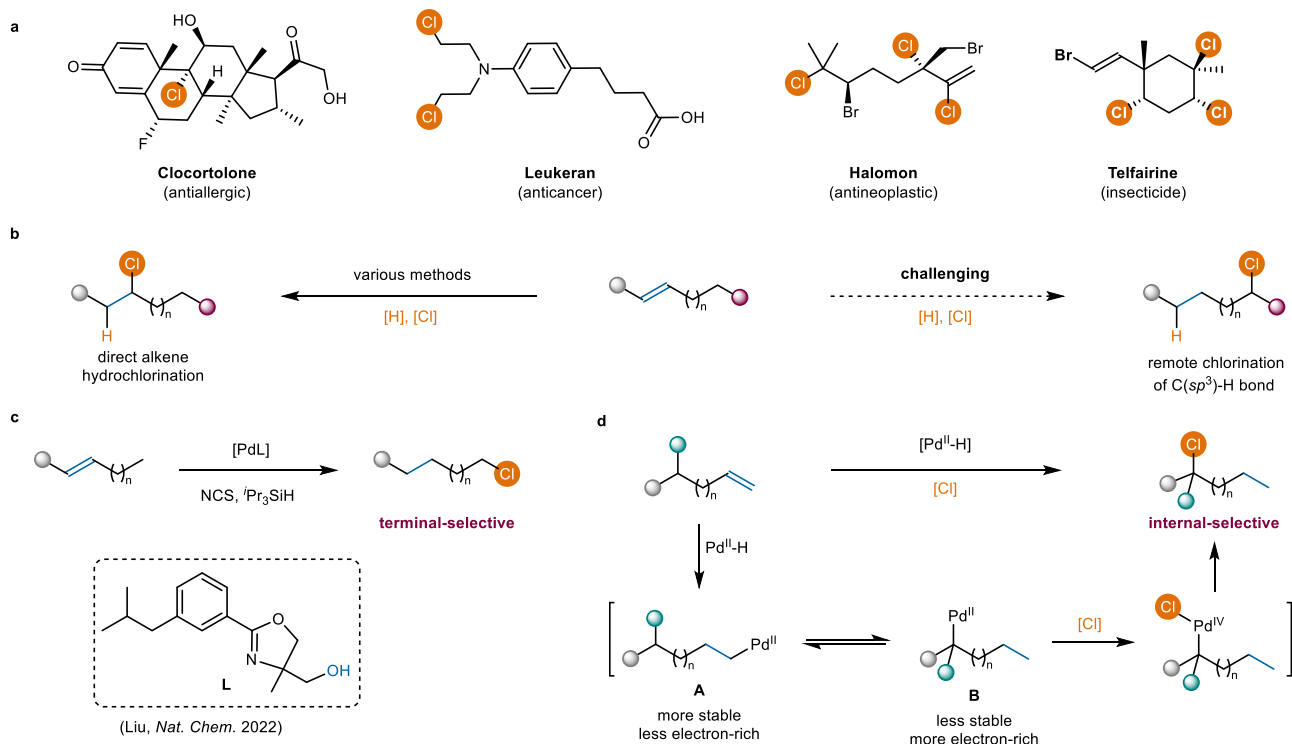
Fig. 1 | Inspiration for internal-selective C(sp^3)−H bond chlorination of alkenes.
a, Selected biologically active molecules containing C(sp^3)−Cl bonds.
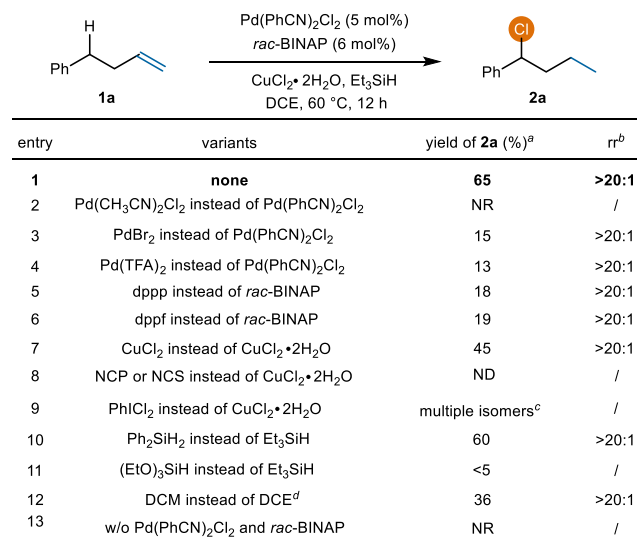**b**, Hydrochlorination of alkenes. **c** Previous work: terminal-selective C(sp^3)−H bond chlorination of alkenes. **d** This work: internal-selective C(sp^3)−H bond chlorination of alkenes.

elimination of an alkene can generate either a linear alkyl Pd^{II} species **A** or a branched alkyl Pd^{II} species **B** (Fig. 1d). Generally, the linear alkyl Pd^{II} species **A** is more stable but less electron-rich compared to the branched alkyl Pd^{II} species **B**[40]. Precedent literatures have demonstrated that chlorination of the branched alkyl Pd^{II} species **B**, which has a more electron-rich palladium center, is kinetically more favorable than that of the linear alkyl Pd^{II} species **A** when exposed to relatively less reactive electrophilic chlorinating reagents, such as CuCl$_2$[65,66]. Building on this, we hypothesized that employing appropriate electrophilic chlorinating reagents would predominantly oxidize branched alkyl Pd^{II} species **B**, leading to internal site-selective C(sp^3)−H bond chlorination.

Results and discussion
Reaction development
To investigate our hypothesis, we initiated this study with the remote chlorination of 4-phenyl-1-butene **1a** (Fig. 2). After carefully evaluating palladium precatalysts, ligands, electrophilic chlorinating reagents, hydride sources, and solvents, we found that this reaction performed well using a combination of Pd(PhCN)$_2$Cl$_2$ and *rac*-BINAP as the catalyst, CuCl$_2$•2H$_2$O as the oxidant and chloride source, and Et$_3$SiH as a hydride source (entry 1), providing the desired benzylic chloride **2a** with 65% yield and excellent internal site-selectivity (>20:1 rr). Other palladium precatalysts, such as Pd(CH$_3$CN)$_2$Cl$_2$, PdBr$_2$, or Pd(TFA)$_2$, were less efficient, resulting primarily in isomerization and reduction of alkenes (entries 2–4). Chlorination was completely halted even in the presence of an additional 20 mol% CH$_3$CN under standard conditions. We speculate that CH$_3$CN, which coordinates more readily with palladium than PhCN, interferes with ligand binding and thus inhibits the chlorination process. Consequently, when Pd(CH$_3$CN)$_2$Cl$_2$ was used instead of Pd(PhCN)$_2$Cl$_2$, the desired chloride **2a** was not obtained. Both dppp and dppf led to the desired product but with low yields (entries 5 and 6). Bisphosphine ligands are critical to the reaction, and nitrogen-based ligands and *N*-heterocyclic carbene (NHC)

entry	variants	yield of **2a** (%)[a]	rr[b]
1	**none**	**65**	**>20:1**
2	Pd(CH$_3$CN)$_2$Cl$_2$ instead of Pd(PhCN)$_2$Cl$_2$	NR	/
3	PdBr$_2$ instead of Pd(PhCN)$_2$Cl$_2$	15	>20:1
4	Pd(TFA)$_2$ instead of Pd(PhCN)$_2$Cl$_2$	13	>20:1
5	dppp instead of *rac*-BINAP	18	>20:1
6	dppf instead of *rac*-BINAP	19	>20:1
7	CuCl$_2$ instead of CuCl$_2$•2H$_2$O	45	>20:1
8	NCP or NCS instead of CuCl$_2$•2H$_2$O	ND	/
9	PhICl$_2$ instead of CuCl$_2$•2H$_2$O	multiple isomers[c]	/
10	Ph$_2$SiH$_2$ instead of Et$_3$SiH	60	>20:1
11	(EtO)$_3$SiH instead of Et$_3$SiH	<5	/
12	DCM instead of DCE[d]	36	>20:1
13	w/o Pd(PhCN)$_2$Cl$_2$ and *rac*-BINAP	NR	/

[a]Determined by GC using 1,3,5-trimethoxybenzene as an internal standard. [b]rr is the regioisomeric ratio, represents the ratio of **2a** to the sum of all other isomers as determined by GC. *rac*-BINAP, 2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene; TFA, trifluoroacetate; dppp, 1,3-Bis(diphenylphosphino)-propane; dppf, 1,1'-Bis(diphenylphosphino)-ferrocene; DCE, 1,2-dichloroethane; DCM, dichloromethane. [c]using DPEphos (Bis[(2-diphenylphosphino)phenyl]ether). [d]at 40 °C.

Fig. 2 | Reaction optimization.

ligands give only a hydrogenation product (see SI for details). Replacement of CuCl$_2$•2H$_2$O with CuCl$_2$ resulted in a lower yield, possibly because water can activate silane to promote the formation of Pd−H (entry 7)[67]. No desired chlorinated products were observed when using chlorinating reagents such as *N*-chlorophthalimide (NCP) and NCS; only isomerization and reduction of alkenes were obtained (entry 8).

There are two possible explanations for this result. One is that NCP and NCS, due to their greater steric hindrance, are unable to oxidize the branched alkyl Pd^{II} species. The other possibility is that these oxidants may be converted into the corresponding imides in the presence of silane, which could subsequently coordinate with the catalyst and lead to its deactivation. When using the stronger oxidant PhICl$_2$, a mixture of chlorination products at different positions, along with a dichlorination product, was detected by GC-MS (entry 9). This result is likely due to the increased rate of oxidative chlorination facilitated by the stronger chlorinating reagent, which closely matches the rate of migration of the Pd−H species along the carbon chain, leading to the formation of a mixture of isomers. Ph$_2$SiH$_2$ also performed well (entry 10), but (EtO)$_3$SiH gave a poor result with a significant amount of

hydrogenation product (entry 11). Another chlorine-containing solvent, such as DCM, led to diminished yields (entry 12). Finally, a control experiment demonstrated the essential role of a palladium catalyst, as no hydrochlorination product was formed when using only CuCl$_2$•2H$_2$O and silane (entry 13).

Scope of remote internal C(sp^3)−H bond chlorination of alkenes
With these optimal conditions, we subsequently investigated the reaction generality. As illustrated in Fig. 3, a variety of aliphatic alkenes could undergo remote migratory hydrochlorination smoothly, providing the corresponding benzylic chlorides with moderate to good yields and excellent site-selectivity (**2b−2h**, 57−63% yield, >20:1 rr). Isomerization and reduction of alkenes are
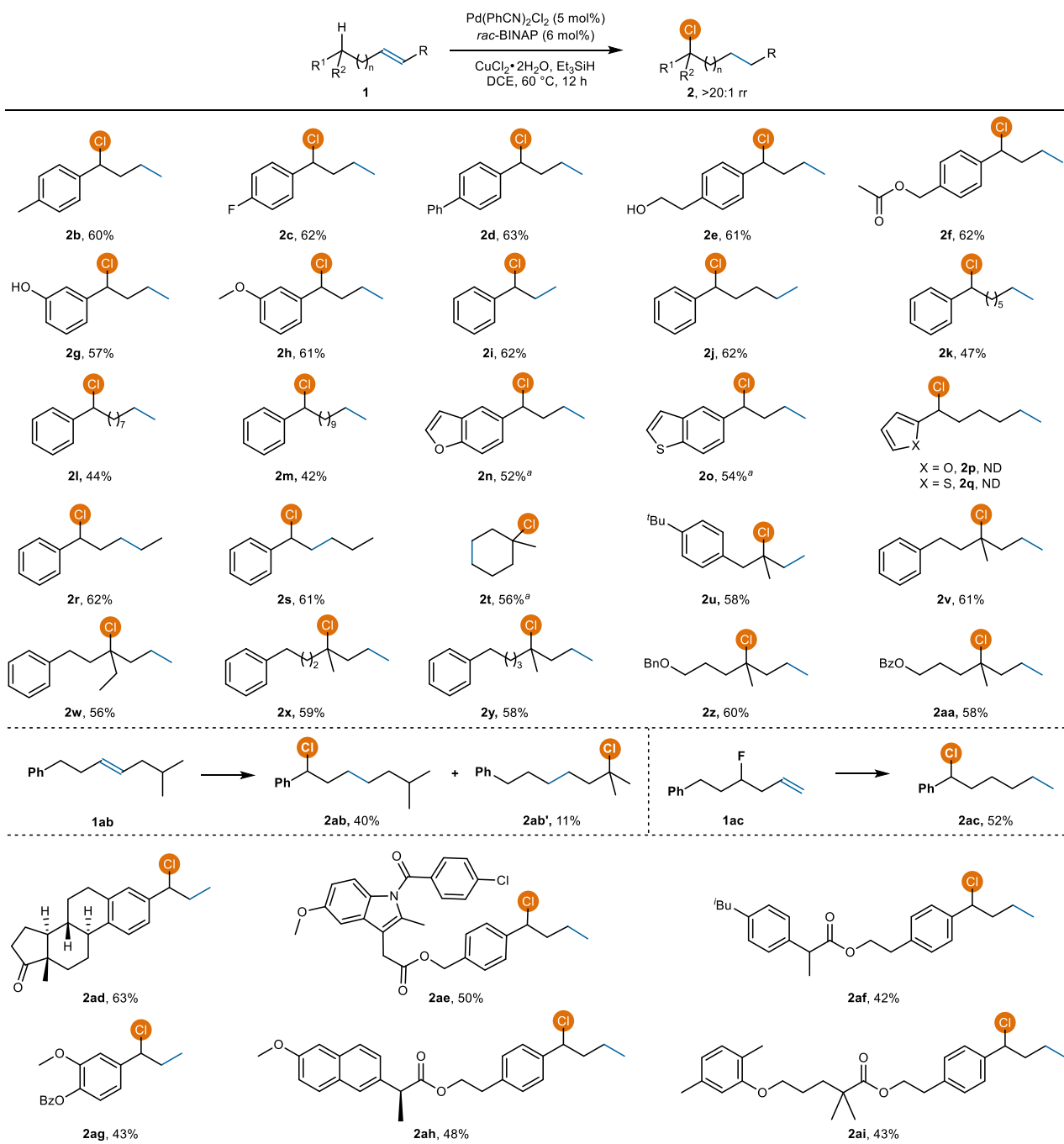

Reaction conditions: **1** (0.1 mmol), Pd(PhCN)$_2$Cl$_2$ (5 mol%), *rac*-BINAP (6 mol%), CuCl$_2$ • H$_2$O (3.5 eq.), Et$_3$SiH (3.5 eq.), 60 °C. ^{a}^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard.

Fig. 3 | Remote internal C(sp^3)−H bond chlorination of alkenes.

the primary by-products observed in substrates with moderate yields. The reaction is insensitive to the chain length between the C=C bond and the remote aryl group, ranging from 1 to 10 C-atoms (**2i–2m**, 42–62% yield). Heteroaromatic rings, such as furan and thiophene, demonstrate compatibility with the reaction (**2n** and **2o**); however, they cannot serve as termination sites for benzylic chlorination (**2p** and **2q**, see SI for other alkene substrates that show no reactivity). Internal alkenes were found to be competent substrates, regardless of the initial position of the C=C bond (**2r** and **2s**, 62 and 61% yield, respectively). Chlorination of the alicyclic substrate **1t** delivered the desired product **2t** in 56% yield. Interestingly, chlorination of the tertiary C(sp^3)–H bond rather than the benzylic C(sp^3)–H bond was successfully achieved when using alkenes that feature a tertiary carbon in the chain (**2u–2aa**, 56–61% yield). A mixture of benzylic chloride (**2ab**) and tertiary chloride (**2ab′**) was obtained when chlorinating an alkene with a benzylic C(sp^3)–H bond on one side and a tertiary C(sp^3)–H bond on the other side. Using an alkene **1ac** with an F-substituent in the aliphatic chain, a defluorinated chlorination product **2ac** was obtained with a 52% yield. This result suggests that β-F elimination likely occurred, leading to the formation of a Pd–F species. The presence of silane further facilitates the conversion of the Pd–F complex to Pd–H, allowing the chlorination reaction to continue.

The introduction of C(sp^3)–Cl bonds can impart beneficial properties to biologically active molecules, such as altering the electronic properties of nearby functional groups, enhancing their lipophilicity, and preventing metabolic oxidation at the chlorinated locus[68,69]. Consequently, we expanded our investigation to encompass a diverse array of substrates originating from bioactive molecules, including estrone (**2ad**), indomethacin (**2ae**), ibuprofen (**2af**), eugenol (**2ag**), naproxen (**2ah**), and gemfibrozil (**2ai**), successfully achieving the corresponding chlorides with excellent site-selectivities (>20:1 rr) and moderate to good yields (42–63% yield). Hydroxyl, ester, amide, and carbonyl groups are well tolerated in our reactions.

Scope of direct hydrochlorination of alkenes

Despite the development of several approaches for the catalytic hydrochlorination of alkenes, the efficient chlorination of styrene derivatives remains a challenge due to their easy oligomerization[14–20]. In this context, the hydrochlorination of styrenes under optimized conditions was also investigated (Fig. 4). To our delight, the hydrochlorination of diverse styrenes bearing different substituents on the phenyl ring afforded the benzylic chlorides exclusively (**4a–4f**, 60–80% yield). Electron-rich styrenes are highly prone to oligomerization under these conditions, and no hydrochlorination products were obtained. Poly-substituted terminal and internal alkenes were also competent substrates and were transformed into the corresponding chlorides in good yields (**4g–4j**, 62–72% yield). Hydrochlorination of osthol and estrone derivatives worked well, yielding the desired chlorination products in 63% and 80% yields (**4k** and **4l**), respectively.

Mechanism investigation

Based on literature reports on remote internal hydrofunctionalization of alkenes and our own investigations, we propose the mechanism shown in Fig. 5a[40,65,66,70,71,72–74]. The catalytic cycle is initiated by the formation of a Pd–H complex **II** from LPd^{II} and silane. A series of iterative β-H elimination and migratory insertion processes ultimately provides benzyl or tertiary palladium intermediate **IV**. In line with Sanford's arylhalogenation of alkenes[65,66], we propose oxidizing the Pd^{II}-alkyl species **IV** with CuCl$_2$·2H$_2$O to generate a high oxidation state Pd^{IV}-intermediate **V**. Reductive elimination of the intermediate **V** provides the desired chlorination products. Oxidative chlorination of intermediate **IV** is more favorable than that of intermediate **III**, allowing for internal C(sp^3)–H bond chlorination.

Reaction conditions: **3** (0.1 mmol), Pd(PhCN)$_2$Cl$_2$ (5 mol%), *rac*-BINAP (6 mol%), CuCl$_2$·2H$_2$O (3.5 eq.), Et$_3$SiH (3.5 eq.), 60 °C.
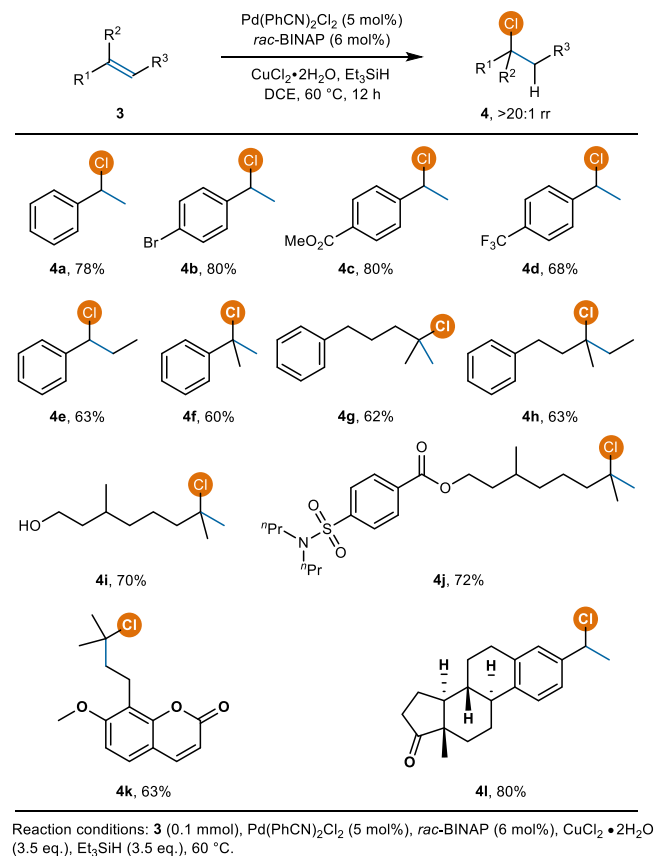
Fig. 4 | Hydrochlorination of styrenes and poly-substituted alkenes.

To gain insights into this internal migratory hydrochlorination, a series of mechanistic experiments were performed. When we subjected alkene **1d** to the standard reaction conditions in the absence of CuCl$_2$·2H$_2$O, a mixture of alkenes resulting from alkene isomerization was observed (Fig. 5b, top). We also performed the chlorination reaction in the absence of CuCl$_2$ but with 7 eq. of H$_2$O, and observed that the styrenyl derivatives **1d′** emerged as the major product (Fig. 5b, bottom). These results suggest that alkene isomerization is independent of the presence of CuCl$_2$·2H$_2$O and indicate that water facilitates the isomerization process by activating the silane[67]. Furthermore, a mixture of alkenes was obtained when the reaction was run to partial conversion (Fig. 5c), suggesting that alkene isomerization proceeds through rapid dissociation and reassociation of the Pd–H species during the chain-walking process. To further support this rapid dissociation and reassociation proposal, the chlorination of alkene (*S*)-**1aa**, which contains a pre-existing stereocenter in the chain, was studied (Fig. 5d). The observation of the racemization is consistent with the dissociated chain-walking mechanism[75]. Moreover, a crossover experiment was conducted using a mixture of deuterated **d–3m** and undeuterated **3c**. The detection of deuterium in the product **d–4c** provides additional evidence for the dissociation of the Pd–H species from the alkene (Fig. 5e). Additionally, an isotopic labeling experiment was performed using deuterated silane. Deuterium was observed at all methylenes, suggesting that migration of Pd–H species along the carbon chain of the alkenes indeed occurred (Fig. 5f, top). No deuterium incorporation into the desired product was observed when D$_2$O was used, indicating that the silane is the sole hydrogen source (Fig. 5f, bottom).

Transformations

Since isomeric mixtures of alkenes can be extracted directly from petrochemical sources and are widely available on an enormous
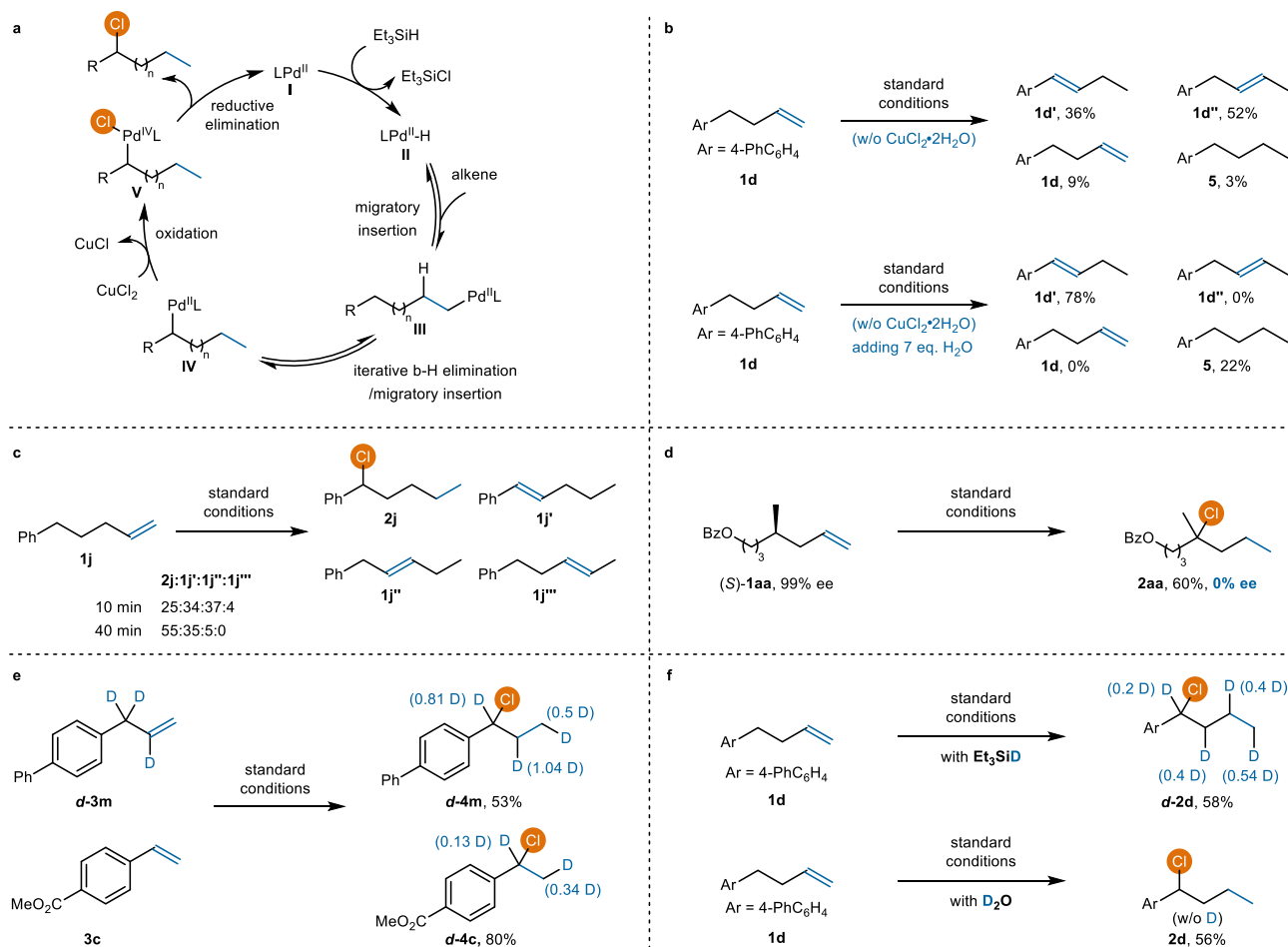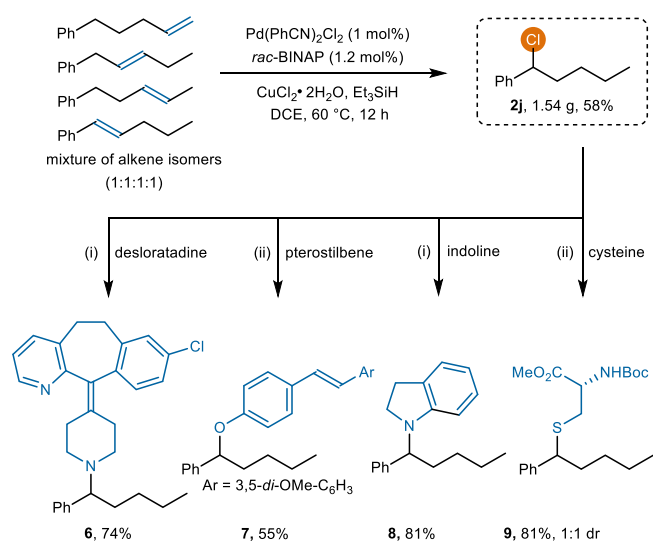
Fig. 5 | Mechanistic studies. a Proposed mechanism. **b** Alkene isomerization in the absence of CuCl$_2$•2H$_2$O or CuCl$_2$. **c** Reaction monitor. **d** Hydrochlorination of stereocenter-containing alkene. **e** Crossover experiment. **f** Deuterium-labeling experiments.

Fig. 6 | Regioconvergent hydrochlorination and its applications. (i) KI (2.5 eq.), K$_2$CO$_3$ (2.5 eq.), MeCN, 80 °C, 24 h. (ii) KI (2.5 eq.), K$_2$CO$_3$ (2.5 eq.), DMF, 80 °C, 24 h.

scale as industrial feedstocks, their use in regioconvergent reactions is of considerable interest. Our method enables the remote internal chlorination of alkene isomer mixtures with a catalyst loading as low as 1 mol%, yielding a single benzylic chlorination

product **2j** on a gram scale (1.54 g, 58% yield, Fig. 6). Alkyl chlorides serve as useful synthons for further transformations, providing various valuable organic compounds. Chlorination product **2j** could react with bioactive pharmaceuticals and natural products, such as desloratadine, pterostilbene, indoline, and cysteine, to yield their derivatives.

Hydrochlorination represents an attractive method for transforming feedstock alkenes into valuable chlorinated bioactive molecules and building blocks. By combining Pd-catalysis with the electrophilic chlorinating agent CuCl$_2$•2H$_2$O, we successfully achieved a remote internal site-selective C(sp^3)−H bond chlorination of alkenes via remote migratory hydrochlorination, enabling the synthesis of both benzylic and tertiary chlorides with excellent site-selectivities. This transformation proceeds under mild conditions, making it practical for late-stage chlorination of bioactive molecules and unrefined mixtures of isomeric alkenes. Ongoing investigations in our laboratory involve exploring other electrophiles of significant synthetic utility, and results will be reported in due course.

Methods
General procedure for hydrochlorination of alkenes

In an N$_2$-filled glovebox, Pd(PhCN)$_2$Cl$_2$ (1.9 mg, 0.005 mmol), *rac*-BINAP (3.8 mg, 0.006 mmol), and DCE (0.5 mL) were added sequentially to a 1-dram vial. The resulting mixture was stirred at ambient temperature for 15 min. Then Et$_3$SiH (41.0 mg, 0.35 mmol), olefin (0.10 mmol), and CuCl$_2$•2H$_2$O (59.0 mg, 0.35 mmol) were added sequentially to the reaction. The reaction mixture was stirred at 60 °C

for 12 h. After this time, the reaction was concentrated and purified by flash silica gel chromatography to give the pure product.

Data availability

All other data were available from the corresponding author upon request. For experimental details and procedures, spectra for all unknown compounds, see supplementary files.

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Y.-X.W. and Z.W. performed the experiments and collected and analyzed the data. X.-H.Y. directed the project and wrote the manuscript with feedback from all authors.

Competing interests

The authors declare no competing interests.

Additional information

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