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Mechanism-based enhancement of scope and enantioselectivity for reactions involving a copper-substituted stereogenic carbon centre

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A rapidly emerging set of catalytic reactions involves intermediates that contain a copper-substituted stereogenic carbon centre. Here, we demonstrate that an intimate understanding of this distinction provides ways for addressing limitations in reaction scope and explaining why unexpected variations in enantioselectivity often occur. By using catalytic enantioselective Cu–boryl addition to alkenes as the model process, we elucidate several key mechanistic principles. We show that higher electrophile concentration can lead to elevated enantioselectivity. This is because diastereoselective Cu–H elimination may be avoided and/or achiral Cu–boryl intermediates can be converted to allyl–B(pin) rather than add to an alkene. We illustrate that lower alkene amounts and/or higher chiral ligand concentration can minimize the deleterious influence of achiral Cu–alkyl species, resulting in improved enantiomeric ratios. Moreover, and surprisingly, we find that enantioselectivities are higher with the less reactive allylphenyl carbonates as chemoselective copper–hydride elimination is faster with an achiral Cu-alkyl species.

An early case of a transformation that proceeds via a compound that bears a Cu-substituted stereogenic centre entails addition of a Cu–B(pin) (pin, pinacolato) complex to an (*E*)-β-alkylstyrene (Fig. 1). The resulting Cu-alkyl species (**i**) then reacts with MeOH or MeOD *in situ* to give products in >98% e.e. (>98:2 e.r.) and d.r., respectively[1]. In such processes, the final e.e. depends on how stereoselectively an organometallic species is formed and by what mechanism the electrophile is trapped. Another example involves a chiral Cu complex along with an achiral bis-phosphine–Pd co-catalyst and an allyl carbonate (via **ii**, Fig. 1)[2]. Generally, additions to aliphatic olefins are less efficient, but aryl and heteroaryl olefins or alkenyl boronates[3] and silanes[4] are suitable and Cu–C and/or C–B(pin) bonds can be functionalized further. Reactions that begin with enantioselective Cu–H addition (via **iii**)[5] are a notable subset.

Despite numerous reports and advances, key shortcomings persist. In the disclosure corresponding to the two-catalyst protocol[2] there is no mention of allyl–boron additions to electron-rich aryl alkenes or those involving more hindered (for example, 2-substituted) electrophiles. Furthermore, enantioselective Cu–B(pin) or Cu–H additions with electron-deficient aryl olefins are either not mentioned[6–10] or are found to be less enantioselective[11–14] (for example, halo-, trifluoromethyl- or ester-substituted). It is unclear why enantioselectivity is lower with some substrates or at times depends on electrophile identity, despite the fact that the Cu–B(pin)/Cu–H addition step is stereochemistry-determining (for example, 94% e.e. compared to 76% e.e., Fig. 1).

Electronic effects are central in these matters. Addition of a Cu–B(pin) or Cu–H complex to an electron-deficient alkene is faster[1,15], but the resulting Cu-alkyl compound is probably less nucleophilic. Conversely, an electron-rich olefin probably generates a more reactive Cu-alkyl species slowly. It has been surmised[11] that some kinetic enantioselectivity might be lost if an organocopper intermediate were to react slowly, whereas rapid trapping, for example with higher electrophile concentration, could improve e.e. The central question, then, is exactly how does the enantiomeric purity of a Cu-alkyl intermediate erode, and is the dearth of examples with strongly electron-rich and electron-deficient alkenes tied to these issues?

Results

We chose an enantioselective allyl–boron addition that would be promoted by a single Cu-based complex (that is, no Pd-based co-catalyst) as the platform for this investigation. The lure of avoiding a precious metal notwithstanding, comparison of the one- versus two-catalyst approach would be more informative (for example, does a co-catalyst help minimize enantioselectivity fluctuation?); the study would offer additional relevant data vis-à-vis Cu–H-catalysed reactions[16], which are also facilitated by a single catalyst.

Efficient one-catalyst process. We used the transformation shown in entry 1, column A, Table 1, to identify an appropriate chiral catalyst. NHC ligands and most phosphines were ineffective (for example, <10% yield with **L1** or **L2**, Fig. 1; see Supplementary Section 4 for details). The exceptions were **L3a** and **L3b**[17], the use of which led to the formation of **2a** in 90% and 88% e.e., respectively. Although, in this particular instance, the e.e. was slightly lower compared to when the Cu/Pd regime[2] was adopted (90% compared to 95% e.e.), this is a useful selectivity level, ligand loading was less (total of 5.5 mol% as opposed to 17 mol%) and room temperature sufficed (rather than 0 °C). Still, our main goal was to expand the scope of the method through a stronger appreciation of the mechanistic details.

Electronic properties of alkenes and e.e. Organoboron products were in most instances obtained in ≥55% yield and ≥90% e.e. (Table 1; for additional examples see Supplementary Section 6). As expected, there were several shortcomings. (1) Reactions with electron-deficient olefins were much less enantioselective. *ortho*-Trifluoromethyl **2d** (entry 4, column A) and *meta*-carboxylic ester styrene **2g** (entry 7, column A) were formed in 66% and 64% e.e., respectively and *para*-ester- and trifluoromethyl-substituted

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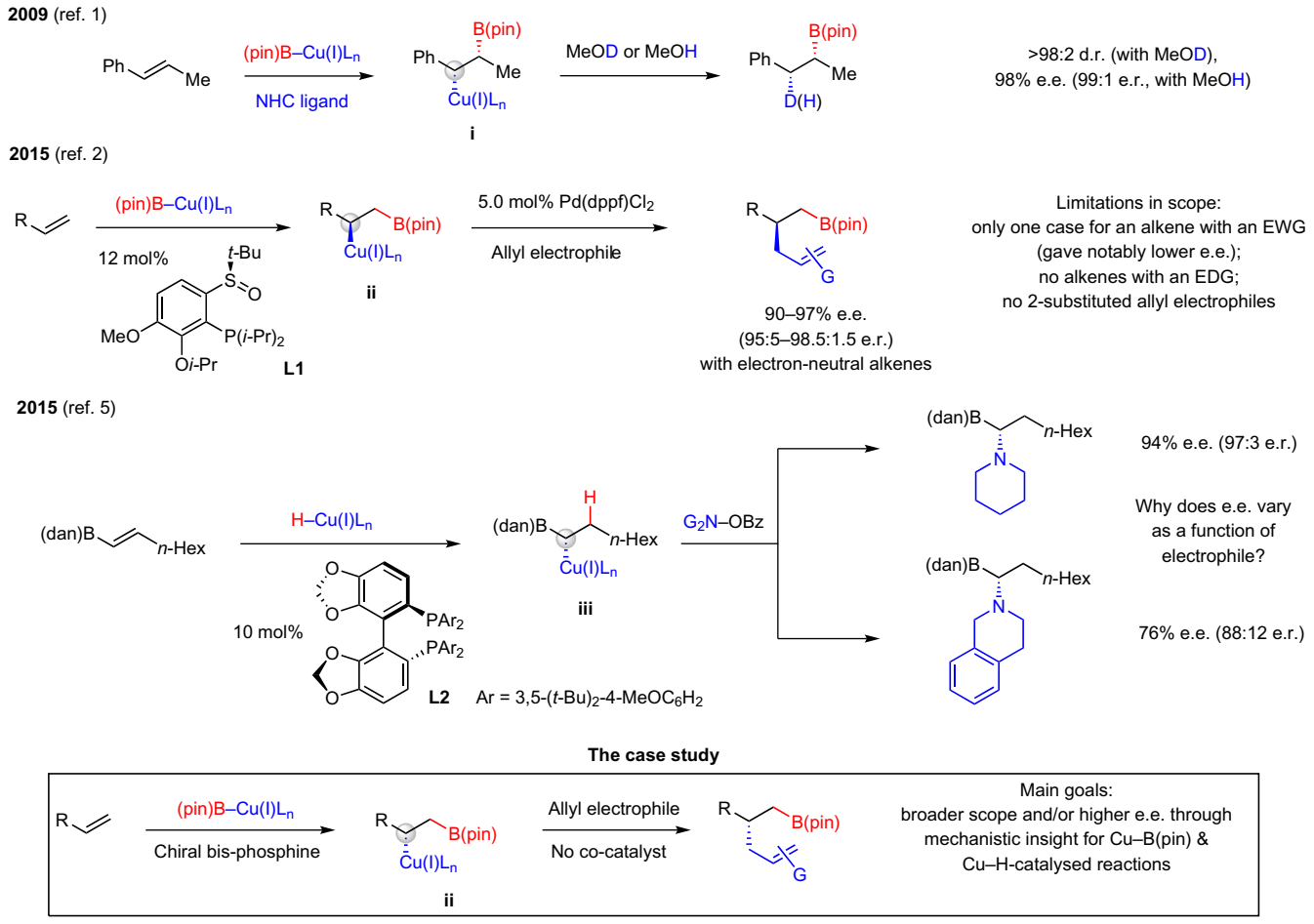


Figure 1 | Key problems and goals of this study. Despite significant advances, notable questions remain unanswered. Cu–B(pin) addition to aryl alkenes is site- and *syn*-selective, and the Cu-alkyl species can react *in situ* with an allyl electrophile. However, reactions require high ligand loading and a precious metal co-catalyst, and scope is limited. Transformations involving Cu–H additions have also been developed, where enantioselectivities can vary widely depending on electrophile identity, despite organocopper formation being stereochemistry-determining. With the development of catalytic site- and enantioselective boron–allyl additions as the model study, several key mechanistic issues will be examined that allow for the scope of the reactions to be expanded considerably. NHC, *N*-heterocyclic carbene; L_n, ligands; e.r., enantiomeric ratio; pin, pinacolato; dppf, 1,1′-bis(diphenylphosphino)ferrocene; EWG, electron-withdrawing group; EDG, electron-donating group; dan, 1,8-diaminonaphthalene; Bz, benzoyl; G, functional group.

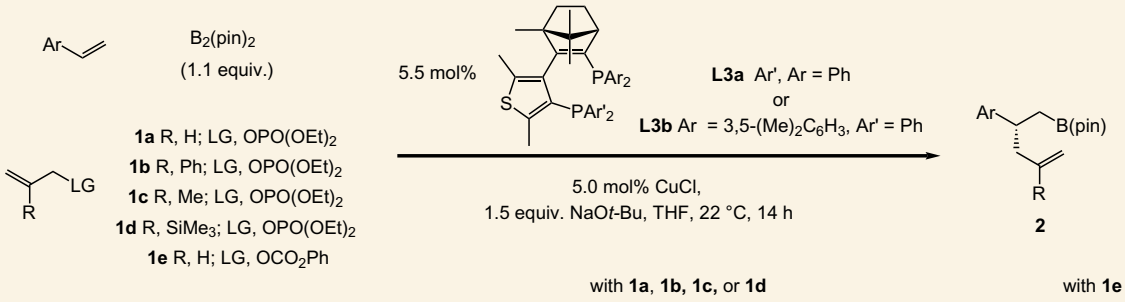
2k and **2l** (entries 11–12, column A) were generated in 2% and 16% e.e., respectively. The same was true with the Cu/Pd approach. For the sole reported example with a clearly electron-deficient alkene, **2l** was formed in 82% e.e.[2] (compared to 95% e.e. for **2a**; for more on this see below). No rationale was provided for this significant selectivity gap. (2) *para*-Methoxy-substituted **2h** (entry 8, column A; not reported previously[2]) was obtained in 94% e.e. and 28% yield. The lower efficiency is probably because reaction of a Cu–B(pin) complex to a more electron-rich substrate is slower and its addition to an allylic phosphate (to give allyl–B(pin))[18,19] becomes the major side reaction (see Fig. 5a for optimal conditions). The data for **2d**, **2g** and **2k** were not included in the disclosure on the Cu/Pd approach[2] (the same for **2f**, **2j** and **2n–p**, Table 1).

Alkene:electrophile ratio and e.e. Enantioselectivity variations might arise from a difference in kinetic selectivity in the Cu–B(pin) addition step, or it might be that a slower forming but more nucleophilic Cu-alkyl intermediate (**2h**, entry 8, column A, Table 1) reacts faster so that the initial (and high) enantioselectivity is better preserved. The less nucleophilic Cu-alkyl species derived from electron-deficient alkenes would react less readily and there could be more extensive e.e. loss before C–C bond formation. In this latter scenario, higher allylphosphate concentration should lead to faster alkylation and the kinetic selectivity would be less diminished[11]. Indeed, whereas **2g** was formed in 64% e.e. with a 3:1 aryl olefin:**1a** mixture (entry 7, column A), when the ratio was reversed, the selectivity improved to 90% e.e. (entry 7, column B). 2-Naphthyl-substituted **2e** (92% e.e. for entry 5, column B compared to 78% e.e. for entry 5, column A), *meta*-B(pin)-substituted **2f** (93% e.e. for entry 6, column B compared to 66% e.e. for entry 6, column A) and *para*-B(pin)-substituted **2j** (84% e.e. for entry 10, column B compared to 64% e.e. for entry 10, column A) were also generated with notably higher enantioselectivity. Therefore, the differences in kinetic selectivity in the initial Cu–B(pin) addition step are not the reason for the e.e. variations.

Nonetheless, we soon discovered that matters are more complex. On several occasions, increasing the allylphosphate concentration did not improve e.e. For example, although the yield for **2k** was much higher (72% for entry 11, column B compared to 14% for entry 11, column A), there was little impact on enantioselectivity of its formation or that of *para*-trifluoromethyl-substituted **2l** (entry 12, column A and B; see 'Epimerization' section for rationale). With *para*-methoxy-substituted **2h** (entry 8) the Cu-alkyl species is exceedingly nucleophilic and reversing the alkene:electrophile ratio does not improve the e.e.

Electrophile size and e.e. With a 2-substituted allylphosphate, Cu-alkyl trapping should be slower and enantioselectivity would be expected to suffer. Indeed, transformations leading to **2n** (entry

Table 1 | Scope of the catalytic process, and the effect of substrate ratio and electrophile identity.



			with **1a**, **1b**, **1c**, or **1d**				with **1e**	
			A: 3:1, Alkene: Electrophile		**B:** 1:3, Alkene: Electrophile		**C:** 3:1 (i) or 1:3 (ii), Alkene: Electrophile	
Entry	**Ar; Electrophile**	**Product**	**Conv. (%)*; Yield (%)†**	**e.e.§**	**Conv. (%)*; Yield (%)†**	**e.e.§**	**Conv. (%)*; Yield (%)†**	**e.e.§**
1	Ph; **1a**	**2a**	>98; 67	90				
2	*o*-$MeOC_6H_4$; **1a**	**2b**	>98; 59	90				
3	*o*-FC_6H_4; **1a**	**2c**	98; 54	78			79; 64 (i)	92
4	*o*-$F_3CC_6H_4$; **1a**	**2d**	>98; 46	66			68; 50 (ii)	92
5	2-naphthyl; **1a**	**2e**	>98; 65	78	80; 50	92		
6	*m*-(pin)BC_6H_4; **1a**	**2f**	>98; 44	66	71; 52	93		
7	*m*-*tert*-$BuO_2CC_6H_4$; **1a**	**2g**	>98; 69	64	83; 62	90		
8	*p*-$MeOC_6H_4$; **1a**	**2h**	>98; 28	94				
9	*p*-FC_6H_4; **1a**	**2i**	>98; 66	84			98; 65 (i)	96
10	*p*-(pin)BC_6H_4; **1a**	**2j**	>98; 48	64	66; 56	84		
11	*p*-*tert*-$BuO_2CC_6H_4$; **1a**	**2k**	22; 14	2	>98; 72	4		
12	*p*-$F_3CC_6H_4$; **1a**	**2l**	>98; 70	16	>98; 79	34	>98; 68 (ii)	92
13	3-Boc-indolyl; **1a**	**2m**	>98; 58	96				
14	Ph; **1b**	**2n**	>98; 60	80	>98; 51	92		
15	Ph; **1c**	**2o**	45; 29	80	>98; 84	90		
16	Ph; **1d**	**2p**	>98; 63	90	>98; 84	92		

Reactions were carried out under a N_2 atmosphere with **L3a** as the chiral ligand, except for **L3b** in the case of **2l** when **1a** serves as the electrophile and also with **2n** and **2o**). *Conv. determined by analysis of the ^{1}H NMR spectra of the unpurified mixtures (±2%). †Yields are of isolated and purified product (±5%); differences between conv. and yield are due to allyl–B(pin) formation (excess alkene) or of proto-boryl addition products (excess allyl electrophile). §e.e. determined by high-performance liquid chromatography analysis (±1%). Experiments were performed at least in triplicate. See Supplementary Section 5 for experimental and analytical details. pin, pinacolato; Boc, *tert*-butoxycarbonyl.

14, column A and B) and **2o** (entry 15, column A and B), which contain 2-substituted alkenes, were more enantioselective when additional amounts of electrophile was present (92% e.e. compared to 80% e.e. and 90% e.e. compared to 80% e.e.). With alkenylsilane **2p** (entry 16, column A and B), the same alteration was less consequential (see Supplementary Section 5 for analysis).

Advantage of the one-catalyst method. Under the Cu/Pd conditions, where higher electrophile concentration means increasing the amount of allyl carbonate as well as the co-catalyst, e.e. could not be improved by adjusting the electrophile and co-catalyst concentration (see Supplementary Section 13 for details). This might be because the presence of achiral bis-phosphine Pd species causes an achiral Cu–B(pin) complex to be generated by ligand exchange[20], and the resulting non-enantioselective pathways offset any advantage that might result from a change in conditions.

Higher e.e. with a less reactive electrophile. Faster Cu-alkyl trapping is not the only way to obtain high enantioselectivity. Regardless of the alkene:electrophile ratio, use of allylphenyl carbonate **1e**, shown to be less reactive than allylphosphate (Supplementary Section 11)[21,22], generally led to higher e.e. (compared to **1a**; enties 3, 4, 9 and 12, column C, Table 1). To counter the lower reactivity of **1e**, larger amounts of this electrophile were used with the more electron-withdrawing aryl olefins **2d** and **2l** (less nucleophilic copper–alkyl intermediates). Thus, **2c**, **2d**, **2i** and **2l** were obtained in 92–96% e.e. (entries 3, 4, 9 and 12, column C, compared to 16–84% e.e. for entries 3, 4, 9 and 12, column A). With electron-neutral or electron-rich olefins, the use of allylphosphate was often preferred due to better yields as opposed to higher e.e. (see Supplementary Sections 5 and 11 for details).

Mechanism. Labelling, spectroscopic and computational experiments were carried out to elucidate the basis of the reactivity and enantioselectivity trends. These studies revealed that while epimerization at the Cu-substituted stereogenic centre has limited relevance, alkene concentration and Cu–H elimination have considerably broader influence.

Epimerization. Reactions with (*E*)- and (*Z*)-β-deuterio-*para*-*tert*-butyl ester substituted styrene afforded **2k**-*d* in low d.r. (Fig. 2a), indicating that epimerization is fast[23]. The same was observed with the Cu/Pd system[2] (see Supplementary Section 13 for details). For

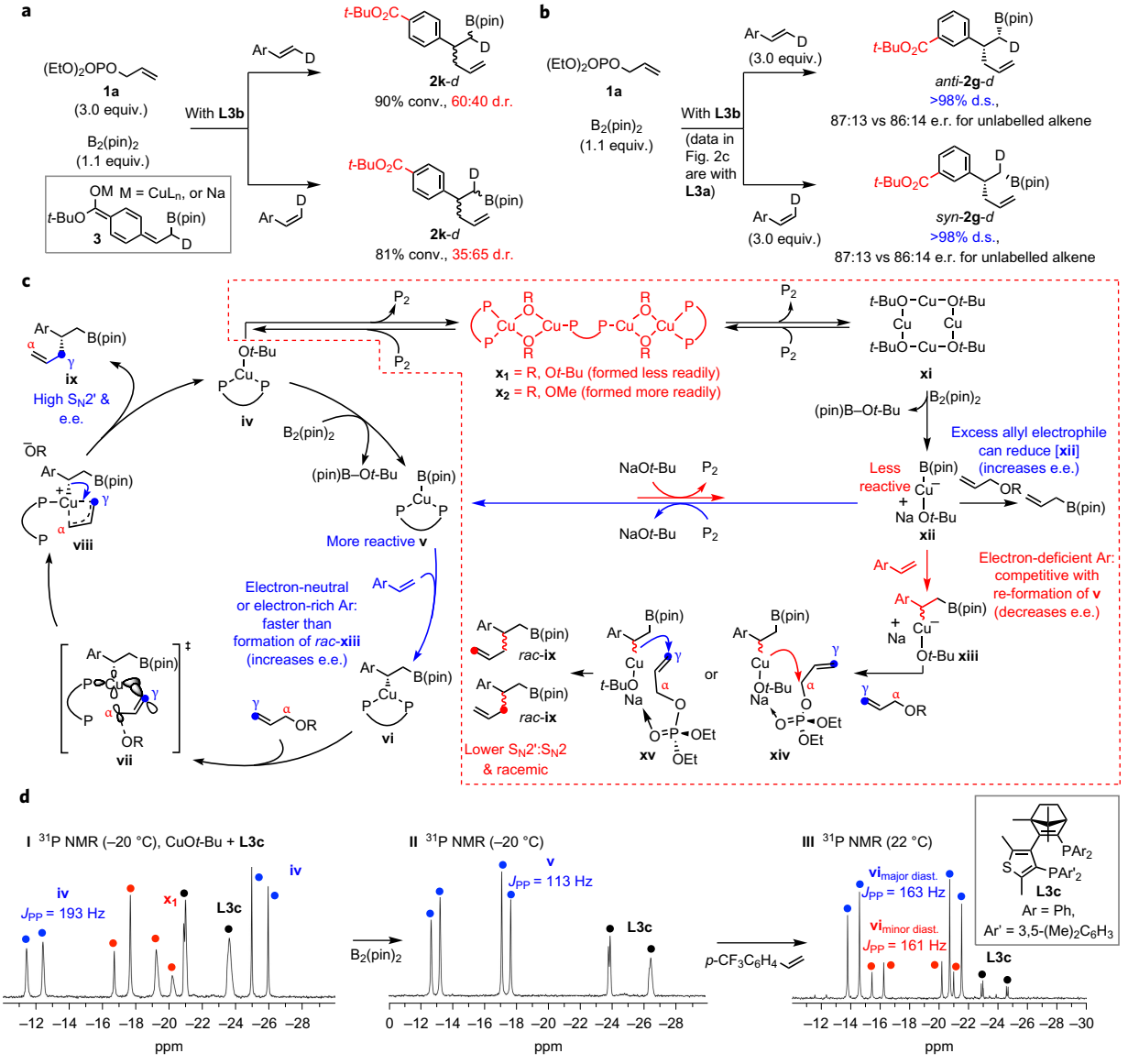


Figure 2 | Labelling studies, the catalytic cycle and temporary loss of the chiral ligand. a, Labelling experiments shed critical light, and it appears that at one point in the catalytic cycle the chiral ligand might dissociate from the Cu centre to cause a lowering of e.e. **b**, Labelling experiments reveal that e.e. variations have different origins, depending on the nature of the aryl olefin involved. **c**, The most efficient catalytic cycle involves transition structure **vii** leading to **ix** with high enantioselectivity. However, a competitive pathway consistent with the experimental data involves dislodging the bis-phosphine ligand (**iv** → **x** → **xi**) and formation of an achiral complex (**xii**), resulting in lower S_N2' selectivity and formation of *rac*-**ix** (via **xiv** or **xv**). **d**, Spectroscopic analysis (A–C, with **L3c**) reveals that there is a considerable amount of free chiral ligand except at the Cu–alkyl stage of the catalytic cycle and at certain points competitive addition by an achiral Cu–B(pin) species can lead to lower S_N2' and enantioselectivity. Reducing the concentration of the alkene thus leads to higher e.e. See Supplementary Section 14 for details. pin, pinacolato; P, diaryl-phosphine ligand; P_2, bis-phosphine ligand; R, $PO(OEt)_2$ or CO_2Ph; bis-phos., unbound bis-phosphine.

supporting 'radical clock' experiments, see Supplementary Section 10. Changes in catalyst concentration did not impact e.e., showing that epimerization does not proceed via a bimetallic transition state[24]. The electron-deficient aryl unit probably stabilizes electron density at the benzylic site, facilitating heterolytic cleavage/re-formation of the Cu–C bond through epimerization via metal-enolate **3** (Fig. 2a). A *para*-ester-substituted aryl olefin was the only case where increasing the electrophile concentration (Table 1, entry 11, column A and B) or the use of allylphenyl carbonate did not enhance e.e. Loss of enantioselectivity is too facile in this particular case.

Temporary ligand loss at the Cu–alkoxide stage. Reactions with other mono-deuterated alkenes, such as those shown in Fig. 2b, were completely diastereospecific (>98% d.s.; see Supplementary Section 9 for details). Again, similar results were obtained under Cu/Pd conditions[2]. Thus, in most instances, diminution in e.r. does not arise from Cu–alkyl trapping with inversion of stereochemistry[25] or Cu–C bond rupture[26], as, otherwise, d.r. would be lower when labelled alkenes were used.

What might be behind the loss of enantioselectivity? Why does increasing electrophile concentration not lead to higher e.e. with the more strongly electron-deficient olefins (for example, *para*-ester-substituted **2k** (entry 11, column A and B, Table 1) in contrast to *para*-trifluoromethylphenyl-substituted **2l** (entry 12))? Could it be that in some cases, e.e. improves (for example, **2g**, entry 7, Table 1) by reversal of the alkene:electrophile ratio because the alkene concentration is reduced and not simply as a result of higher electrophile concentration?

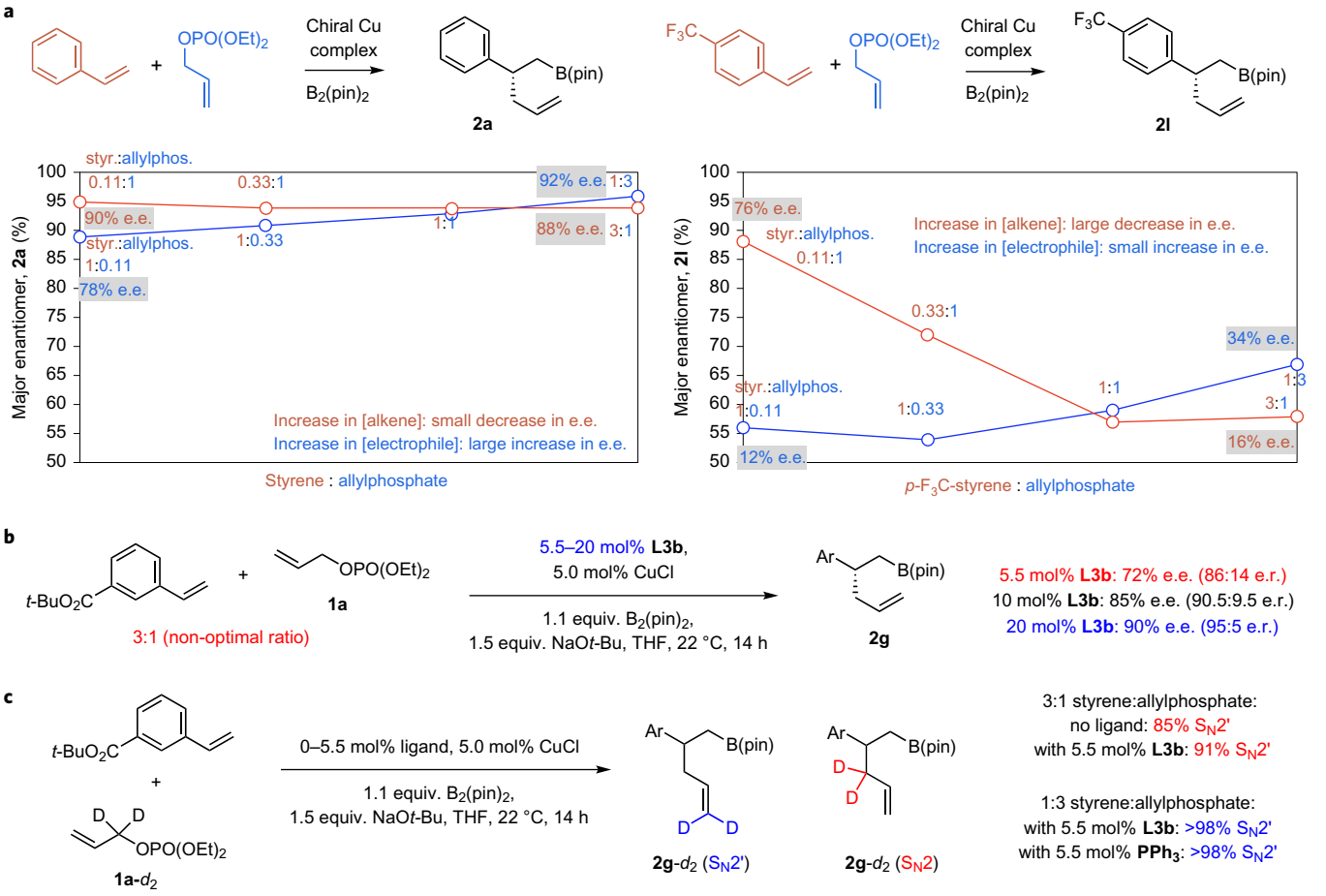


Figure 3 | Effect of olefin concentration on e.e. and S_N2' selectivity. Lower alkene concentration and higher electrophile concentration can improve e.e. **a**, Changing the concentration of aryl olefin and/or allylic phosphate can impact e.e. With electron-neutral olefins the concentration of the allylic electrophile is mildly influential. However, with electron-deficient alkenes it is the olefin concentration that plays a major role. **b**, Higher chiral bis-phosphine loading leads to a significant increase in e.e. See Supplementary Section 5 for experimental and analytical details. pin, pinacolato. **c**, Studies with D-labelled allylphosphate show that a phosphine ligand is needed for high S_N2'selectivity and that selectivity is reduced when there is excess aryl olefin, implying competitive reaction by an achiral Cu–B(pin) species.

The most likely enantioselective route is shown in Fig. 2c—conversion of chiral Cu-alkoxide **iv** to Cu–alkyl **vi** would deliver **ix** via transition structure **vii**, which in turn affords Cu-alkyl **viii** (more on this later), and reductive elimination would then generate the final product **ix**. Spectroscopic studies show that the chiral ligand dissociates from the metal centre at the Cu–O*t*-Bu stage. Subjection of Cu–O*t*-Bu to 1.1 equiv. of **L3c** (spectrum **I**, Fig. 2d) generated an equal mixture of **iv**, the derived aggregates (for example, $\mathbf{x_1}$), 30 mol% of unbound ligand and thus in all likelihood the well-characterized copper-alkoxide, **xi**[27] (Fig. 5a). Addition of $B_2(pin)_2$ yielded **L3c**–Cu complex **v**, which is stable enough for analysis at –20 °C (spectrum **II**). There was also ~30% unbound bis-phosphine ligand, the same amount present at the Cu–O*t*-Bu stage; this indicates that there is no chiral ligand reassociation upon Cu–B bond formation and that at this point achiral Cu–(pin) complex is available (see Supplementary Section 14 for a spectroscopic analysis). Addition of *para*-CF_3-styrene at –20 °C afforded **vi** in 99:1 d.r. (~75% conv.). When the mixture was allowed to warm to 22 °C (spectrum **III**, Fig. 2d) there was complete conversion and stereoselectivity was reduced to 72:28 d.r. with ~10% of unbound **L3c** remaining, which is equal to the excess 0.1 equiv. used initially.

A Cu–alkoxide oxygen atom can form a bridge between transition metals and facilitate aggregation[28–30], ligand dissociation and generation of achiral Cu–B(pin) species. Accordingly, when bis-phosphine–Cu–O*t*-Bu **iv** is regenerated, ligand loss becomes problematic. Spectroscopic studies confirm that with excess chiral ligand the equilibrium shifts towards the bis-phosphine–Cu complex (see Supplementary Section 14 for details). An achiral Cu–B(pin) species (**xii**) lacks the Lewis basic phosphine ligand, is less nucleophilic, and cannot readily react with an electron-rich alkene (**xii** → **xiii**). Density functional theory (DFT) calculations confirm that addition of an achiral Cu–B(pin) to an electron-poor olefin is more favourable and can be problematic (Fig. 4a; for full-system calculations see Supplementary Section 18). Faster reaction between an achiral Cu–B(pin) complex and an electron-poor alkene suggests that olefin concentration must be kept low for higher e.e., allowing ligand association to convert **xii** to **v** before Cu–B(pin) reacts with an alkene (Curtin–Hammett kinetics). This is unlike when an electron-neutral or electron-rich olefin is used, where altering the alkene concentration is largely inconsequential and only increasing the electrophile amount positively impacts e.e. The involvement of achiral Cu–B(pin) species (**xii**) explains why higher electrophile concentration elevates e.e. Increasing the amount of allylic phosphate facilitates conversion of chiral as well as achiral Cu–B(pin) complexes (**v** and **xii**) to allyl–B(pin) by-product (Fig. 2c)[18,19]. However, the net effect would be more diminution in the concentration of achiral **xii**, which probably alkylates faster than bis-phosphine-containing **v** because, as supported by DFT calculations, in

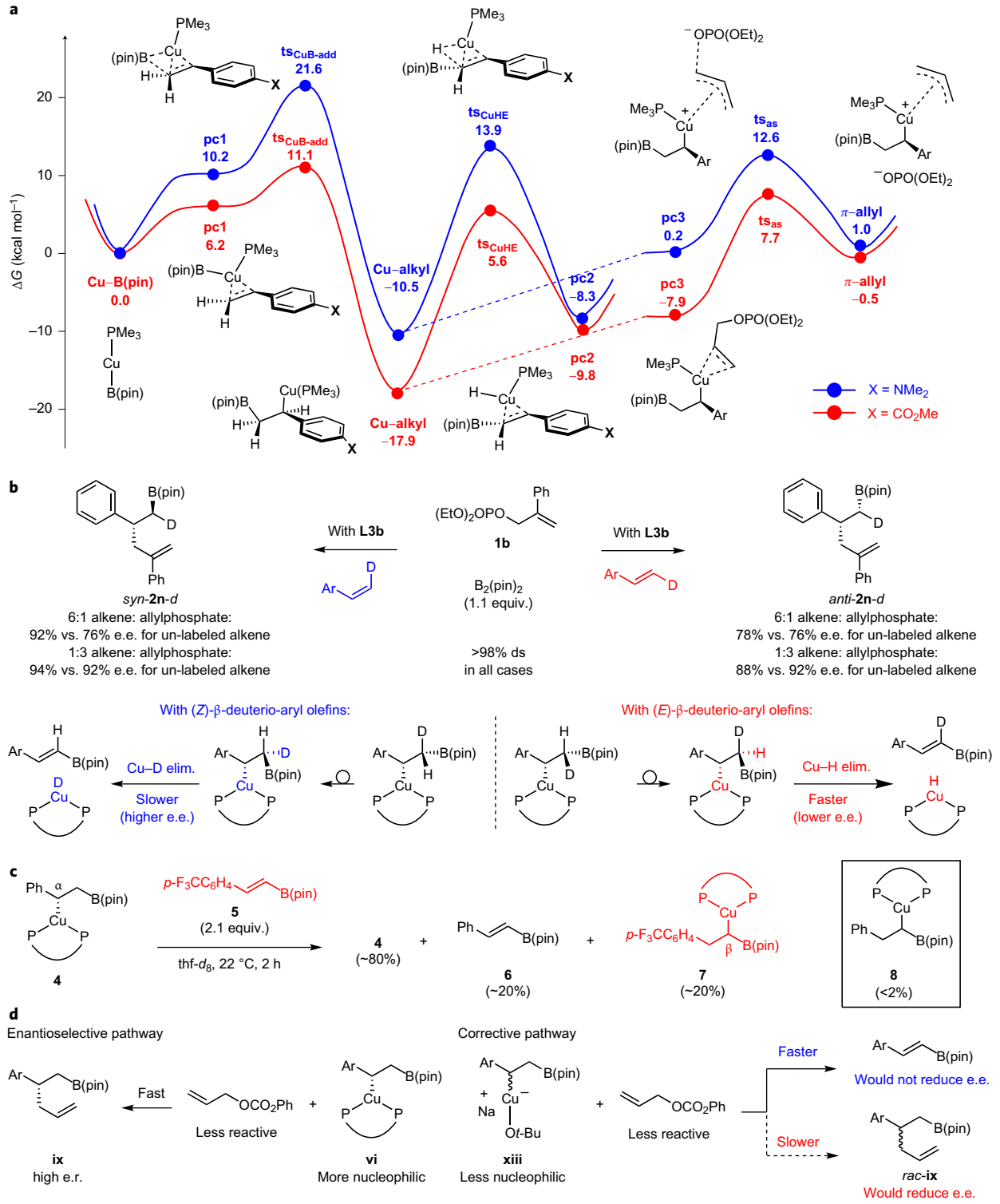


Figure 4 | Different roles of Cu–H elimination. Cu–H elimination can have a negative or a positive impact on e.e. **a**, DFT calculations (PMe_3 as model ligand as monodentate complex alkylates) suggest that Cu–H elimination can be competitive with allylic substitution (**Cu-alkyl** → $\mathbf{ts_{CuHE}}$ → **pc2** versus **Cu-alkyl** → **pc3** → $\mathbf{ts_{as}}$ → **π-allyl**). Cu–H elimination can thus impact e.e. when C–C bond formation is slower. These studies also show that Cu–B(pin) addition to an electron-deficient alkene is favoured, leading to a decrease in e.e. due to temporary chiral ligand dissociation (Fig. 2). DFT calculations were performed at the MN12SX/Def2TZVPP//ωB97XD/Def2SVP level in THF (SMD: solvation model based on density). **b**, Indeed, with a slower reacting 2-substituted allylic phosphate (with lower electrophile concentration), reaction with (*Z*)-β-deuterioalkene is more enantioselective, indicating that inhibiting Cu–H elimination can lead to higher e.e. In one D-labelled aryl olefin Cu–D elimination/re-addition is slower for (*Z*)-β-deuterioalkenes and less prone to loss of enantioselectivity. **c**, A crossover experiment (with **L3c**) support the involvement of Cu–H elimination, also demonstrating that re-addition does not cause a diminution in e.e. (that is, a β-Cu–C bond is formed). **d**, Because an achiral Cu-alkyl intermediate is less nucleophilic (**xiii** versus **vi**) but might undergo Cu–H elimination readily, use of a less reactive electrophile can lead to higher e.r. See Supplementary Information for details (for Fig. 4a, Supplementary Section 18; for Fig. 4b, c, Supplementary Sections 9 and 14). pin, pinacolato; pc, π complex; ts, transition state; B-add, boryl addition; CuHE, Cu–H elimination; as, allylic substitution.

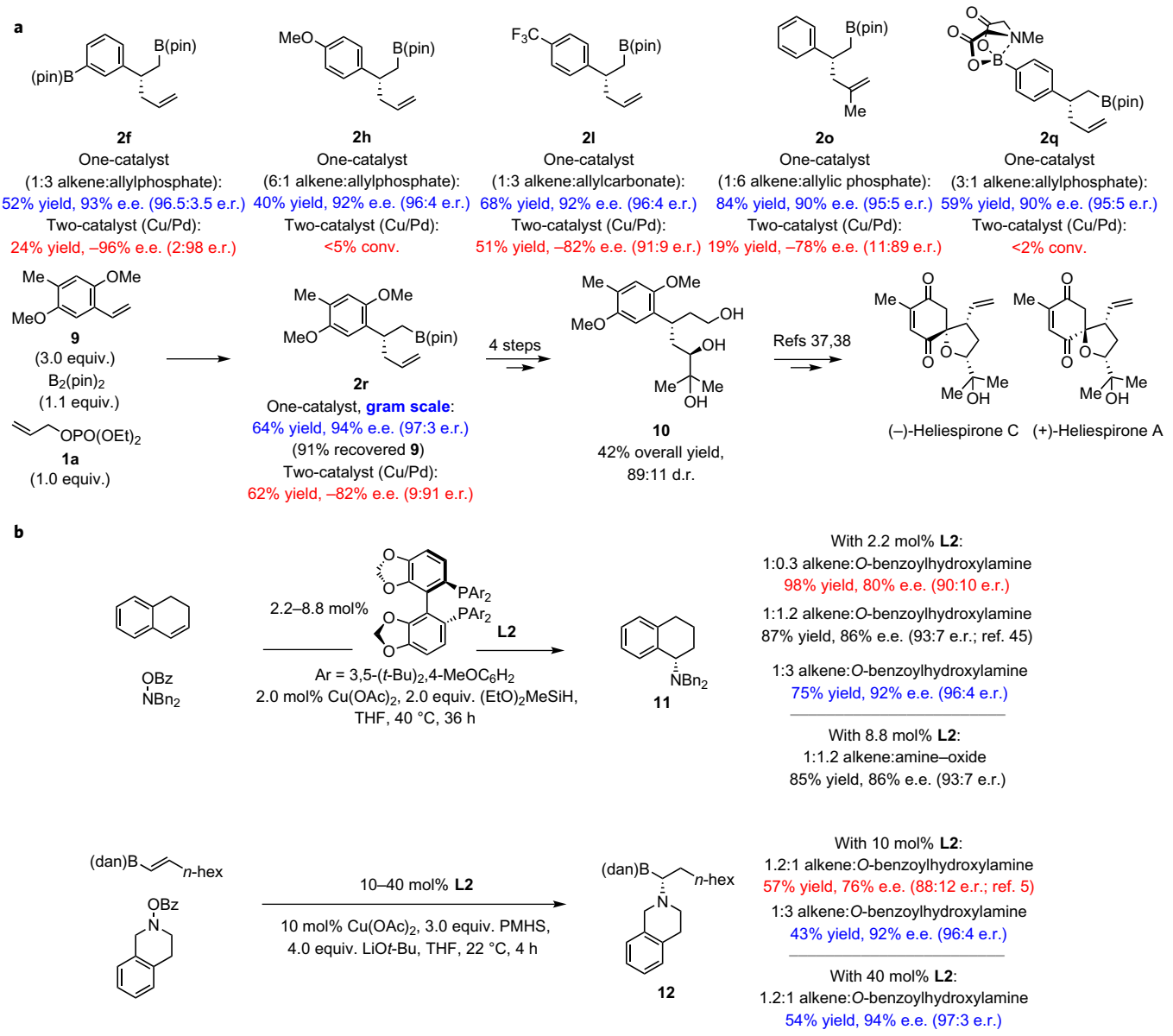


Figure 5 | Broader scope and generality. The new mechanistic knowledge allows for a broader scope. **a**, Without a Pd-based co-catalyst and by adjusting the alkene:electrophile ratio based on the structural attributes of the substrates, the scope of a catalytic process may be significantly broadened. This is illustrated by the representative examples shown here. Experiments were performed at least in triplicate. **b**, The impact of the findings resulting from the present study extend to transformations involving enantioselective Cu–H addition as the initial step. Thus, higher enantioselectivity, at times significant (for example, **16** obtained in 92% versus 76% e.e.), can be achieved by modifying the reaction conditions. Moreover, it is now easier to understand why higher catalyst loading makes little impact in reactions involving an electron-rich alkene by have a more substantial effect when an electron-deficient olefin is involved. See Supplementary Sections 7 and 12 for the complete synthesis route and all experimental and analytical details. pin, pinacolato; PMHS, polymethylhydrosiloxane.

the chiral complex one arm of the bidentate ligand must dissociate before allylic substitution can occur (see **vi** → **vii** → **viii**, Fig. 2c). Less Cu–alkyl intermediate **xiii** is thus formed and enantioselectivity improves. The following observations offer more clarification.

Systematic study of the effect of concentration (changing only one substrate concentration at a time; Fig. 3a) indicated that although increasing the amount of electrophile can lead to higher e.e. with an electron-neutral styrene, variations in olefin concentration have a stronger influence on reactions with a more electron-deficient olefin (90% to 88% e.e. for **2a** compared to 76% to 16% e.e. for **2l**; pathways shown in red). With excess alkene, addition of achiral Cu–B(pin) to the more reactive electron-deficient π bond is faster than its association with the chiral ligand (**xii** → **v**) and there is a further decrease in e.e.; above a certain point in olefin concentration (that is, 1:1–3:1 alkene:allylphosphate, sequence shown in red) the adventitious pathway becomes sufficiently competitive that there is no longer a major change in enantioselectivity (non-Curtin–Hammett regime). The following data support the proposed scenario. (1) With 20 mol% **L3b** (Fig. 3b), **2g** was obtained in 90% e.e. (compared to 72% e.e. at 5.5 mol% ligand and 3:1 alkene:allylphosphate). (2) With the smaller NaOMe (versus NaO*t*-Bu), expected to bridge Cu centres and cause ligand dissociation more efficiently ($\mathbf{x_2}$ versus $\mathbf{x_1}$, Fig. 2c), e.e. was lower (**2g** in 44% e.e. with NaOMe compared to 72% e.e. with NaO*t*-Bu and 5.5 mol% **L3b**).

Fluctuations in S_N2' selectivity elucidate matters further. A bis-phosphine–Cu complex would deliver high S_N2' selectivity

due to the maximum overlap between the largest highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) coefficients in transition structure **vii** (Fig. 2c, d_{xy} orbital and at Cγ, respectively)[31]. The Cu–alkyl bond in square planar **viii** is thus formed *syn* to Cγ, favouring the S_N2' mode of addition (**ix**). With an achiral alkyl–Cu complex (**xiv**–**xv**, Fig. 2c), S_N2' selectivity is lower because sodium ion chelation with the alkoxide oxygen[32] and phosphate moiety directs the reaction. These scenarios are supported by DFT calculations (Supplementary Section 18). In the reaction with *meta*-*tert*-butylester-substituted styrene and **1a**-d_2 (non-optimal conditions, 3:1 alkene:electrophile) without a ligand and with **L3b** present, the S_N2':S_N2 ratios were 85:15 and 91:9, respectively (Fig. 3c). In contrast, with an optimal alkene:electrophile ratio (1:3) and a chiral bis-phosphine present, the S_N2':S_N2 ratio was >98:2. As long as the alkene concentration was kept low, regardless of the ligand identity (**L3b** or PPh_3), the S_N2 product could not be detected.

The above findings show that, for higher e.e., particularly with electron-deficient alkenes, it is more crucial to counter the deleterious effect of achiral Cu–B(pin) complex formation by lowering the alkene concentration and/or increasing ligand loading. There was less increase in e.e. at higher electrophile concentration for products such as **2l** because alkene concentration was still too high (unlike electron-neutral alkenes, Table 1).

Cu–H elimination. Cu–H elimination is well documented[15,33–35] and has been used in reaction development[36]. Through computational studies (Fig. 4a) we find that, especially with an electron-deficient alkene substrate (red versus blue pathway), Cu–H elimination is able to compete with allylic substitution (**Cu–alkyl** → $\mathbf{ts_{CuHE}}$ → **pc2** versus **Cu–alkyl** → **pc3** → $\mathbf{ts_{as}}$ → **π-allyl**). In the following, we illustrate that such processes can adversely or favourably impact enantioselectivity, depending on the alkene and/or the electrophile involved.

Cu–H elimination can reduce e.e. The data in Fig. 4b show that adventitious Cu–H elimination is one reason why enantioselectivity is lower if Cu–alkyl trapping is slow (that is, when excess alkene is used). With the unlabelled alkene or *E*-β-deuteriostyrene there was only a small change in e.e., especially considering experimental error, irrespective of the relative amounts of styrene or its 2-phenyl-substituted variant, **1b**. With excess *Z*-β-deuteriostyrene, on the other hand, *syn*-**2n**-*d* was generated in notably higher e.e. compared to when unlabelled styrene was used (92% versus 76%). Thus, while reaction for the *Z* isomer would either involve a slower Cu–D elimination (primary isotope effect) or Cu–H elimination via a sterically hindered intermediate (eclipsing Ar and B(pin)), β-hydride elimination can proceed readily with the *E* isomer (Fig. 4b).

Additional insight was gained by spectroscopic studies (Fig. 4c). Treatment of a sample of Cu-alkyl complex **4** (82:18 d.r.) with *para*-trifluoromethyl alkenyl–B(pin) (**5**) afforded ~20% alkenyl–B(pin) **6** and isomeric species **7** (22 °C, 2 h; Supplementary Section 14). Hence, Cu–H elimination converts **4** to **6** and the metal–hydride complex generated adds preferentially to the more electrophilic alkene (**5** versus styrene; <2% **8**).

Because of the polarity reversal in the olefin in alkenyl–B(pin) **5** (versus an aryl olefin or phenyl alkenyl–B(pin)) Cu–H re-addition yields a homobenzylic Cu–C bond[15]. This indicates that, under unoptimal conditions (excess alkene versus allyl electrophile), lowering of e.e. does not originate from Cu–H re-addition with the same regioselectivity but on the opposite enantiotopic face of the alkenyl–B(pin) (see Supplementary Section 18 for DFT studies). Instead, diminished enantioselectivity might be attributed to the major Cu-alkyl diastereomer undergoing faster Cu–H elimination. At higher electrophile concentration, Cu-alkyl trapping can compete better with diastereoselective Cu–H elimination and e.e. improves. It would be difficult to anticipate to what extent and how much faster one isomer might undergo Cu–H elimination. What is key is the feasibility of Cu–H elimination, which, as will be shown in the following, has a more general influence on product enantiopurity.

High e.e. due to Cu–H elimination. Although counterintuitive, use of the less reactive allylphenyl carbonate Cu–H elimination gives rise to higher e.e. One clue to the reason for this effect was the larger amounts of alkenyl–B(pin) formed in reactions with allylphenyl carbonate (~40% compared to <5% with allylphosphate without a chiral bis-phosphine and ~10% versus ~2% with allylphosphate under catalytic enantioselective conditions). Unlike when an allylic phosphate is involved (see above), there is minimal trapping of the achiral Cu–B(pin) species (**xiii**, Fig. 4d, namely insignificant formation of the allyl–B(pin) by-product).

The racemic pathway may be circumvented by chemoselective Cu–H elimination of an achiral Cu-alkyl intermediate (versus the derived bis-phosphine complex). This is for two reasons: (1) a bis-phosphine–Cu-alkyl species is less prone to undergo Cu–H elimination than its unbound, achiral variant[34]; and (2) with the less reactive carbonate and under the more dilute catalytic conditions, intramolecular Cu–H elimination in **xiii** (Fig. 4d) is probably faster compared to intermolecular events, such as allylic substitution (to give *rac*-**ix**), or reassociation with the chiral ligand (**xiii** → *rac*-**vi**). Therefore, especially for **2d** and **2l**, the e.e. is high only when carbonate **1e** is used (Table 1, entries 4 and 12, column C). The adverse effect of Cu–H elimination when Cu-alkyl trapping is slow is applicable here (Fig. 4c), but the ability of the same process to block an achiral Cu-alkyl complex to generate racemic products appears to be the dominant factor.

Broader scope. At this point, a rational platform for achieving broader applicability is available. The cases in Fig. 5a are illustrative; except for **2l**, none were previously reported under the two-catalyst conditions[2]. With relatively electron-rich substrates (for example, **2h** or **2r**), where Cu–alkyl formation is more sluggish, higher alkene concentration led to high yield and e.e. The positive effect of a less reactive electrophile in reactions with a strongly electron-deficient alkene is underscored by the improved yield and e.e. for **2l**. When electron-neutral styrene is used (for example, **2o**), larger amounts of allylic phosphate reduce the possibility of diastereoselective Cu–H elimination and lower the concentration of achiral Cu–B(pin), resulting in higher e.e. Gram-scale synthesis of **2r** proceeded in higher enantioselectivity (94% e.e. compared to 82% e.e. with the two-catalyst method). Diol **10**, applicable to synthesis of heliespirones A and C[37,38], was prepared from **2r** in four steps and 42% overall yield (89:11 d.r.; see Supplementary Section 7 for details). Unreacted **9** was recovered easily (91% yield). Compounds **2r** or **10** cannot be accessed by enantioselective hydroboration[39–43] or conjugate addition of an aryl or a prenyl group to an enoate[44].

Relevance to Cu–H-catalysed processes. Reactions with electronic-neutral dihydronaphthalene and electron-deficient alkenyl–B(dan) were investigated to see if the abovementioned principles apply to Cu–H additions as well (Fig. 5b). With dihydronaphthalene[8], increasing the hydroxyamine concentration led to improvement in enantioselectivity (**11** from 80% to 92% e.e.); similarly, in the reaction with alkenyl–B(dan)[5] there was a significant increase in e.e. when larger electrophile amounts were present (from 76% to 92% e.e.). However, based on the above studies, with the more electron-deficient alkenyl–B(dan), e.e. variations are probably caused by a lesser contribution by adventitious addition of an

achiral Cu–H complex. This is supported by the distinct way by which increased ligand loading impacts these reactions: with dihydronaphthalene there was no change in e.e. when 2.0 or 8.0 mol% **L2** was used, but **12** was generated in 94% e.e. compared to 76% e.e. with fourfold lower ligand loading. Only in the latter instance is competitive addition by an achiral Cu–B(pin) complex an issue and a shift in equilibrium away from the achiral Cu–H complex becomes consequential.

Conclusions

These investigations shed light on several factors that directly impact the efficiency and enantioselectivity of a rapidly developing class of transformations, offering cogent strategies for maximizing efficiency and/or enantioselectivity. The study reveals that enantioselectivity increases with higher electrophile concentration due to minimization of diastereoselective Cu–H elimination within the major chiral Cu–alkyl intermediate and largely for reactions with electron-neutral or -rich alkenes (Table 1). There are other notable (and less expected) findings. One is that because a bis-phosphine–Cu–alkoxide species is especially vulnerable to ligand loss, the resulting achiral Cu–B(pin) or Cu–H complex can lead to lower e.e. (Fig. 2). A consequence is that lower alkene concentration can lead to enhanced enantioselectivity when electron-deficient alkenes are involved (Fig. 3). Another discovery is that Cu–H elimination may elevate e.e. by channelling racemic pathways towards the formation of other by-products (Fig. 4). Thus, product enantiopurity may be improved when a less reactive electrophile is employed—a surprising twist considering that in certain cases e.e. is boosted by faster Cu-alkyl trapping (Table 1). As highlighted by the representative applications in Cu–H-catalysed processes (Fig. 5b), the newly acquired understanding and its strategic implications are likely to be instrumental in the success of future endeavours in this area.

Data availability. X-ray crystallographic data for compound **38** (see Supplentary Information) is freely available from the Cambridge Crystallographic Data Centre (CCDC 1547732).

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Author contributions

J.L. and S.R. identified the optimal catalyst and conditions, developed the catalytic enantioselective transformations and performed the labelling and related experiments. S.T. and J.d.P. designed and performed the computational and spectroscopic studies, respectively, and developed the related mechanistic hypotheses. A.H.H. directed the investigations and composed the manuscript with revisions provided by the other authors.

Additional information

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Competing financial interests

The authors declare no competing financial interests.