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Palladium-catalysed Tsuji–Trost-type vinyl epoxide cross-coupling with umpolung hydrazones†

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Selective functionalisation of synthetically useful vinyl epoxides *via* carbon–carbon (C–C) bond formation has been a major challenge for many years due to its unique inherent chemical reactivity. Non-stabilised carbanions in the form of organometallic reagents have been shown to be robust and versatile reagents in C–C bond formation; however, they are employed in superstoichiometric quantities, require the protection of active functional groups, and generate copious amounts of metallic waste. Therefore, the development of mild carbanion sources as simple alternatives is highly desired. In this work, we report a highly chemo- and regioselective palladium-catalysed vinyl epoxide cross-coupling utilising hydrazones as organometallic equivalents (HOME). Hydrazones, generated from carbonyl-containing renewable feedstocks, enable a more sustainable reaction, and provide an alternative to highly reactive and sensitive unstabilized organometallic reagents. A broad substrate scope, with high functional group tolerance, is demonstrated along with the late-stage functionalisation of natural product derivatives.

Introduction

Characterised by a C–C double bond adjacent to an oxirane ring, vinyl epoxides have been recognised as a crucial building block in a diverse array of reactions.¹ Vinyl epoxides exhibit unique reactivity, often acting as potent electrophiles^{2–4} and radical acceptors,⁵ and serve as substrates in sigmatropic rearrangements,⁶ showcasing their versatility in various synthetic transformations. With three different electrophilic sites, these substrates can be readily transformed into synthetically useful linear allylic or branched homoallylic alcohols *via* S_N2' (1,4-addition) and S_N2-type (1,2-addition) ring openings. Over the past few decades, various studies have employed numerous unstabilized carbon nucleophiles for vinyl epoxide functionalisation.^{1,7–10} Despite these efforts, many alkylation methodologies frequently yielded mixtures of S_N2 and S_N2' products,^{7,10,11} and site-selective alkylation of vinyl epoxides has proven to be difficult. Owing to the inherent steric interactions between the alkyl carbanion and the vinyl epoxide, S_N2' alkylation onto the least hindered alkenyl terminus is typically observed, while exclusive S_N2 alkylation is uncommon.

The development of transition metal catalysis provides a venue for the regioselective alkylation of vinyl epoxides. Since its discovery in 1973, the palladium-catalysed Tsuji–Trost allylation has been a cornerstone for allylic alkylations.^{12,13} Enhanced with the introduction of chiral ligands,¹⁴ this reaction

has been demonstrated to be a powerful tool in crafting intricate, chiral molecules.^{15–17} With structural similarities shared between vinyl epoxides and allyl acetates, Trost and his colleagues broadened the scope to encompass the alkylation of vinyl epoxides in 1981.¹⁸ Non-stabilised alkyl carbanions, such as Grignard, organolithium, organozincate and organostannane reagents, have been shown to be robust and versatile nucleophiles in the generation of new C–C bonds with vinyl epoxides (Fig. 1A).^{19–22} Nevertheless, limitations are presented in these methodologies, as they employ highly reactive and air/moisture-sensitive reagents with low chemoselectivity, often requiring handling under inert conditions during preparation and use. Organometallic reagents also generate stoichiometric amounts of toxic metallic waste and show a high dependence on alkyl halide precursors from non-renewable petroleum feedstocks. The use of non-renewable carbon resources does not provide a route for sustainable chemistry, and therefore, the development of alternatives to organometallic reagents is highly desired.

Carbonyl-derived pronucleophiles in conjunction with palladium catalysis have recently been reported to display selectivity towards S_N2-type vinyl epoxide openings (Fig. 1B). Conventionally, malonate substrates are utilised as stabilised nucleophiles,¹⁸ but recently, this field has expanded to include enolates derived from pre-functionalised esters.^{23,24} In 2021, Lundgren and his coworkers reported a Pd-catalysed benzylolation of isoprene with 2,2,2-trifluoroethyl (hetero)arylacetae ester enolates to generate lactone intermediates that were subjected to subsequent hydrolysis and decarboxylation to form the branched homoallylic alcohol.²⁵ These 2-alkyl-β-γ-unsaturated alcohol products also possess high synthetic value, as

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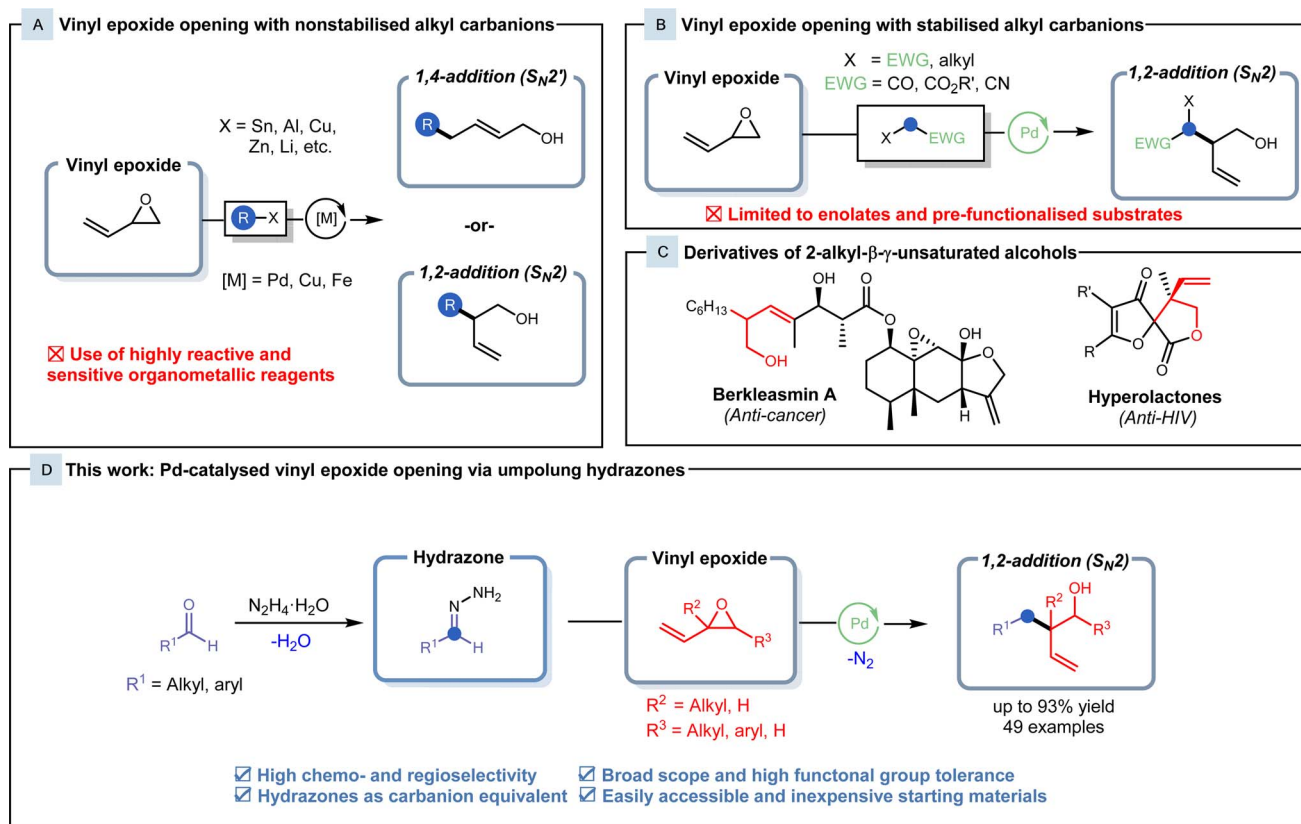


Fig. 1 (A) Known methods in metal-catalysed vinyl epoxide opening with non-stabilised alkyl carbanions. (B) Recent reports on Pd-catalysed $\text{S}_{\text{N}}2'$ -type vinyl epoxide opening with stabilised alkyl carbanions. (C) Bio-active natural products containing 2-alkyl- β - γ -unsaturated alcohol motifs. (D) This work: regioselective synthesis of 2-alkyl- β - γ -unsaturated alcohols via Pd-catalysed Tsuji–Trost type vinyl epoxide opening with HOME chemistry.

their derivatives appear as core motifs of various natural products and bio-active compounds, such as berkleasmins and hyperolactones (Fig. 1C).^{26,27} Although these methods provide highly efficient routes for the synthesis of these branched homoallylic alcohols, pre-functionalised and commercially unavailable starting materials hinder the applicability of these methods.

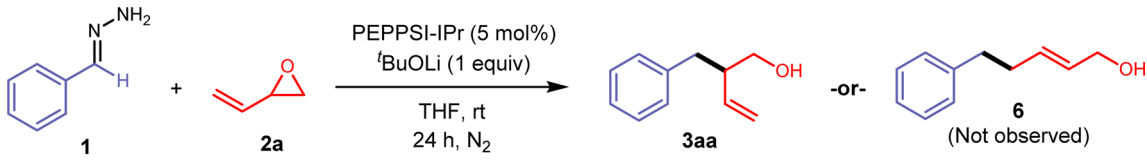
Hydrazones generated from inexpensive, naturally occurring carbonyls can serve as alkyl carbanion equivalents and undergo various reactions with carbon electrophiles.^{28,29} In our research group, we have been extensively developing this methodology and exploring the use of hydrazones as organometallic equivalents (HOME) in classical nucleophilic addition and cross-coupling reactions.²⁸ This Umpolung strategy allows for efficient transformations under mild conditions comparable to classical organometallic reagents, with the benefit of generating nitrogen gas and water as inert byproducts. Hydrazones also exhibit lower basicity and reactivity along with air/moisture stability in comparison to organometallic reagents, allowing for safer handling. Herein, we report the palladium-catalysed cross-coupling of vinyl epoxides with hydrazones as alkyl organometallic reagent surrogates to generate branched homoallylic alcohols with high regio- and chemoselectivity (Fig. 1D).

Results and discussion

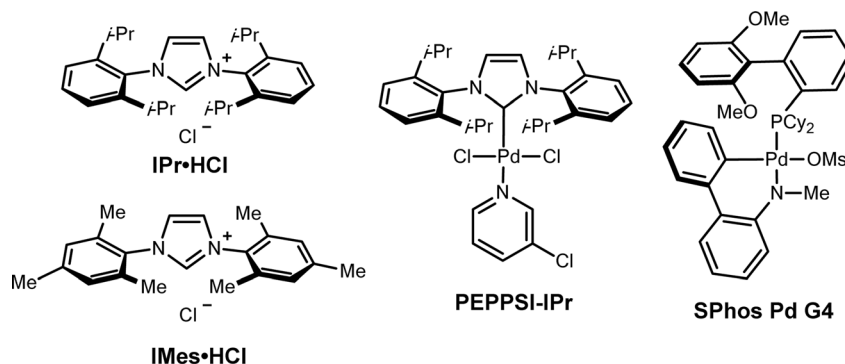
We began our investigation with the cross-coupling of benzaldehyde hydrazone **1a** (1.25 equiv) with vinyl epoxide (0.23 mmol) **2a** using a Pd(0)/triphenylphosphine catalyst system (Table 1) with lithium *tert*-butoxide (2 equiv) as the base. Under these conditions, we primarily observed a C-alkylated product, and *N*-alkylated products were not detected. Only racemic branched homoallylic alcohol **3a** was observed in 29% yield and the linear allylic alcohol product **6** was not detected (entry 2). We hypothesised that only one equivalent of the base was required for the transformation, as the alkoxy-intermediate generated from the vinyl epoxide ring opening potentially acts as an equivalent of base to facilitate the deprotonation of the hydrazone (see ESI Fig. S1†). Vinyl epoxides are also known to undergo reactions and rearrangements in the presence of Lewis acids.^{6,30} While palladium is the catalyst for our system, it could also potentially act as a Lewis acid. This theory was validated through a control experiment with 1 equivalent of PEPPSI-IPr, where **3a** was not detected and we primarily observed decomposition of **2a**. With these results, a lower Pd catalyst loading of 5% and 1 equivalent of base gave higher yields. Any further decrease of the Pd loading and base diminished the yield. *N*-heterocyclic carbene (NHC) ligands were previously reported to



Table 1 Reaction optimisation for the Pd-catalysed vinyl epoxide opening with hydrazones



Entry	Deviation from standard conditions ^a	3aa (yield%)
1	None	90
2	Pd ₂ (dba) ₃ (5 mol%), PPh ₃ (10 mol%), 2 equiv ^t BuOLi, 45 °C	29
3	Pd ₂ (dba) ₃ (2.5 mol%), IMes HCl (5 mol%)	19
4	Pd ₂ (dba) ₃ (2.5 mol%), IPr HCl (5 mol%)	36
5	[Pd(allyl)Cl] ₂ (2.5 mol%), IPr HCl (5 mol%)	48
6	SPhos Pd G4 (5 mol%)	58
7	Cs ₂ CO ₃ instead of ^t BuOLi	82
8	K ₂ CO ₃ instead of ^t BuOLi	24
9	DBU instead of ^t BuOLi	n.d.
10	45 °C	64
11	Dioxane instead of THF	84
12	Toluene instead of THF	78
13	No base	n.d.
14	No catalyst	n.d.
15	Under air	69



^a Standard conditions: benzaldehyde hydrazone, **1a** (0.28 mmol, 1.25 equiv), vinyl epoxide, **2a** (0.23 mmol), PEPPSI-IPr (5 mol%), and ^tBuOLi (0.23 mmol, 1 equiv) in 1.5 mL THF for 24 h at room temperature under N₂. Yields were determined by ¹H NMR with 1,3,5-trimethoxybenzene as an internal standard.

be an efficient ligand for the Pd-catalysed C-allylations of hydrazones.^{31,32} Electron-rich, bulky NHC ligands such as 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (IMes HCl) and 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr HCl) were tested in combination with Pd₂(dba)₃ and afforded **3aa** with yields of 19% (entry 3) and 36% (entry 4). A pre-ligated IPr (PEPPSI-IPr) was very efficient in this transformation and gave **3aa** in a 90% yield (entry 1). Other *tert*-butoxide salts, organic bases (1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5,7-triazabicyclo(4.4.0)dec-5-ene (TBD)), and lithium salt bases were screened but all gave reduced yields (entries 8 and 9, see ESI Table S2[†]). Cs₂CO₃ was the only other base that gave **3aa** with a high yield of 82% (entry 7). Finally, various solvents such as 2-MeTHF, dioxane, toluene, and DMF were screened, but THF remained as the best solvent for this reaction (see ESI Table S3[†]). Control experiments show that no homoallylic alcohol **3aa** was produced in the absence of a Pd catalyst and base.

Substrate scope

With our optimised conditions for the cross-coupling of hydrazone **1aa** and vinyl epoxide **2a**, we proceeded to our substrate scope. Various substituted benzaldehyde hydrazones were explored (Fig. 2A). Initially, we observed complete conversion with benzaldehyde hydrazone **1aa** and **2a** within 24 hours, but incomplete conversion for *para*-substituted benzaldehyde hydrazones and polyaromatic hydrazones was observed. Lithium *tert*-butoxide was increased to 1.5 equivalents and a reaction time of 36 h was employed to ensure complete conversion and to improve reproducibility of the procedure (See ESI Table S4[†]). In some cases, the product was unable to be separated from the *tert*-butanol side-product, therefore cesium carbonate (1.25 equiv) was used instead of lithium *tert*-butoxide. In general, hydrazones with various substituents and substitution patterns gave moderate to excellent yields. Aryl hydrazones



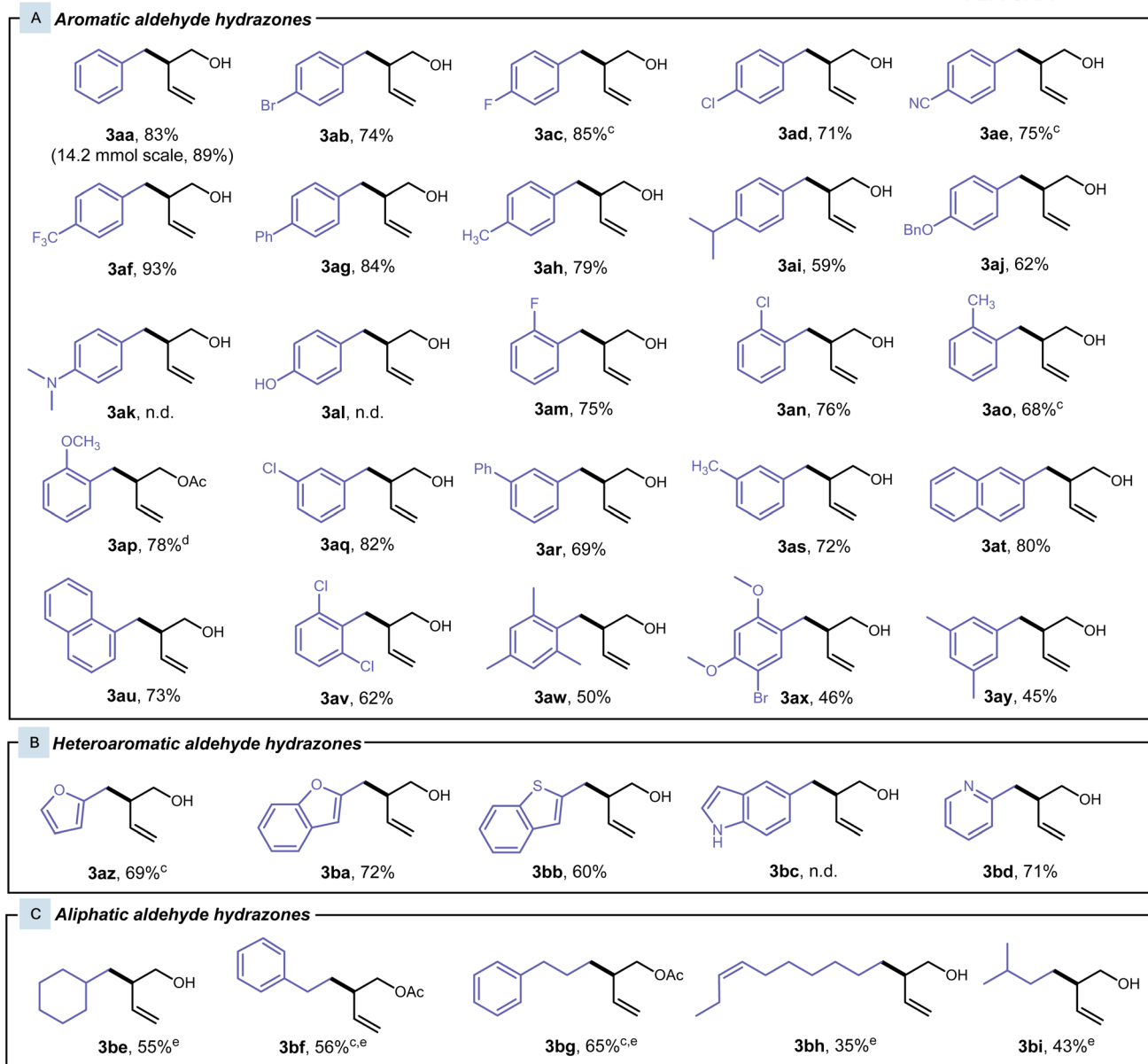
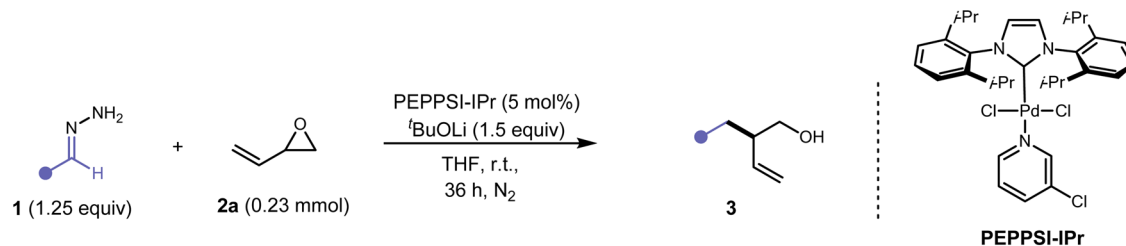


Fig. 2 Aldehyde hydrazone substrate scope.^{a,b} (a) Reaction conditions: Hydrazone **1** (0.28 mmol, 1.25 equiv), vinyl epoxide **2a** (0.23 mmol), PEPPSI-IPr (5 mol%), and ^tBuOLi (0.34 mmol, 1.5 equiv) in 1.5 mL THF at room temperature for 36 h under N₂. (b) Yields of isolated products. (c) Hydrazone **1** (0.28 mmol, 1.25 equiv), vinyl epoxide **2a** (0.23 mmol), PEPPSI-IPr (5 mol%), and Cs₂CO₃ (0.28 mmol, 1.25 equiv) in 1.5 mL THF at room temperature for 36 h under N₂. (d) Acetylation conditions: crude compound (purified with a silica plug), Ac₂O (500 μL), and pyridine (500 μL) at room temperature overnight. (e) Hydrazone **1** (0.45 mmol, 2 equiv), vinyl epoxide **2a** (0.23 mmol), PEPPSI-IPr (5 mol%), FeCl₃ (10 mol%) and ^tBuOLi (0.34 mmol, 1.5 equiv), in 1.5 mL THF at 45 °C for 24 h under N₂.

containing halogens, heteroatoms, and polyaromatic systems worked well under our conditions and this reaction exhibited excellent functional group tolerance. *Para*-substituted benzaldehyde hydrazones were first investigated. Hydrazones bearing

electron-withdrawing groups, such as fluoro-, bromo-, chloro-, trifluoromethyl-, cyano- and phenyl-, at this position gave desired products **3ab–3ag** at high yields of 71–93%. With electron-donating groups in the *para*-position, in the case of



methyl-, isopropyl-, and benzyloxy-benzaldehyde hydrazones, the yield of the desired product **3ah–3aj** had slightly diminished (59–79%). This is due to an electronic effect, where the electron-donating group destabilises the carbanion formed at the benzylic position. In the case of **3ak**, **3al**, and **3bc**, the strong electron-donating group did not favour the formation of the carbanion, and we did not observe any desired product. Only the aryl hydrazone starting material was observed and recovered. Electron-donating and electron-withdrawing *ortho*-substituted benzaldehyde hydrazones also performed well in these conditions, giving desired products **3am–3ap** in 68–78% yield. Regarding **3ap**, the pre-coordination of the methoxy-

group onto the Pd catalyst could direct the hydrazone coordination to the Pd catalyst after deprotonation, leading to an increased yield compared to the other cases with electron-donating groups in the *ortho*-position. *Meta*-substituted benzaldehyde hydrazones were also investigated and gave desired products **3aq–3as** in moderately high yields of 69–82%. 1- and 2-Naphthaldehyde hydrazones proved to be effective substrates, giving the desired products **3au** and **3at** in high yields of 80% and 73%, respectively. Multiply-substituted benzaldehyde hydrazones worked well to yield alcohols **3av–3ay** in moderate yields of 45–62%, where the steric hindrance and electron-donating properties of the *ortho*-substituents hinder the yield.

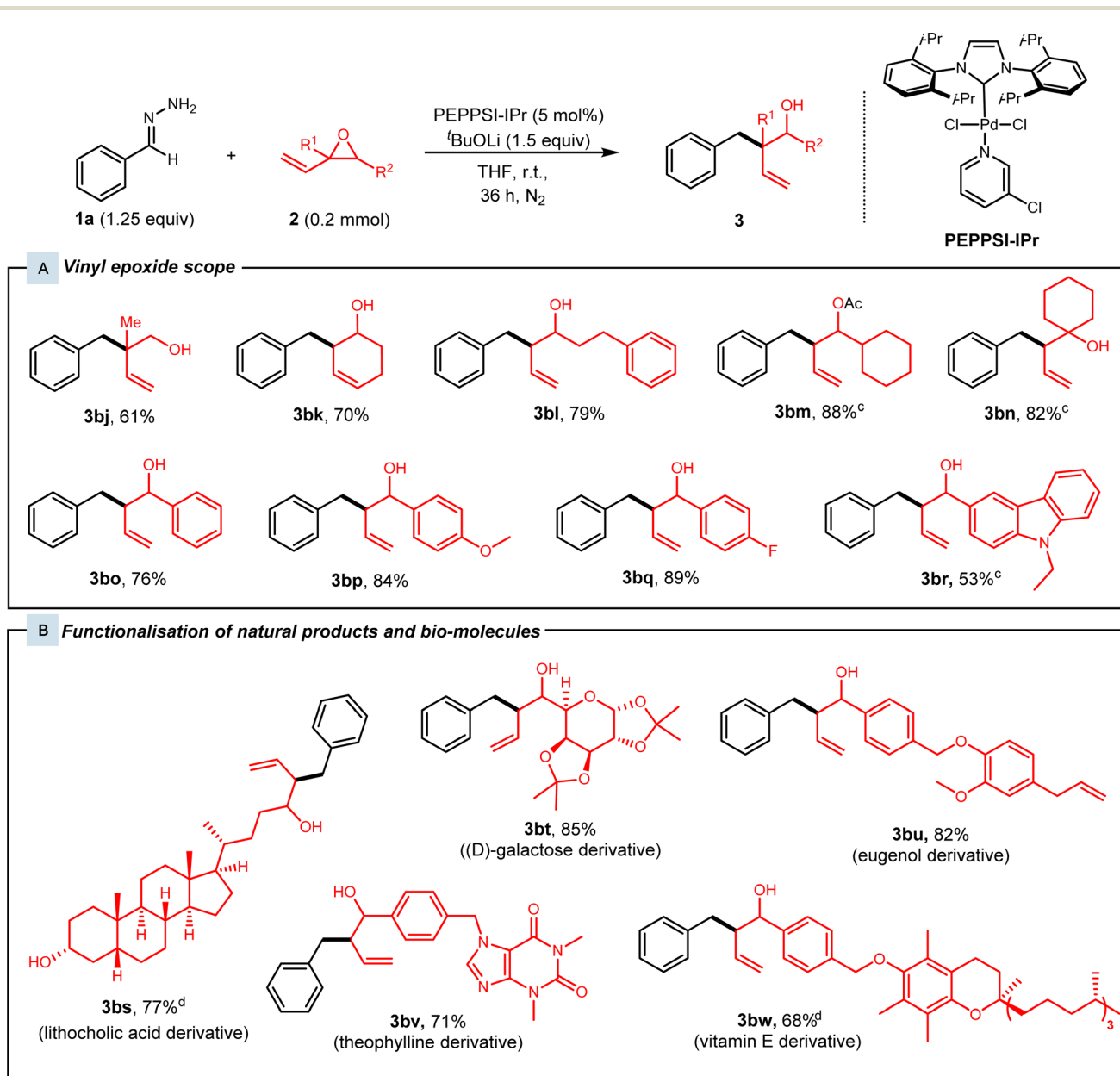


Fig. 3 Vinyl epoxide substrate scope.^{a,b} (a) Reaction conditions: Hydrazone **1** (0.25 mmol, 1.25 equiv), vinyl epoxide **2** (0.2 mmol), PEPPSI-IPr (5 mol%), and ^tBuOLi (0.38 mmol, 1.5 equiv) in 1.5 mL THF at room temperature for 36 h under N₂. (b) Yields of isolated products. (c) Reaction conditions: Hydrazone **1** (0.20 mmol), vinyl epoxide **2** (0.25 mmol, 1.25 mmol), PEPPSI-IPr (5 mol%), and ^tBuOLi (0.38 mmol, 1.5 equiv) in 1.5 mL THF at room temperature for 36 h under N₂. (d) 0.15 mmol vinyl epoxide.



Heteroaryl aldehyde hydrazones were also well tolerated (Fig. 2B), and moderately high yields of 60–71% were achieved for branched homoallylic alcohols **3az–3bd**.

We then shifted our focus to aliphatic aldehyde hydrazones (Fig. 2C), since generating carbanions from aliphatic aldehyde hydrazones presents a greater challenge. Without a neighbouring aromatic group, resonance stability of the carbanion is absent, and these hydrazones tend to react with themselves to form their inactive azine counterpart at an increased rate. Our initial optimised conditions showed low yields, and the reaction was reoptimized (See ESI Table S5† for more details). A Lewis acid catalyst (10 mol% FeCl₃) was added to increase the reactivity of the vinyl epoxide, while the reaction was heated at 50 °C for 24 h to accelerate the reaction and to out-compete the azine side reaction. We were able to achieve the desired products **3be–3bi** from cyclohexanecarboxaldehyde, 3-phenylpropionaldehyde, phenylacetaldehyde, *cis*-dec-7-enal, and isovaleraldehyde hydrazones in low to moderate yields of 35–65%, where the stability of the hydrazone mainly dictated the yield. Acetophenone-derived hydrazones were also subjected to the standard conditions and these modified conditions. However, only trace amounts of product were able to be detected by GCMS. This could be attributed to the added steric bulk about the benzylic position of the generated carbanion.

Subsequently, various substituted vinyl epoxides were then investigated (Fig. 3). Alkyl-substituted vinyl epoxides afforded the desired products **3bj–3bn** in high yields of 61–88%. Next, benzaldehyde-derived vinyl epoxides present as a mixture of diastereomers were subjected to our protocol, and high yields of 76–89% were achieved for racemic alcohols **3bo–3bq**. We also

tested our conditions with a heteroaryl-substituted vinyl epoxide, which gave **3br** in 53% yield.

With the high functional group tolerance and efficiency of this protocol, we then turned our attention to the late-stage derivatisation of natural products (Fig. 3B). Vinyl epoxides synthesised from various natural product derivatives were subjected to standard conditions. Lithocholic acid and (D)-galactose-derived vinyl epoxides were superior substrates as they afforded the branched homoallylic alcohols **3bs** and **3bt** in yields of 77% and 85% respectively. Alkaloids such as theophylline-derived vinyl epoxide **2m** were tested with our conditions and alcohol **3bv** was achieved with 71% yield. Lastly, eugenol and vitamin E-derived vinyl epoxides **2n** and **2o** reacted smoothly under our catalytic system and gave alcohols **3bu** and **3bw** in 82% and 68% yield.

Mechanistic investigation

Several control experiments were performed to gain preliminary insight into the reaction mechanism (see the ESI† for more details). We first investigated the participation of the alkoxy-intermediate in our reaction. In previous literature, it was theorised that the alkoxy-intermediate deprotonates the nucleophile which directs the 1,2-addition onto the vinyl epoxide.³³ In the absence of base, no reaction occurred between **1** and **2a** (Fig. 4A). When 10 mol% base was employed, **3aa** was only observed in 10% yield. These results suggest that the added base performs the initial deprotonation step to form a 2,3-diazaallyl anion. Otherwise, we would expect an adduct of the hydrazone and the vinyl epoxide if the alkoxy-intermediate

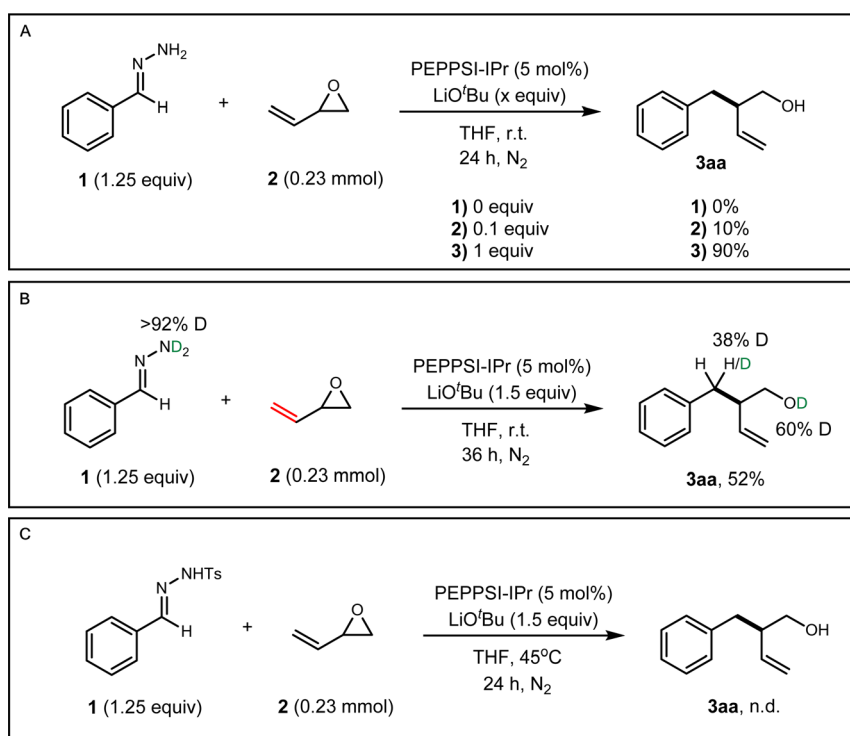


Fig. 4 Mechanistic studies. (A) Base control studies. (B) Deuterium labelling studies. (C) Carbene mechanism probe experiment.



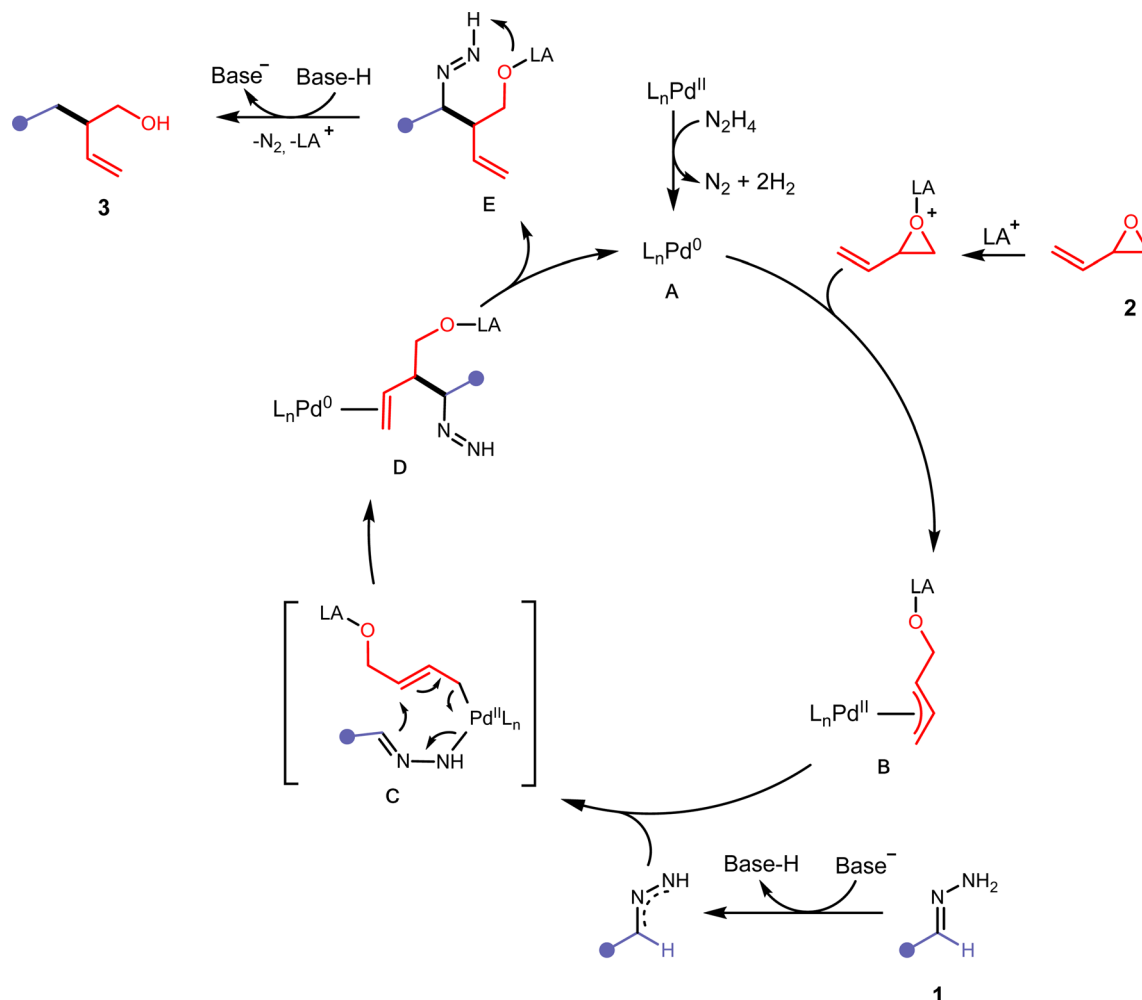


Fig. 5 Proposed mechanism for the Pd-catalysed cross-coupling of hydrazones and vinyl epoxides.

performs the first deprotonation of the hydrazone. Subsequently, we performed deuterium isotope experiments. Deuterated benzaldehyde hydrazone **1** was subjected to our protocol and we observed deuteration of both the benzylic position (38% **D**) and the alcohol (60% **D**) of **3aa** (Fig. 4B). Deuteration of the alcohol is evidence that the alkoxy-intermediate participates in one deprotonation step. We then subjected vinyl epoxide **2a** with *N*-tosyl benzaldehyde hydrazone, a common carbene precursor. No reaction occurred, which deemed a carbene mechanism to be implausible and the reaction likely proceeds through a two-electron pathway (Fig. 4C). The high regioselectivity could be attributed to a 3,3'-elimination step analogous to diallylpalladium complexes in the work of Morken and coworkers (See ESI Fig. S2†).^{34,35}

Based on the previously described experimental observations, and preceding literature in similarly operating catalytic systems,^{31,34–36} we have proposed the following mechanism (Fig. 5). Initially, the Pd(II) pre-catalyst is activated with residual hydrazine in the reaction mixture leading to the IPr-Pd(0) active catalyst **A**. Hydrazine has been shown to reduce Pd(II) to Pd(0) efficiently.³⁷ **A** then undergoes oxidative addition with an activated vinyl epoxide **2** to form the π -allylpalladium complex **B**.

Deprotonation of the hydrazone **1** with ^tBuOLi would allow the formation of a 2,3-diazaallyl anion, which then coordinates to **B** and forms **C**. A 3,3'-elimination would occur, leading to **D** in a regioselective manner. After ligand dissociation to reform active catalyst **A**, intermediate **E** undergoes intramolecular deprotonation and releases nitrogen with the assistance of a protonated base to form compound **3**.

Conclusions

In summary, we have developed a regioselective and high-yielding Pd-catalysed method for the synthesis of 2-alkyl- β - γ -unsaturated alcohols utilising vinyl epoxides and Umpolung hydrazones. Highlights of this methodology include the efficient transformation of various substituted aryl/alkyl aldehyde-derived hydrazones and substituted vinyl epoxides. A broad substrate scope, high functional group tolerance, and late-stage modification of complex, diverse molecules demonstrate its synthetic utility. HOME chemistry provides a sustainable route for the functionalisation of vinyl epoxides with the deployment of carbonyl precursors as mild carbanion sources, and the absence of alkyl halides or external organometallic reagents.



Our laboratory is currently conducting further research on the mechanism and exploring an asymmetric variant of this reaction.

Data availability

All experimental procedures, mechanistic investigations, and characterisation data of all synthesised compounds are available in the ESI.†

Author contributions

EC and CJL conceptualised the idea of this work. EC designed and conducted experiments for the optimisation and scope, and wrote the manuscript. CJL provided general guidance, project direction and manuscript revision.

Conflicts of interest

The authors declare no conflict of interest.

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