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Palladium-catalyzed enantioselective β-hydride elimination for the construction of remote stereocenters

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The β-H elimination is a crucial elementary step in transition-metal catalysis, but controlling the stereochemistry of this process has been underdeveloped. The limited works reported so far have only focused on creating axial chirality in allenes, and no report has been able to build central chirality using asymmetric β-H elimination. In this study, we report a Trost ligand-enabled enantioselective desymmetric β-H elimination reaction from π-allyl-Pd. This transformation provides rapid access to cyclohexenes bearing a C4-remoted stereocenter, and total synthesis of (-)-oleuropeic acid and (-)-7-hydroxyterpineol is demonstrated. Computational studies have shown that the β-H elimination is the rate-determining step, and the non-covalent interactions between the amide moiety of the Trost ligand and the benzene and cyclohexane moieties of the substrate play a key role in stereocontrol during the β-H elimination.

The β-hydride elimination is a fundamental chemical process that appears in many transition-metal catalyzed transformations[1], such as the Heck reaction[2–5], Saegusa oxidation[6,7], and migratory cross-coupling reactions[8–11]. Chemists have carried out several experimental and theoretical studies to investigate the chemoselectivity and regioselectivity of β-hydride elimination[12–24]. However, there have been very few attempts to study the stereoselectivity because this elimination step transforms two sp^3 carbons into an alkene without generating a common stereocenter. The development of methods to achieve enantioselective β-hydride elimination is an attractive research topic in asymmetric transition-metal catalysis[25–28]. Frantz and coworkers reported the first successful asymmetric β-hydride elimination from vinyl Pd(II)-complexes derived from enol triflates. This reaction features an asymmetric desymmetrization strategy, producing 1,3-disubstituted allenes with high enantioselectivities that bear axial chirality[25]. Zhang et al. disclosed a Heck reaction-triggered β-hydride elimination, and their Pd-Xuphos system could furnish 1,1,3-trisubstituted chiral allenes[26,27]. More recently, Tan et al. reported an elegant asymmetric Heck reaction of anthracenylidenes, which utilized the asymmetric β-hydride elimination to establish an axially chiral anthracenylidene skeletons[28]. Despite these achievements, the construction of central chiralities by asymmetric β-H elimination has never been addressed (Fig. 1a).

The β-H elimination from the π-allyl-palladium species in the Tsuji-Trost reaction can lead to the formation of undesired product 1,3-dienes[29–35]. However, this reaction has not been fully explored for its synthetic potential, particularly in enantioselective variants. Our group has a long-standing interest in Pd-H involving asymmetric hydrofunctionalization of 1,3-dienes[36–43], which prompts us to consider the possibility of implying the reversed Pd-H elimination reaction to generate 1,3-dienes with a chiral center. Taking inspiration from the desymmetrization strategy[44–47] to prepare remote stereocenters[48–53], we proposed a desymmetric enantioselective β-H elimination from the π-allyl-Pd might yield 1,3-dienes with a remote central chirality (Fig. 1b). Specifically, 1-vinylcyclohexyl acetate, derived from 4-substituted cyclohexanone, was designed to react with LPd(0) to give π-allyl-Pd. The latter species was then isomerized to the C1-σ-Pd complex to occur β-H elimination. We believed that a proper chiral ligand could help differentiate the two adjacent *cis*-hydrogen atoms, making it possible to forge cyclohexenes bearing a C4-remoted stereocenter. Notably, more than three hundred natural products and bioactive molecules, including (-)-perillaldehyde, (-)-oleuropeic acid,

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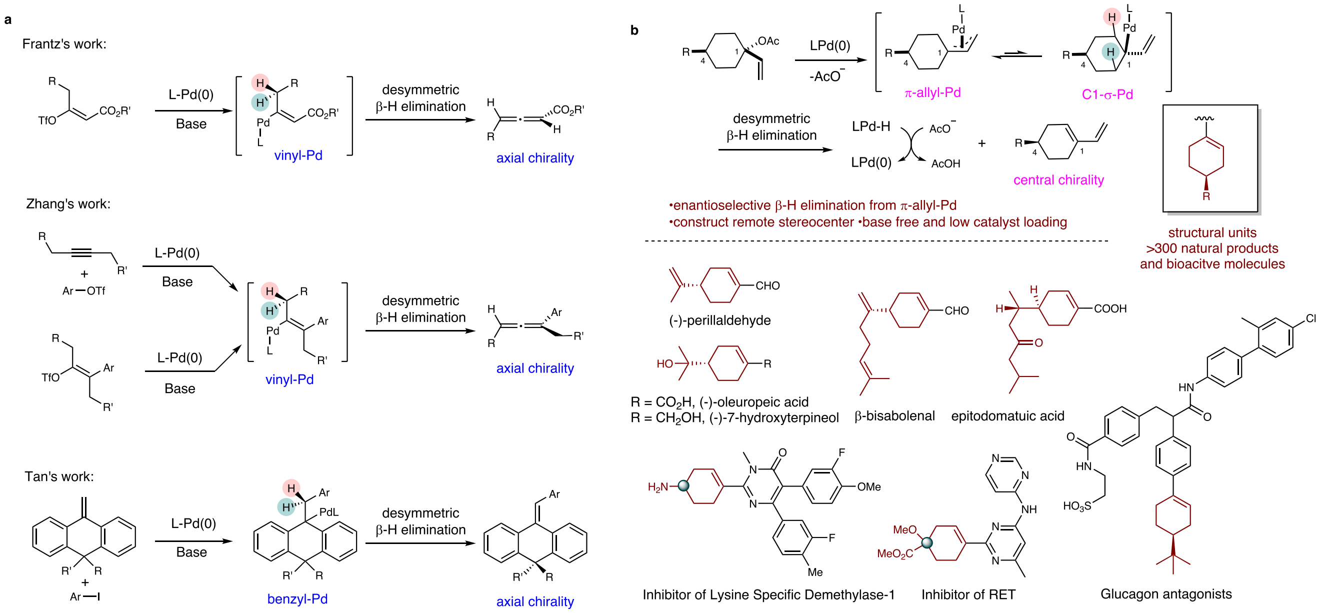


Fig. 1 | Palladium-catalyzed enantioselective β-H elimination. a Previous works on palladium-catalyzed enantioselective β-H elimination to construct axial chirality. **b** This work on palladium-catalyzed enantioselective β-H elimination to construct central chirality.

β-bisabolenal and epitodomatuic acid, contain such structural units (statistics are based on the Reaxys database). However, only rare catalytic methods are available to access these chiral motifs. These elegant works include Liu's cobalt-catalyzed olefin isomerization reaction[54,55] and Jacobsen's asymmetric Wittig reaction[56].

Herein, we disclose a Trost ligand-enabled enantioselective desymmetric β-H elimination process from π-allyl-Pd. This transformation provides rapid access to cyclohexenes bearing a C4-remoted stereocenter from 1-vinylcyclohexyl acetate. Application of this method to the total synthesis of (-)-oleuropeic acid and (-)-7-hydroxyterpineol is demonstrated.

Results and discussion

Reaction development

We commenced our study by using **1a** as the model substrate, $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%) as the catalyst precursor, and THF as the reaction solvent. Various chiral ligands (12 mol%) were first investigated (Table 1). The desired reaction was very sensitive to the ligand's structure (entries 1-11). Although (*R*,*Sp*)-Josiphos (**L3**), (*R*,*R*)-Ph-BPE (**L4**), and (*S*)-DTBM-MeO-Biphep (**L9**) showed very poor activity for this reaction, (*S*)-Phosphinooxazoline (**L1**), (*R*,*Rp*)-Ferrophox (**L2**), (*S*,*S*,*S*,*S*)-BIBOP (**L5**), (*S*,*S*)-QuinoxP (**L6**), Xuphos (**L7**), and (*R*)-MeO-Biphep (**L8**) were competent ligands and produced the product **2a** in 37–72% yields. However, the enantioselectivity was quite low (less than 41% ee). When (*S*,*S*)-DACH-naphthyl Trost ligand (**L10**) was employed, we were pleased to find **2a** was obtained in a 73% yield with 75% ee (entry 10). By switching to (*R*,*R*)-DACH-phenyl Trost ligand (**L11**), both the yield and ee could be significantly improved (96% yield, 89% ee, entry 11). We found that the catalyst loading could be reduced to 0.75 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 1.8 mol% **L11** (entry 12). While the yield was maintained, the ee was slightly decreased. Then, using **L11** as the optimal ligand, different solvents were screened. Changing the solvent to toluene, dichloromethane, or *tert*-butyl methyl ether resulted in dropped ee values (entries 13–15). However, when 1,4-dioxane was used, the desired product **2a** was obtained quantitatively (90% isolated yield) with 90% ee (entry 16). Although one molecular AcOH was produced during the reaction, adding extra bases, such as K_2CO_3, $^iPr_2NEt$, and DBU, proved to be detrimental to either the ee value or the yield (comparing entry 16 with entries 17–19).

Substrate scope

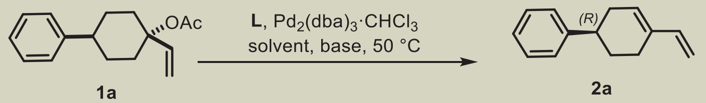
Having the optimal conditions in hand, we began to explore the substrate generality of this reaction (Fig. 2). The 4-aryl substituted substrates were first examined. Phenyl groups with electron-donating (Me, MeO) or electron-withdrawing (Cl, F, CN, CF_3) substituents were well tolerated, and the desired products (**2a**–**2g**) were obtained in 81-94% yields with 88–93% ee. The yield of the electron-withdrawing substituted phenyl group is slightly higher than that of electron-donating. We observed no significant differences in reactivity and enantioselectivity when comparing *para*-, *meta*-, and *ortho*-substitutions (**2b, 2h** vs. **2j** and **2i** vs. **2g**). In addition to phenyl groups, substrates with other aromatic rings such as naphthalene and quinolone were also competent for this elimination reaction (**2k**–**2m**). Next, we turned our attention to the 4-alkyl substituted substrates. Aliphatic groups such as isopropyl (**2n**), *tert*-butyl (**2o**), and polar groups such as dimethyl malonate (**2p, 2q**) and Meldrum's acid moiety (**2r**) all showed good tolerance to the reaction. When the R group was 2,3-dihydrobenzofuran, **2s** was produced in 96% yield and 1:1 dr ratio, and 84% ee and 91% ee were obtained respectively for the two diastereomers.

We next explored the possibility of constructing a C4-heteroatom substituted chiral center. Substrates with 4-oxygen or nitrogen substitution were therefore evaluated. Products with 4-*O*-benzyl (**2t**) and 4-*O*-benzoyl (**2u**) had slightly reduced ee values (72 and 82%, respectively), while products with C4-*N*-phthalimide (**2v**), C4-*N*-benzoxazolinone (**2w**), and C4-*N*-benzotriazole (**2x**) had good to excellent enantioselectivities. The ʟ-aspartic acid condensed amine substrate was also compatible, yielding **2y** in 98% yield and >20:1 dr. This elimination reaction was also reliable in establishing quaternary stereocenters. Both heterosubstituted (**3a, 3b**) and all-carbon quaternary stereocenters (**3c, 3d**) were efficiently constructed with 86–94% ee. Furthermore, C4-spirobicyclic products were also achievable, as demonstrated in the formation of **3e** and **3f**.

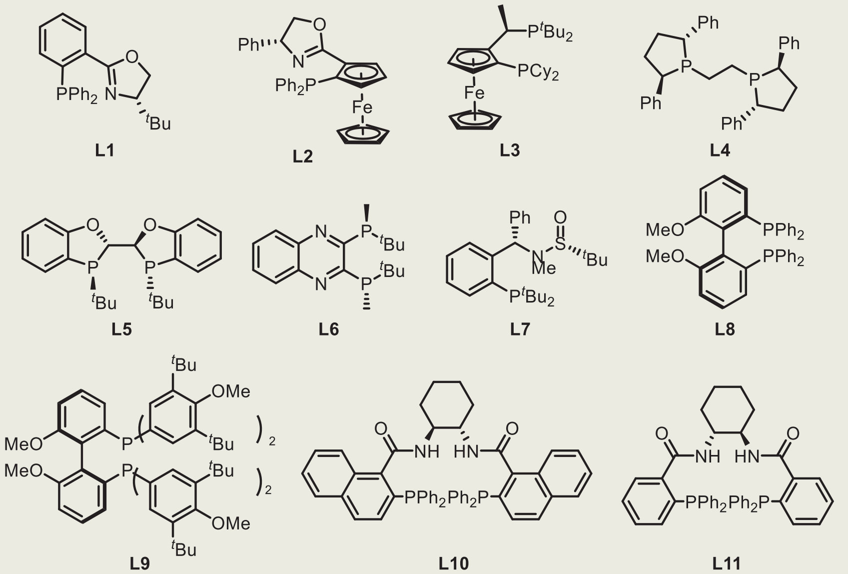
Scaled-up reaction and application

The scalability of this reaction was demonstrated in a gram-scaled preparation of **2a** with a decreased catalyst loading (0.12 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 0.29 mol% **L11**). While the yield dropped slightly, the enantioselectivity was well maintained (Fig. 3a). The diene moiety in the resulting elimination products could undergo diversified

Table 1 | Optimization of reaction conditions.[a]



Entry	L	Solvent	Base	Yield (%)[b]	ee (%)[c]
1	**L1**	THF	w/o	72	-32
2	**L2**	THF	w/o	46	41
3	**L3**	THF	w/o	<5	nd
4	**L4**	THF	w/o	8	-27
5	**L5**	THF	w/o	59	-6
6	**L6**	THF	w/o	37	-14
7	**L7**	THF	w/o	66	8
8	**L8**	THF	w/o	46	35
9	**L9**	THF	w/o	<5	nd
10	**L10**	THF	w/o	73	-75
11	**L11**	THF	w/o	96	89
12[d]	**L11**	THF	w/o	95	82
13[d]	**L11**	$PhCH_3$	w/o	97	66
14[d]	**L11**	CH_2Cl_2	w/o	76	80
15[d]	**L11**	MTBE	w/o	98	78
16[d]	**L11**	1,4-dioxane	w/o	99 (90[e])	90
17[d]	**L11**	1,4-dioxane	K_2CO_3	85	91
18[d]	**L11**	1,4-dioxane	$^{i}Pr_2NEt$	82	89
19[d]	**L11**	1,4-dioxane	DBU	97	80



THF tetrahydrofuran, *MTBE* methyl tert-butyl ether, *w/o* without, *DBU* 1,8-diazabicyclo [5.4.0]undec-7-ene, *nd* not determined.

[a] Reaction conditions, unless otherwise noted: **1a** (0.10 mmol), Pd$_2$(dba)$_3$·CHCl$_3$ (5 mol%), ligand (12 mol%), THF (0.5 mL), 50 °C, 12 h.

[b] Yields were determined by ^{1}H NMR analysis of crude reaction mixtures.

[c] Enantiomeric excess (ee) values were determined by HPLC analysis on a chiral stationary phase.

[d] **1a** (0.20 mmol), Pd$_2$(dba)$_3$·CHCl$_3$ (0.75 mol%), **L11** (1.8 mol%), solvent (0.5 mL), 50 °C, 12 h.

[e] Isolated yield was given in the parentheses.

synthetic transformations. Using **2a** as an example (Fig. 3b), the terminal alkene occurred the dihydroxylation with AD-mix-α, giving **4a** in 75% yield with >20:1 dr. Further cleaving the diol by oxidation with $NaIO_4$ gave aldehyde **4b** in 72% yield with the constant ee. The diene was extended to unsaturated ester **4c** by reaction with ethyl acrylate under Grubbs II catalyst. Moreover, regioselective hydroboration of **2a** with HBpin was achieved by [Ir(cod)Cl]$_2$ catalyst, affording **4d** in 90% yield[57]. Considering the abundant conversion chemistry of boranes, **4d** might serve as a useful synthon in many other transformations. Finally, the Diels-Alder reaction of **2a** with *N*-benzylmaleimide was achieved by heating at 80 °C in toluene, forging diastereomers **4e** in nearly quantitative yield with 1.3:1 dr. Furthermore, the application of this method

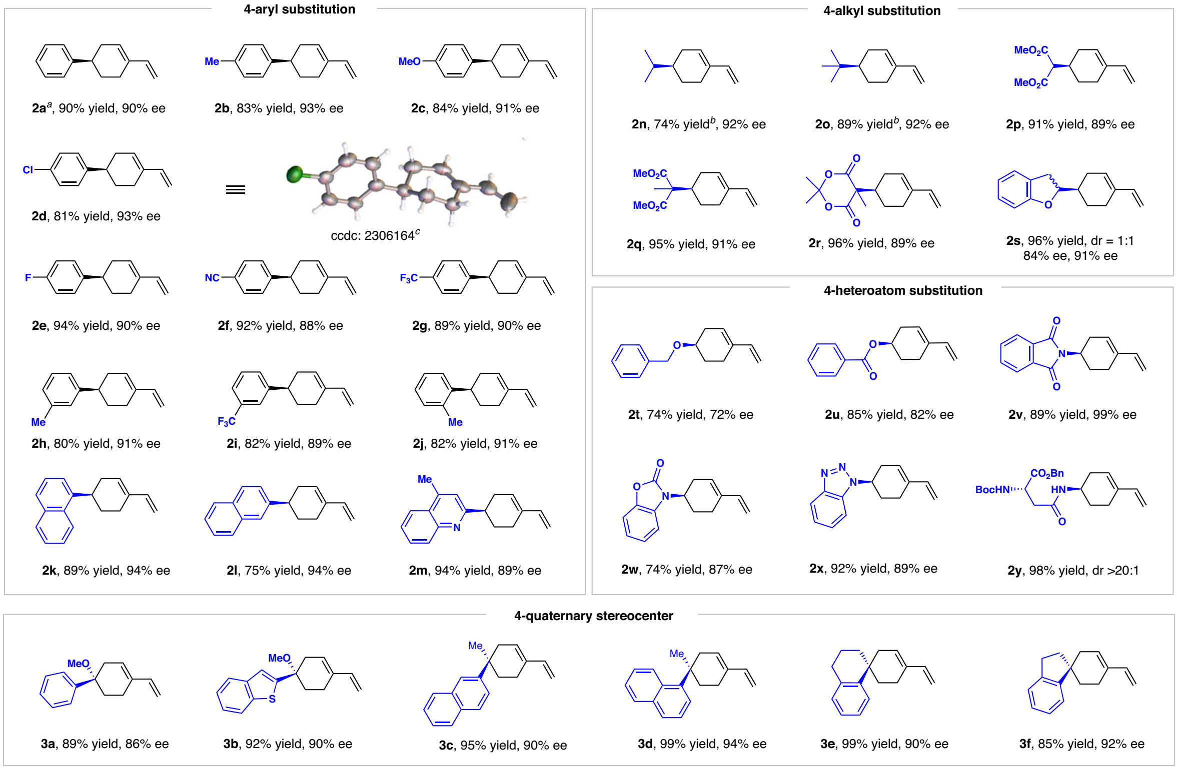


Fig. 2 | Scope of the reaction with respect to the vinylarene. Reaction conditions: **1** (0.20 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (0.75 mol%), **L11** (1.8 mol%), 1,4-dioxane (0.5 mL), 50 °C, 12 h. Enantiomeric excess (ee) values were determined by HPLC on a chiral stationary phase. [a]When substrates with *cis*-1-vinyl-4-aryl relative configuration were used in this investigation, moderate enantioselectivities were given. For example, *cis*-1-vinyl-4-phenyl substrate **1a** affords **2a** in 62% yield with −55% ee under the standard conditions. [b]Yields were determined by ^1H NMR analysis of crude reaction mixtures. [c]The X-ray crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC) under deposition number CCDC 2306164 (**2d**) can be obtained free of charge from www.ccdc.cam.ac.uk/data_request/cif.

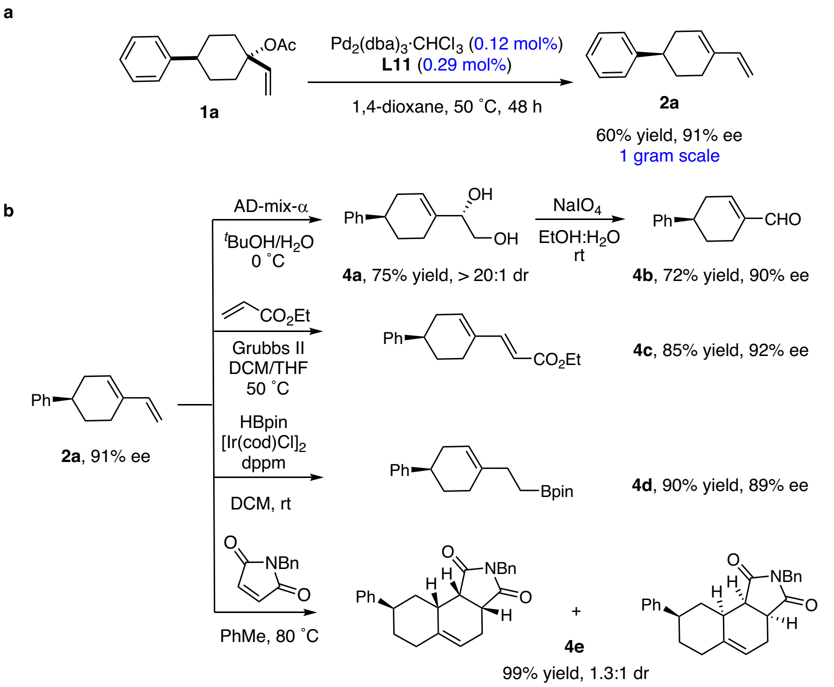


Fig. 3 | Scaled-up reaction and synthetic transformation of 2a. a Scaled-up reaction under reduced catalyst loading. **b** Synthetic transformation of the product **2a**.

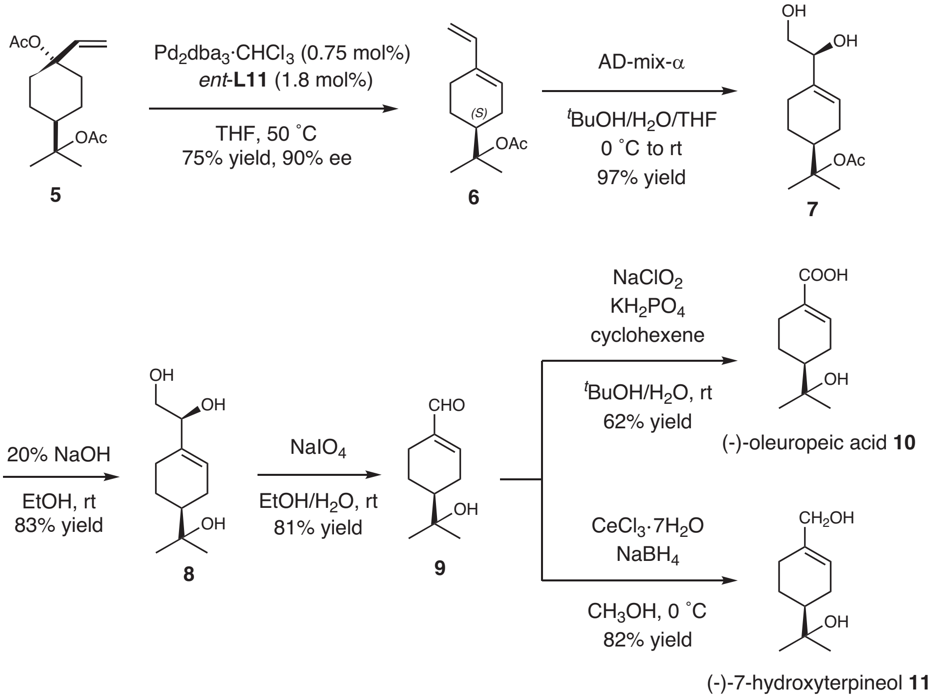


Fig. 4 | Total synthesis of (-)-oleuropeic acid and (-)-7-hydroxyterpineol. Starting material **5** was converted to **6** in 75% yield with 90% ee under the standard conditions. The latter **6** was then transformed into a common intermediate **9** with three steps. Selective oxidation or reduction of the aldehyde moiety of **9** produced (-)-oleuropeic acid **10** and (-)-7-hydroxyterpineol **11**, respectively.

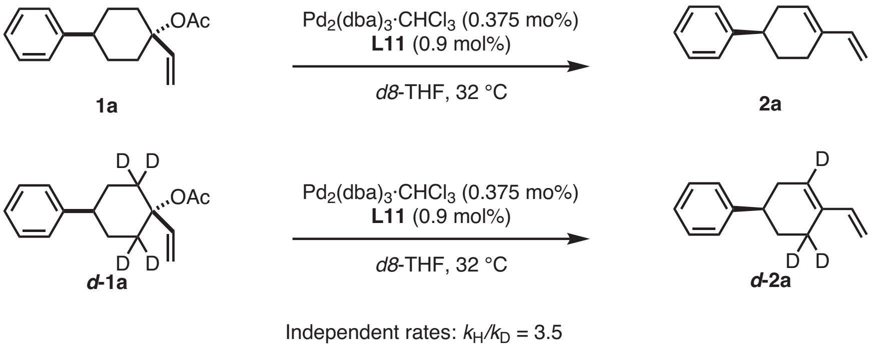


Fig. 5 | Kinetic isotope effect experiments. The reaction of **1a** or *d*-**1a** with 0.375 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 0.9 mol% **L11** in *d*8-THF at 32 °C was performed, and the initial reaction rate constants k_H and k_D were determined. The KIE values was calculated as k_H/k_D.

to total synthesis of (-)-oleuropeic acid and (-)-7-hydroxyterpineol was demonstrated (Fig. 4). Starting from substrate **5**, the enantioselective elimination reaction was conducted with 0.75 mol% $Pd_2(dba)_3{\cdot}CHCl_3$ and 1.8 mol% *ent*-**L11**, affording (*S*)-**6** in 75% yield with 90% ee. The terminal olefin moiety of (*S*)-**6** was dihydroxylated with AD-mix-α reagent to give **7**. Then removal of the acetate and cleavage of the dihydroxyl groups, giving aldehyde **9** in 67% combined yield. Finally, aldehyde **9** underwent the Pinnick oxidation or Luche reduction, furnishing (-)-oleuropeic acid and (-)-7-hydroxyterpineol, respectively.

Mechanistic Studies

The kinetic isotope effect (KIE) experiments were conducted to get insights into the reaction mechanism (Fig. 5). A comparison of the initial reaction rates of **1a** and the deuterated *d*-**1a** revealed a KIE value of 3.5, indicating the potential involvement of β-hydride elimination in the rate-limiting step[58].

Subsequently, DFT calculations were performed to elucidate the detailed mechanism (Fig. 6). The reaction commences with the allylic substitution of the acetate moiety by **L11**-Pd(0), forming the η^3-π-allyl-Pd intermediate **Int C**. The transition state for this step, **TS B**, was found to have an energy barrier of 14.3 kcal/mol. **Int C** then isomerizes to the η^1-allyl-Pd **Int D**, where the adjacent H atom acts as a σ-donor ligand to the Pd center. Subsequently, β-hydride elimination occurs via the transition state **TS E**, giving rise to the observed product (*R*)-**2a** and forming the palladium-hydride species **Int F**. Finally, **Int F** undergoes a rapid reductive elimination through a five-membered transition state **TS G**, regenerating the Pd(0) catalyst **Int A** along with one molecule of HOAc. The overall energy profile confirms that the rate-limiting step is the β-hydride elimination, consistent with the findings from the KIE experiments. We also calculated the pathway to generate the (*S*)-**2a** (indicated in red in Fig. 6). The corresponding transition state of β-hydride elimination for (*S*)-**2a** was located as **TS E′**, which is 5.2 kcal/mol disfavored comparing with **TS E**. These results suggest that (*R*)-**2a** would be the dominant product, consistent with the experimental results.

The IGMH analysis[59] revealed that attractive van der Waals interactions occur between the amide moiety of the ligand and the benzene

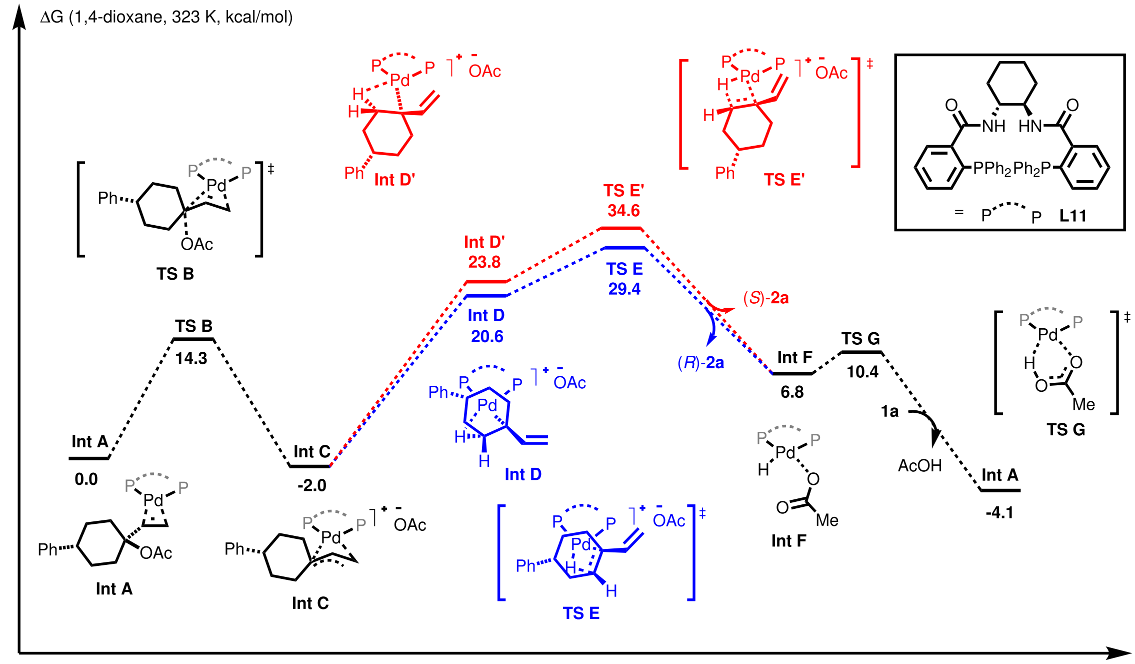


Fig. 6 | DFT calculations. Calculation method: M06(SMD)/SDD(Pd)/6-311 + G(d,p)//B3LYP(D3)/SDD(Pd)/6-311 G(d).

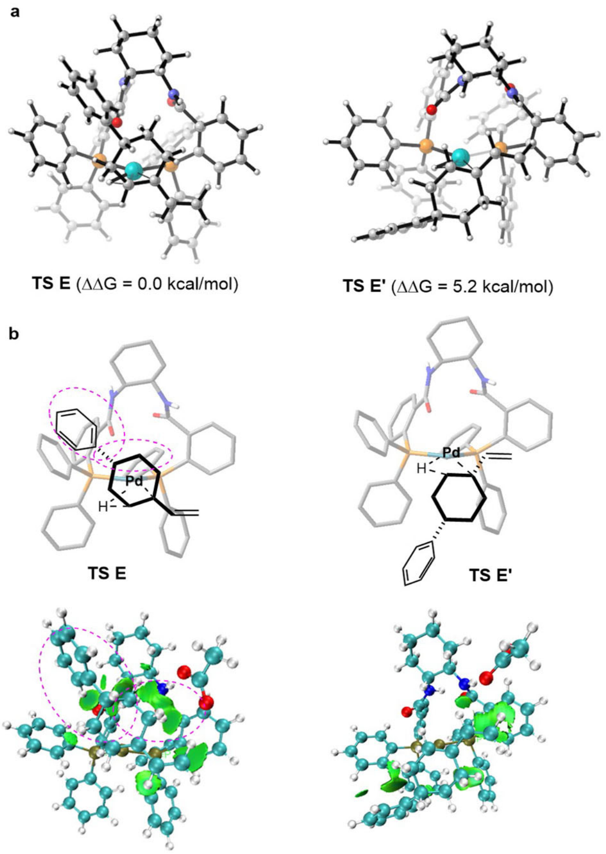


Fig. 7 | Origin of the stereoselectivity. a Calculated transition states **TS E** and **TS E′** for β-H elimination step that form (*R*)-**2a** and (*S*)-**2a**, respectively. **b** Non-covalent interaction analysis with IGMH. The acetate counter anion in **TS E** and **TS E′** was omitted for clarity.

and cyclohexane moieties of the substrate in the transition state **TS E** (Fig. 7). To investigate these weak interactions between the ligand and substrate, energy decomposition analysis (EDA) was performed (Fig. 8). The EDA analysis showed that there was more steric repulsion ($\Delta\Delta E_{\text{exchange}} = 0.95$ kcal/mol) and less dispersion effects ($\Delta\Delta E_{\text{dispersion}} = 0.98$ kcal/mol) between the ligand and substrate in **TS E** as compared to **TS E′**. However, the electrostatics ($\Delta\Delta E_{\text{electrostatics}} = -3.03$ kcal/mol) and induction ($\Delta\Delta E_{\text{induction}} = -1.55$ kcal/mol) compensated for the steric repulsion and resulted in additional non-covalent stabilization energy in **TS E** ($\Delta\Delta E_{\text{total}} = -2.64$ kcal/mol).

In summary, we have developed a palladium-catalyzed enantioselective desymmetric β-hydride elimination from π-allyl-Pd for the construction of remote stereocenters. This transformation features low catalyst loading, base-free conditions, and wide functional group tolerance. A series of 1,3-dienes bearing a C4-chiral center were synthesized efficiently from 1-vinylcyclohexyl acetates. Synthetic application of this method to the total synthesis of (-)-oleuropeic acid and (-)-7-hydroxyterpineol was demonstrated. DFT calculations indicated that the β-hydride elimination is both a rate-limiting and enantioselectivity-determining step. The non-covalent interactions between the chiral ligand and substrate play a key role in stereocontrol.

Methods

General procedure for Pd catalyzed β-H elimination

In an Ar-filled glove box, (*R*,*R*)-DACH-phenyl Trost ligand **L11** (2.5 mg, 0.0036 mmol, 1.8 mol%) and $Pd_2dba_3 \cdot CHCl_3$ (1.6 mg, 0.0015 mmol, 0.75 mol%) were dissolved in dry 1,4-dioxane (0.4 M, 0.5 mL) to stir at room temperature for 1 h. To the solution, substrate (0.2 mmol) was added. The resulting mixture was stirred at 50 °C for 12 h. The mixture was then purified by silica gel column chromatography to give the desired product.

Data availability

The authors declare that the data supporting the findings of this study are available within the article and its Supplementary Information Files

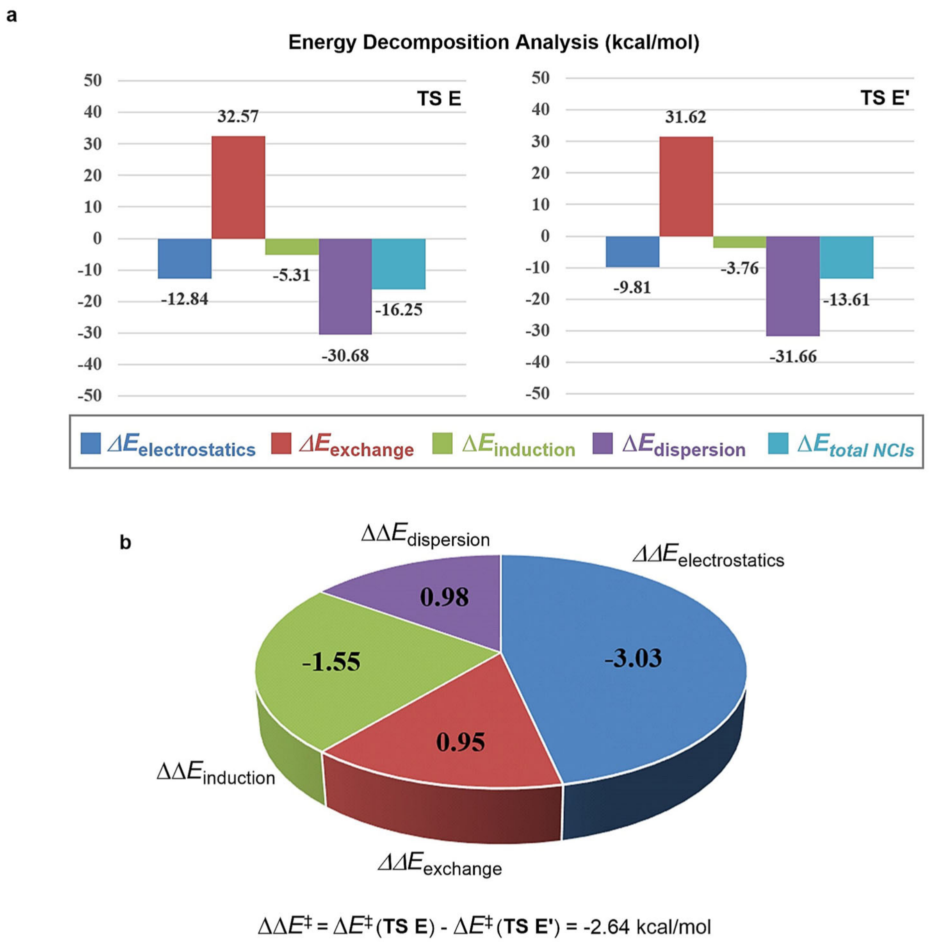


Fig. 8 | Rationalization of the stereochemistry. a Studies of the non-covalent interactions between the ligand and substrate by energy decomposition analysis. The EDA was performed with density-fitted sSAPT0 using the SAPT module (with jun-cc-pVDZ basis set) in the PSI4 package. **b** The $\Delta\Delta E_{dispersion}$, $\Delta\Delta E_{electrostatics}$, $\Delta\Delta E_{induction}$, and $\Delta\Delta E_{exchange}$ between **TS E** and **TS E′**.

(including experimental details, NMR data, HPLC and NMR spectrums) and Supplementary Data 1 (DFT calculated Cartesian coordinates), as well as from the corresponding author on request. The X-ray crystallographic coordinates for the structure reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC 2306164 for **2d**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc. cam.ac.uk/data_request/cif.

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Author contributions

W.Z. conceived the concept and directed the project, conducted the DFT calculations, and wrote the paper with feedback from all other authors. Shaozi Sun made the initial discovery, performed the optimization, and explored the substrate scope. Shaozi Sun and Shengnan Sun conducted the preparation of the starting materials.

Competing interests

The authors declare no competing interests.

Additional information

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