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

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Abstract

A rapidly emerging set of catalytic reactions involves intermediates that contain a copper-substituted stereogenic carbon centre. Here, we demonstrate that 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 have been able to 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-allylstyrene (Fig. 1); the resulting Cu-alkyl species (**i**) then reacts with MeOH or MeOD *in situ* to give products in >98% e.e. (enantiomeric excess; >98:2 enantiomeric ratio or e.r.) and diastereomeric ratio (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 and silanes are suitable, and Cu–C and/or C–B(pin) bonds can be further functionalized. Reactions that begin with enantioselective Cu–H addition (via **iii**)[3] are a notable subset.

Despite numerous reports and notable 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 (e.g., 2-substituted) electrophiles. Furthermore, enantioselective Cu–B(pin) or Cu–H additions with electron-deficient aryl olefins are either not mentioned[4,5,6,7,8] or found to be less enantioselective[9,10,11,12] (e.g., 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 the stereochemistry-determining (e.g., 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[1,13], but the resulting Cu-alkyl compound is probably less nucleophilic. Conversely, an electron-rich olefin likely generates a more reactive Cu-alkyl species slowly. It has been surmised[9] 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 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 (i.e., 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 (e.g., does a co-catalyst help minimize enantioselectivity fluctuation?); the study would offer additional relevant data vis-à-vis Cu–H-catalyzed reactions[14], which are also facilitated by one catalyst.

Efficient one-catalyst process

We used the transformation shown in entry 1, Table 1 to identify an appropriate chiral catalyst. NHC ligands and most phosphines were ineffective (e.g., <10% yield with **L1** or **L2**, Fig. 1). The exceptions were **L3a** and **L3b**[15], use of which led to the formation of **2a** in 90% and 88% e.e., respectively. While, in this particular instance, 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 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 stronger appreciation of 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 the Supplementary Information, Section 5). As expected, there were several shortcomings: (1) Reactions with electron-deficient olefins were much less enantioselective. *ortho*-Trifluoromethyl **2d** (entry 4) and *meta*-carboxylic ester styrene **2g** (entry 7) were formed in 66% and 64% e.e., respectively, and *para*-ester- and trifluoromethyl-substituted **2k** and **2l** (entries 11–12) 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**; more on this below); no rationale was provided for this significant selectivity gap. (2) *para*-Methoxy-substituted **2h** (entry 8; 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)][16,17] becomes the major side reaction (see Fig. 5a for optimal conditions). It merits note that the data regarding **2d**, **2g**, and **2k** were not included in the disclosure on the Cu/Pd approach[2] (the same for **2f**–**j** and **2m**–**o**, 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 (see **2h**, entry 8, 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 e.e. loss before C–C bond formation. In this latter scenario, higher allylphosphate concentration should lead to faster alkylation and the loss in kinetic selectivity would be diminished[9]. Indeed, whereas **2g** was formed in 64% e.e. with a 3:1 aryl olefin:**1a** mixture (entry 7), when the ratio was reversed selectivity improved to 90% e.e. (entry 16). 2-Naphthyl-substituted **2e** (92% e.e., entry 14 compared to 78% e.e., entry 5), *meta*-B(pin)-substituted **2f** (93% e.e., entry 15 compared to 66% e.e., entry 6), and *para*-B(pin)-substituted **2j** (84% e.e., entry 17 compared to 64% e.e., entry 10) 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 allylphosphate concentration did not improve e.e. For example, while the yield for **2k** was much higher (72%, entry 18 compared to 14%, entry 11) there was little impact on its enantioselectivity or that of *para*-trifluoromethyl-substituted **2l** (entries 12 and 19; see the 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 e.e.

Electrophile size and e.e

With a 2-substituted allylphosphate, Cu-alkyl trapping should be slower and enantioselectivity is expected to suffer. Indeed, transformations leading to **2n** (entries 20–21)

and **2o** (entries 22–23), which contain 2-substituted alkenes, were more enantioselective when more electrophile was present (92% e.e. compared to 80% e.e. and 90% e.e. compared to 80% e.e.). With alkenylsilane **2p** (entries 24–25) the same alteration was less consequential (see the Supplementary Information, Section 5, for analysis).

Advantage of the one-catalyst method

Under the Cu/Pd conditions, where higher electrophile concentration means increasing the amount of the allyl carbonate as well as the co-catalyst, e.e. could not be improved by adjusting electrophile and co-catalyst concentration (see the Supplementary Information, 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[18], 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 (see the Supplementary Information, Section 11)[19,20], generally led to higher e.e. (compared to **1a**; entries 26–29, 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 26–29, compared to 16%–84% e.e., entries 3, 4, 9 and 12 with **1a**). With electron- neutral or electron-rich olefins use of allylphosphate was often preferred owing to better yields as opposed to higher e.e. (see the Supplementary Information, Sections 5 and 11, for details).

Mechanism

We then carried out labeling, spectroscopic and computational experiments to elucidate the basis of the reactivity and enantioselectivity trends. These studies revealed that while epimerization at the Cu-substituted stereogenic center have 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[21]. The same was observed with the Cu/Pd system[2] (see the Supplementary Information, Section 13, for details). [For supporting "radical clock" experiments, see the Supplementary Information (Section 10)]. Changes in catalyst concentration did not impact e.e., showing that epimerization does not proceed via a bimetallic transition state[22]. 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 electrophile concentration (Table 1, entries 11 and 18) 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% ds; see the Supplementary Information, Section 9, for details); again, similar results were obtained under the Cu/Pd conditions[2]. Thus, in most instances, diminution in e.r. does not arise from Cu–alkyl trapping with inversion of stereochemistry[23] or Cu–C bond rupture[24], as, otherwise, d.r. would be lower when labeled alkenes were used.

What might be behind loss of enantioselectivity? Why does increasing electrophile concentration does not lead to higher e.e. with the more strongly electron-deficient olefins [e.g., *para*-ester-substituted **2k** (entries 11 and 18, Table 1) in contrast to *para*-trifluoromethylphenyl-substituted **2l** (entries 12, 19 and 29)]? Could it be that in some cases, e.e. improves (e.g., **2g**, entries 7 and 16, Table 1) by reversal of alkene:electrophile ratio because the alkene concentration is reduced and not simply as a result of higher electrophile concentration?

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); 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 equivalents of **L3c** (spectrum A, Fig. 2d) generated an equal mixture of **iv**, the derived aggregates (e.g., x_1), 30 mol % of unbound ligand and thus in all likelihood the well characterized copper-alkoxide, **xi**[25] (Fig. 5a). Addition of $B_2(pin)_2$ yielded **L3c**–Cu complex **v**, which is stable enough for analysis at −20 °C (spectrum B). 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 re-association upon Cu–B bond formation and that at this point achiral Cu–(pin) complex is available (see the Supplementary Information, Section 14, for 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 (C, Fig. 2d) there was complete conversion and stereoselectivity was reduced to 72:28 d.r. with ~10% of un-bound **L3c** remaining, which is equal to the excess 0.1 equivalent used initially.

A Cu–alkoxide oxygen atom can form a bridge between transition metals and facilitate aggregation[26,27,28], ligand dissociation, and generation of achiral Cu–B(pin) species. Accordingly, when bis-phosphine–Cu–O*t*-Bu **iv** is re-generated ligand loss becomes problematic. Spectroscopic studies confirm that with excess chiral ligand the equilibrium shifts towards the bis-phosphine–Cu complex (see the Supplementary Information, Section 14, for details). An achiral Cu–B(pin) complex (**xii**) lacks the Lewis basic phosphine ligand, is less nucleophilic, and cannot readily react with an electron-rich alkene (**xii → xiii**). 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 the Supplementary Information, 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.; this allows 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 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) byproduct (Fig. 2c)[16,17]. 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 the chiral complex one arm of the bidentate ligand must first 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 further clarification.

Systematic study of concentration effect (i.e., changing only one substrate concentration at a time; Fig. 3a) indicated that while increasing electrophile amount can lead to higher e.e. with an electron-neutral styrene, variations in olefin concentration have 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 further decrease in e.e.; above a certain point in olefin concentration (i.e., 1:1–3:1 alkene:allylphosphate, sequence shown in red) the adventitious pathway becomes sufficiently competitive such 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 (vs. NaO*t*-Bu), expected to bridge Cu centers and cause ligand dissociation more efficiently (**x₂** vs. **x₁**, 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 maximum overlap between the largest HOMO and LUMO coefficients in transition structure **vii** (Fig. 2c, d_{xy} orbital and at Cγ, respectively)[29]. The Cu–alkyl bond in square planar **viii** is thus formed *syn* to Cγ, favoring 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[30] and phosphate moiety directs the reaction. These scenarios are supported by DFT calculations (see the Supplementary Information, 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, S_N2':S_N2 ratio was 85:15 and 91:9, respectively (Fig. 3c). In contrast, with optimal alkene:electrophile ratio (1:3) and a chiral bis-phosphine present, S_N2':S_N2 ratio was >98:2. As long as 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 alkene concentration an/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; see Table 1).

Cu–H elimination

Cu–H elimination is well-documented[13,31,32, 33] and has been used in reaction development[34]. Through computational studies (Fig. 4a) we find that, especially with an electron-deficient alkene substrate (red vs. blue pathway), Cu–H elimination is able to compete with allylic substitution (**Cu–alkyl** → **ts$_{CuHE}$** → **pc2** vs. **Cu–alkyl** → **pc3** → **ts$_{as}$** → **π-allyl**). Below, we illustrate that such processes can adversely or favorably 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 (i.e., when excess alkene is used). With the unlabled 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 un-labeled styrene was used (92% vs. 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; see the Supplementary Information, Section 14). Hence, Cu–H elimination converts **4** to **6** and the metal–hydride complex generated adds preferentially to the more electrophilic alkene (**5** vs. styrene; <2% **8**).

Because of the polarity reversal in the olefin in alkenyl–B(pin) **5** [vs. an aryl olefin or phenyl alkenyl–B(pin)] Cu–H re-addition yields a homobenzylic Cu–C bond[13]. This indicates that, under unoptimal conditions (excess alkene vs. 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 the Supplementary Information, 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 below, has a more general influence on product enantiopurity.

High e.e. due to Cu–H elimination

Although counter-intuitive, 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% vs. ~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 allyl–B(pin) byproduct).

The racemic pathway may be circumvented by chemoselective Cu–H elimination of an achiral Cu-alkyl intermediate (vs. the derived bis-phosphine complex). This is for the two reasons. 1) A bis-phosphine–Cu-alkyl species is less prone to undergo Cu–H elimination than its unbound, achiral variant[32]. 2) With the less reactive carbonate and under the more dilute catalytic conditions, intramolecular Cu–H elimination in **xiii** (Fig. 4d) is bound to be faster compared to intermolecular events, such as allylic substitution (to give *rac*-**ix**), or re-association with the chiral ligand (**xiii** → *rac*-**vi**). Thus, especially for **2d** and **2l**, e.e. is high only when carbonate **1e** is used (Table 1, entries 26–29). The adverse effect of Cu–H elimination when Cu-alkyl trapping is slow is applicable here (see 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

A rational platform is now available for achieving broader applicability. 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 (e.g., **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 (e.g., **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[35,36], was prepared from **2r** in four steps and 42% overall yield [89:11 d.r.; see the Supplementary Information, Section 7, for details]. Unreacted **9** could be recovered easily (91% yield). Compounds **2r** or **10** cannot be accessed by enantioselective hydroboration[37,38,39,40,41] or conjugate addition of an aryl or a prenyl group to an enoate[42].

Relevance to Cu–H-catalyzed 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[6], increasing the hydroxyamine concentration led to improvement in enantioselectivity (**11** from 80% to 92% e.e.); similarly, in the reaction with alkenyl–B(dan)[3] there was 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 more likely caused by 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 four-fold lower catalyst loading. Only in the latter instance competitive addition by an achiral Cu–B(pin) complex is problematic 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 enhance enantioselectivity when electron-deficient olefin alkenes are involved (Fig. 3). Another discovery is that Cu–H elimination may elevate e.e. by channeling racemic pathways towards formation of other byproducts (Fig. 4). Thus, product enantio-purity 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-catalyzed processes (Fig. 5b), the newly acquired understanding and its strategic implications are likely to be instrumental in the success of future endeavors in this area.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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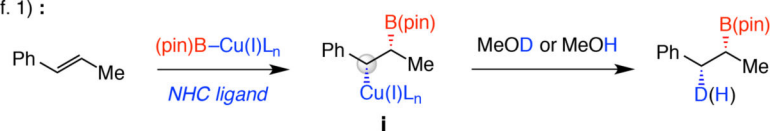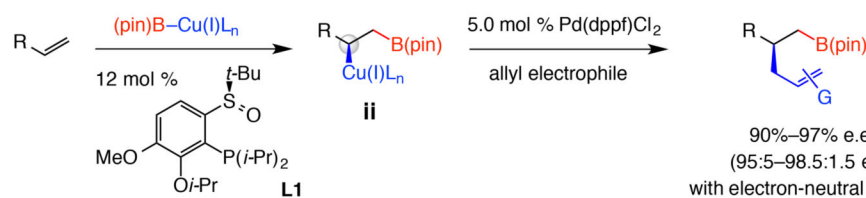
2015 (Ref. 2):

2015 (Ref. 3):

The Case Study:
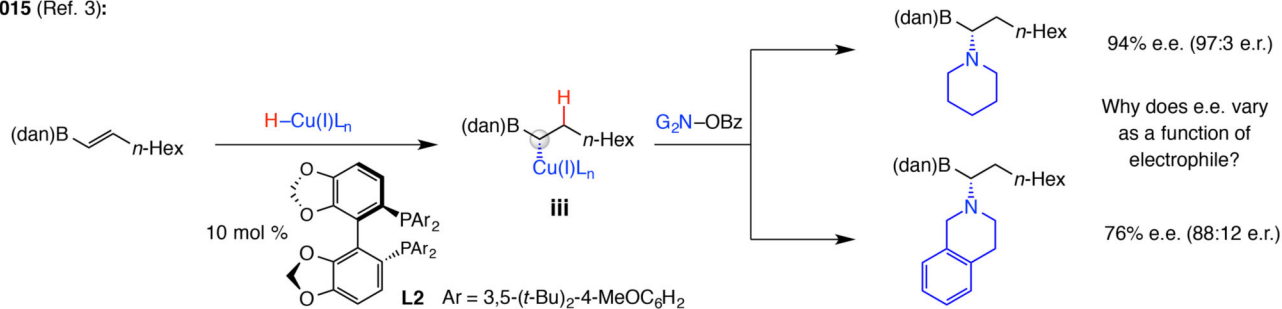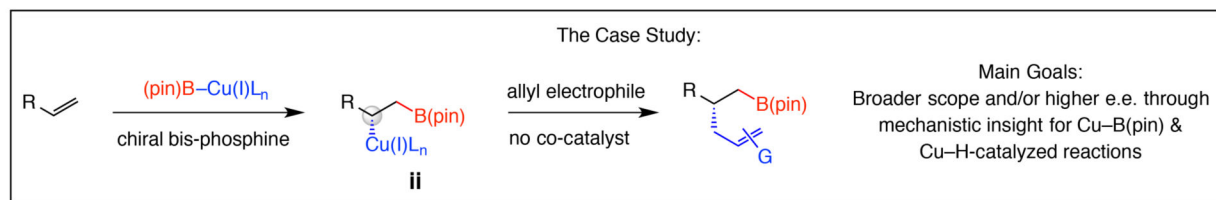
Figure 1. Key problems and the goals of this study

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 development of a catalytic site- and enantioselective boron-allyl additions as the model study, several key mechanistic issues will be examined that allow for 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.

Figure 2. Labeling studies, the catalytic cycle and temporary loss of chiral ligand
Labeling 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 lowering of e.e. **a,** Labeling experiments reveal that e.e. variations have different origins, depending on the nature of the aryl olefin involved. **b,** The most efficient catalytic cycle entails transition structure **vii** to afford **ix** with high enantioselectivity. However, a competitive pathway consistent with the experimental data involves dislodging the bis-phosphine ligand (**iv →×→ xi**) and formation of an achiral complex (**xii**) resulting in lower S_N2' selectivity and formation of *rac*-**ix** (via **xiv** or **xv**). **c,** Spectroscopic analysis (A–C, with **L3c**) reveals that there is 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 the Supplementary Information, 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.

a

b

c
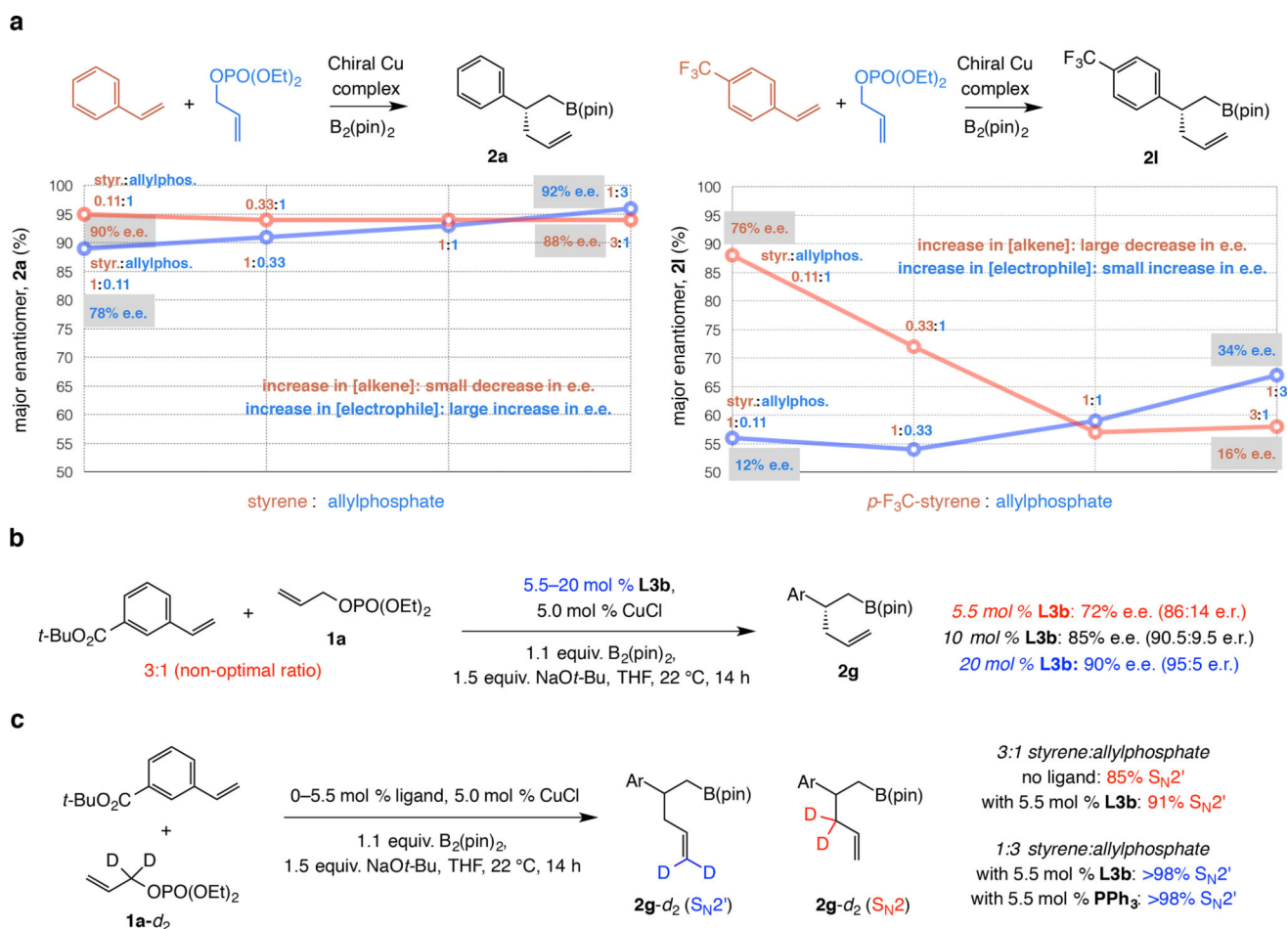
Figure 3. Effect of olefin concentration on e.e. and S$_N$2' selectivity

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 significant increase in e.e. See the Supplementary Information, Section 5, for experimental and analytical details. pin, pinacolato. **c,** Studies with D-labeled allylphosphate show that a phosphine ligand is needed for high S$_N$2'selectivity and that selectivity is reduced when there is excess aryl olefin, implying competitive reaction by an achiral Cu–B(pin) species.
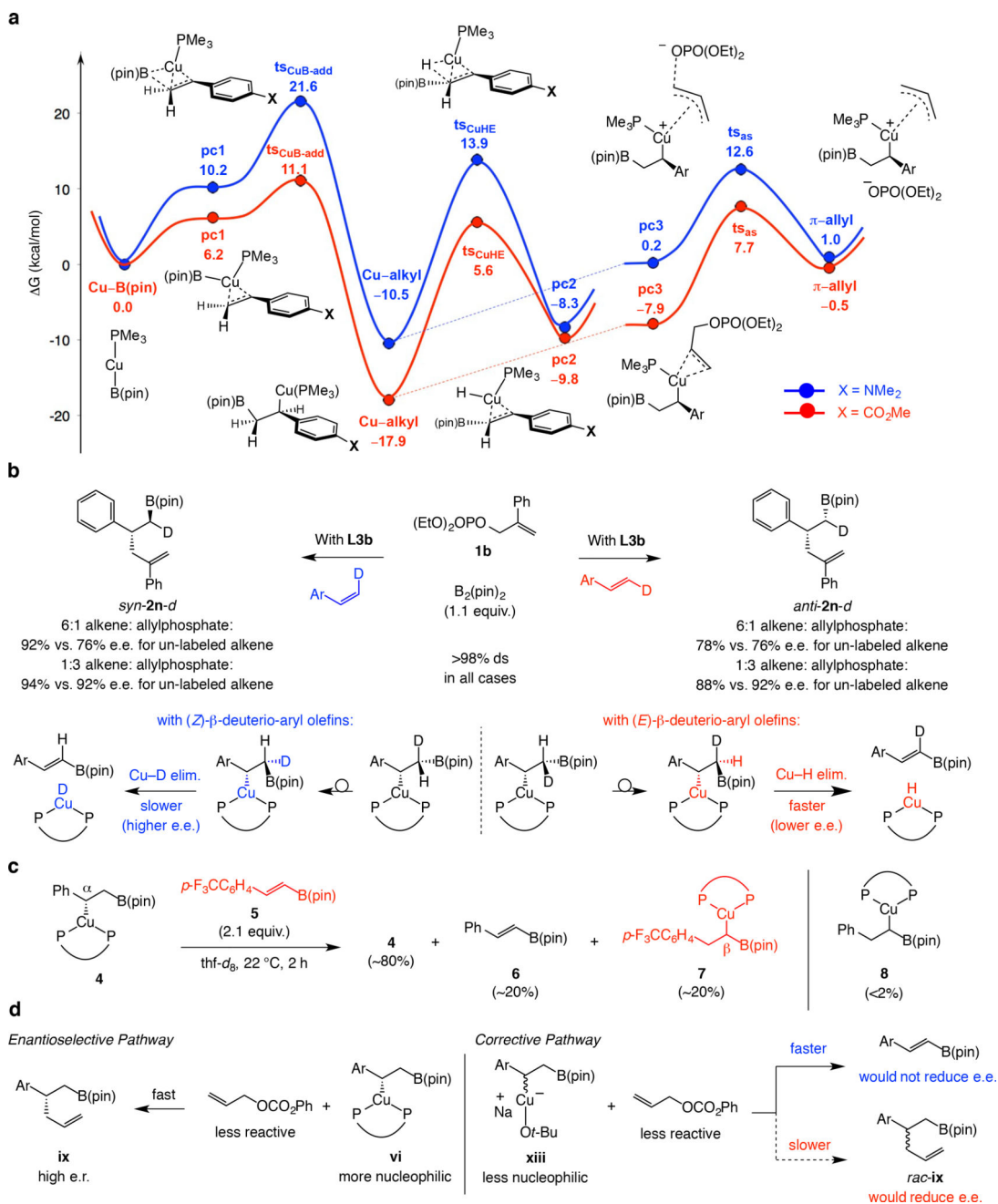
Figure 4. Different roles of Cu–H elimination

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 → ts$_{CHE}$ → pc2** vs. **Cu-alkyl → pc3 → ts$_{as}$ → π-alkyl**). 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 favored, leading to decrease in e.e. due to temporary chiral ligand dissociation (see Fig. 5). DFT calculations were performed at MN12SX/Def2TZVPP//wB97XD/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-labeled aryl olefin Cu–D elimination/re-addition is slower for (*Z*)-β-deuterioalkenes and less prone to loss of enantioselectivity. **c,** A cross-over experiment (with **L3c**) support the involvement of Cu–H elimination, also demonstrating that re-addition does not cause diminution in e.e. (i.e., β-Cu–C bond is formed). **d,** Since an achiral Cu–alkyl intermediate is less nucleophilic (**xiii** vs. **vi**) but might undergo Cu–H elimination readily, use of a less reactive electrophile can lead to higher e.r. See the Supplementary Information for details (for Fig. 6a, see Section 18; for Fig. 7b-c, see Sections 9 and 14). pin, pinacolato; **pc**, π complex; **ts**, transition state; **B-add**, boryl addition; **CuHE**, Cu–H elimination; **as**, allylic substitution.
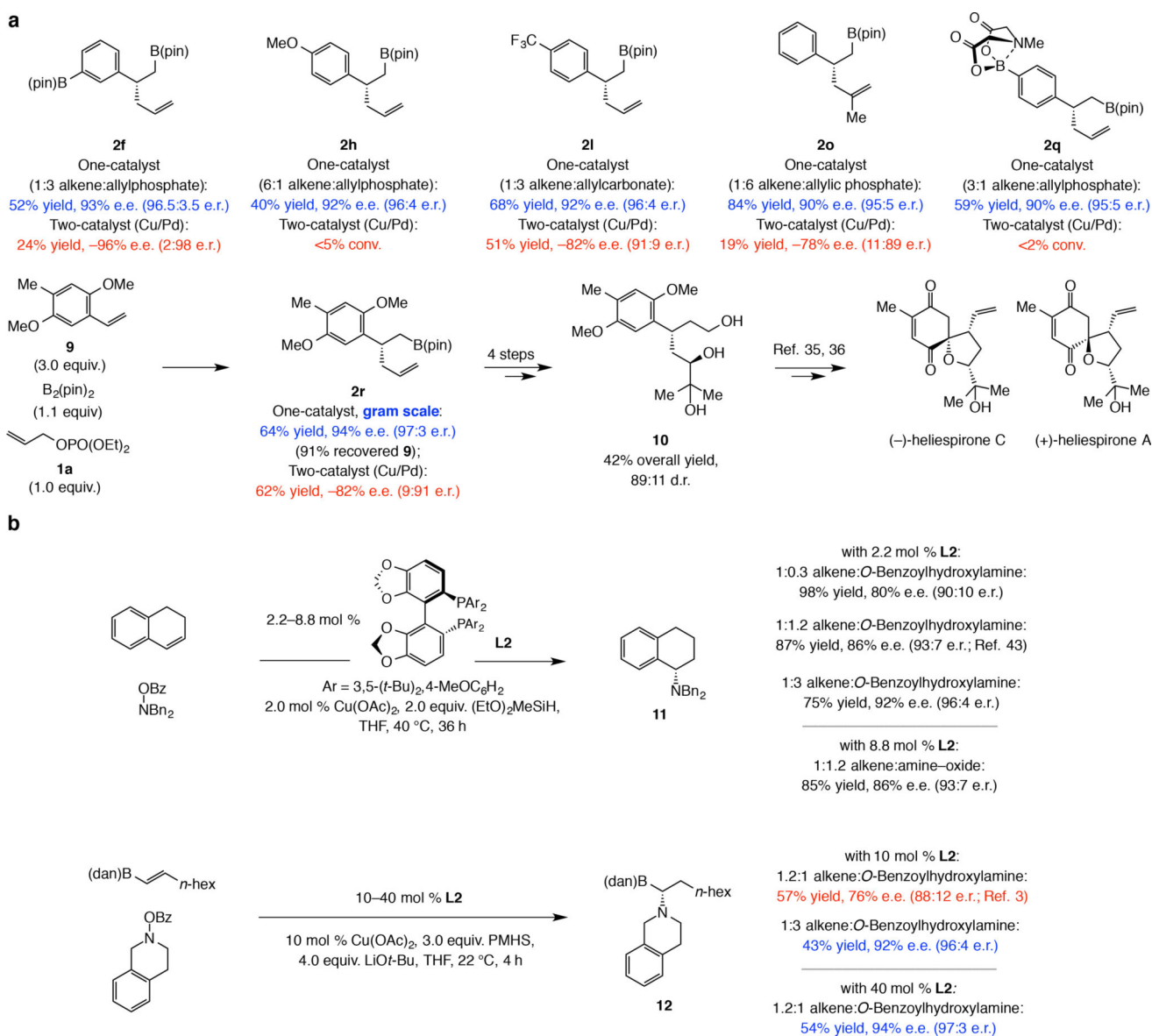
a

2f
One-catalyst
(1:3 alkene:allylphosphate):
52% yield, 93% e.e. (96.5:3.5 e.r.)
Two-catalyst (Cu/Pd):
24% yield, −96% e.e. (2:98 e.r.)

2h
One-catalyst
(6:1 alkene:allylphosphate):
40% yield, 92% e.e. (96:4 e.r.)
Two-catalyst (Cu/Pd):
<5% conv.

2l
One-catalyst
(1:3 alkene:allylcarbonate):
68% yield, 92% e.e. (96:4 e.r.)
Two-catalyst (Cu/Pd):
51% yield, −82% e.e. (91:9 e.r.)

2o
One-catalyst
(1:6 alkene:allylic phosphate):
84% yield, 90% e.e. (95:5 e.r.)
Two-catalyst (Cu/Pd):
19% yield, −78% e.e. (11:89 e.r.)

2q
One-catalyst
(3:1 alkene:allylphosphate):
59% yield, 90% e.e. (95:5 e.r.)
Two-catalyst (Cu/Pd):
<2% conv.

9
(3.0 equiv.)
$B_2(pin)_2$
(1.1 equiv)

1a
(1.0 equiv.)

2r
One-catalyst, **gram scale**:
64% yield, 94% e.e. (97:3 e.r.)
(91% recovered **9**);
Two-catalyst (Cu/Pd):
62% yield, −82% e.e. (9:91 e.r.)

4 steps

10
42% overall yield,
89:11 d.r.

Ref. 35, 36

(−)-heliespirone C

(+)-heliespirone A

b

2.2–8.8 mol %

L2

Ar = 3,5-(t-Bu)$_2$,4-MeOC$_6$H$_2$
2.0 mol % Cu(OAc)$_2$, 2.0 equiv. (EtO)$_2$MeSiH,
THF, 40 °C, 36 h

11

with 2.2 mol % **L2**:
1:0.3 alkene:O-Benzoylhydroxylamine:
98% yield, 80% e.e. (90:10 e.r.)

1:1.2 alkene:O-Benzoylhydroxylamine:
87% yield, 86% e.e. (93:7 e.r.; Ref. 43)

1:3 alkene:O-Benzoylhydroxylamine:
75% yield, 92% e.e. (96:4 e.r.)

with 8.8 mol % **L2**:
1:1.2 alkene:amine–oxide:
85% yield, 86% e.e. (93:7 e.r.)

10–40 mol % **L2**

10 mol % Cu(OAc)$_2$, 3.0 equiv. PMHS,
4.0 equiv. LiOt-Bu, THF, 22 °C, 4 h

12

with 10 mol % **L2**:
1.2:1 alkene:O-Benzoylhydroxylamine:
57% yield, 76% e.e. (88:12 e.r.; Ref. 3)

1:3 alkene:O-Benzoylhydroxylamine:
43% yield, 92% e.e. (96:4 e.r.)

with 40 mol % **L2**:
1.2:1 alkene:O-Benzoylhydroxylamine:
54% yield, 94% e.e. (97:3 e.r.)

**Figure 5. Better mechanistic understanding leads to broader scope**

The mechanistic knowledge obtained through this study 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 (e.g., **12** obtained in 92% vs. 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 the Supplementary Information, Sections 7 and 12, for the complete synthesis route and all

experimental and analytical details. pin, pinacolato; Mes, 2,4,6-trimethylphenyl; dppf, 1,1'-bis(diphenylphosphino)ferrocene.

Conditions the same as those in Table 1. 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 is due to allyl–B(pin) formation (excess alkene) or of proto-boryl addition products (excess allyl electrophile). Enantioselectivity determined by HPLC analysis (±1%). Experiments were performed at least in triplicate. See the Supplementary Information (Section 5) for details.

Table 1

Scope of the catalytic process and the effect of alkene:electrophile ratio.
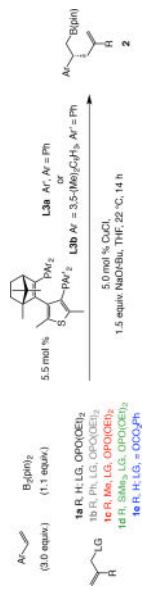
Entry	Ar; Electrophile	Alkene: Electrophile	Product	Conv. (%)*; Yield (%)†	e.e.§
1	Ph; **1a**	3:1	**2a**	>98; 67	90
2	o-MeOC$_6$H$_4$; **1a**	3:1	**2b**	>98; 55	90
3	o-FC$_6$H$_4$; **1a**	3:1	**2c**	98; 54	78
4	o-F$_3$CC$_6$H$_4$; **1a**	3:1	**2d**	>98; 46	66
5	2-naphthyl; **1a**	3:1	**2e**	>98; 65	78
6	m-(pin)BC$_6$H$_4$; **1a**	3:1	**2f**	>98; 44	66
7	m-tert-BuO$_2$CC$_6$H$_4$; **1a**	3:1	**2g**	>98; 69	64
8	p-MeOC$_6$H$_4$; **1a**	3:1	**2h**	>98; 28	94
9	p-FC$_6$H$_4$; **1a**	3:1	**2i**	>98; 66	84
10	p-(pin)BC$_6$H$_4$; **1a**	3:1	**2j**	>98; 48	64
11	p-tert-BuO$_2$CC$_6$H$_4$; **1a**	6:1	**2k**	22; 14	2
12	p-F$_3$CC$_6$H$_4$; **1a**	3:1	**2l**	>98; 70	16
13	3-Boc-indolyl; **1a**	3:1	**2m**	>98; 58	96
14	2-naphthyl; **1a**	1:3	**2e**	80; 50	92
15	m-(pin)BC$_6$H$_4$; **1a**	1:3	**2f**	71; 52	93
16	m-tert-BuO$_2$CC$_6$H$_4$; **1a**	1:3	**2g**	83; 62	90
17	p-(pin)BC$_6$H$_4$; **1a**	1:3	**2j**	66; 56	84
18	p-tert-BuO$_2$CC$_6$H$_4$; **1a**	1:3	**2k**	>98; 72	4
19	p-F$_3$CC$_6$H$_4$; **1a**	1:3	**2l**	>98; 79	34
20	Ph; **1b**	3:1	**2n**	>98; 60	80
21	Ph; **1b**	1:3	**2n**	>98; 51	92
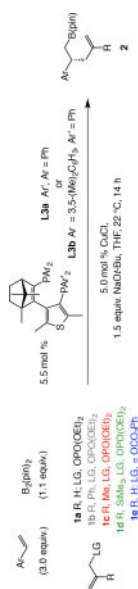
Entry	Ar; Electrophile	Alkene: Electrophile	Product	Conv. (%)*; Yield (%)†	e.e.§
22	Ph; **1c**	3:1	**2o**	45; 29	80
23	Ph; **1c**	1:6	**2o**	>98; 84	90
24	Ph; **1d**	3:1	**2p**	>98; 63	90
25	Ph; **1d**	1:3	**2p**	88; 73	92
26	o-FC$_6$H$_4$; **1e**	1:3	**2c**	79; 64	92
27	o-F$_3$CC$_6$H$_4$; **1e**	1:3	**2d**	68; 50	92
28	p-FC$_6$H$_4$; **1e**	3:1	**2i**	>98; 65	96
29	p-F$_3$CC$_6$H$_4$; **1e**	3:1	**2l**	>98; 68	92

Reactions were carried out under N$_2$ atmosphere with **L3a** as the chiral ligand, except for **L3b** in the case of **2n**, **2o** and **2p**.

*
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 is due to allyl–B(pin) formation (excess alkene) or of proto-boryl addition products (excess allyl electrophile).

§
Enantiomeric excess (e.e.) determined by HPLC analysis (±1%). Experiments were performed at least in triplicate. See the Supplementary Information (Section 5) for experimental and analytical details. pin, pinacolato; Boc, *tert*-butoxycarbonyl.