Asymmetric Conjugate Addition of Organoboron Reagents to Common Enones Using Copper Catalysts

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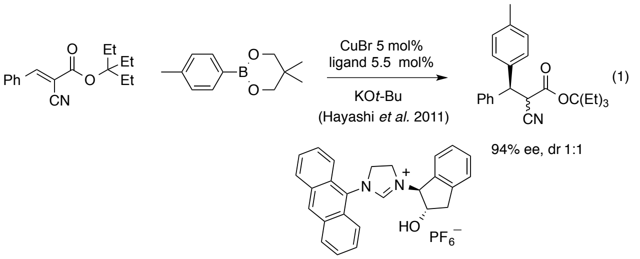
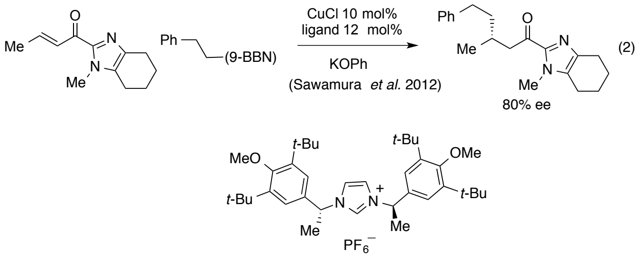
Supporting Information Placeholder

ABSTRACT: Copper complexes of phosphoramidites efficiently catalyzed asymmetric addition of arylboron reagents to acyclic enones. Importantly, rare 1,4–insertion of arylcopper(I) was identified which led directly to *O*–bound copper enolates. The new mechanism is fundamentally different from classical oxidative addition/reductive elimination of organocopper(I) on enones.

Asymmetric conjugate additions of organometallic reagents constitute an important class of carbon–carbon bond forming reactions.[1] In particular, rhodium catalysts were extensively developed in addition reactions of air–stable organoboron reagents, due to efforts by Miyaura, Hayashi, Lin and others. Thus far, the reaction has been applied in kilogram synthesis of drug candidates.[2] In general, dienes and other weakly donating ligands produced more active rhodium catalysts than bisphopshines.[3] In the past decade, this reaction has also been extensively developed with palladium catalysts.[4] In particular, Stoltz *et al.* recently reported efficient nitrogen-based catalysts for highly asymmetric addition to hindered cyclic enones.[5] In both cases of Rh and Pd catalysis, experiments and DFT calculations supported 1,2–insertion of arylmetal species to olefins to form *C*-bound enolates as key steps.[6]





Copper, an abundant base metal, is over thousands–fold cheaper than rhodium and palladium. Historically, chiral copper catalysts were extensively developed in conjugate addition of reactive organometallic reagents, even for the formation of quaternary centers.[7] However, air–sensitive organometallic reagents of Li,[8] Mg,[9] Al,[10] Zn,[11] and Zr[12] must be used in those reactions. Only recently, conjugate addition using air–stable organoboron reagents was reported by Shintani /Hayashi[13] and Sawamura[14] using copper/NHC catalysts (Eqs 1-2). In both cases, only highly activated Michael acceptors such as α–cyanoacrylates and acroylimidazoles were used. Recently, organocatalytic conjugate addition of vinylboron reagents also emerged by activation of enones, but the arylation afforded rather unsatisfactory *ee*.[15]

We envisioned to combine the best of two worlds, i.e., air–stable organoboron reagents and cheap copper catalysts in conjugate reaction (Table 1). Unfortunately, when we attempted a model reaction of a chalcone derivative and phenylboronic acid, no product was detected with many different catalysts and conditions. Accidentally, we found that phenylboronic acid underwent spontaneous dehydration to form phenylboroxine during storage in a dry box. The latter was very active and afforded the adduct in good yield and 94% *ee*, in the presence of a copper/**L1** catalyst.[16] In comparison, PhB(pin) and $PhBF_3K$ did not react at all while PhB(neop) gave only 10% conversion of the enone under similar conditions. Moreover, only weakly basic acetates such as KOAc and NaOAc efficiently promoted this reaction, while stronger bases (e.g., KO*t*Bu, NaOH and KOH) surprisingly inhibited it. Notably, when the amount of KOAc was reduced to 20 mol%, 90% conversion of the enone was seen after 3 days at 70 °C, so the acetate was not consumed during catalysis (see the Supporting Information).

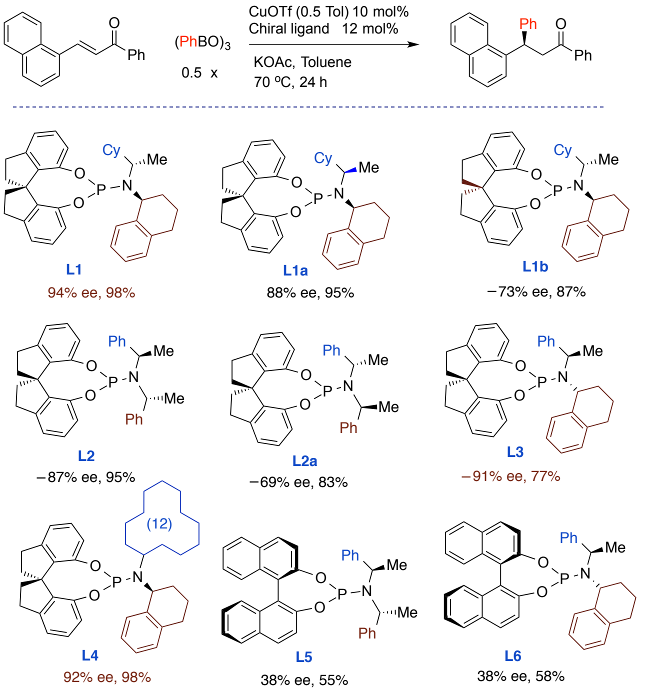
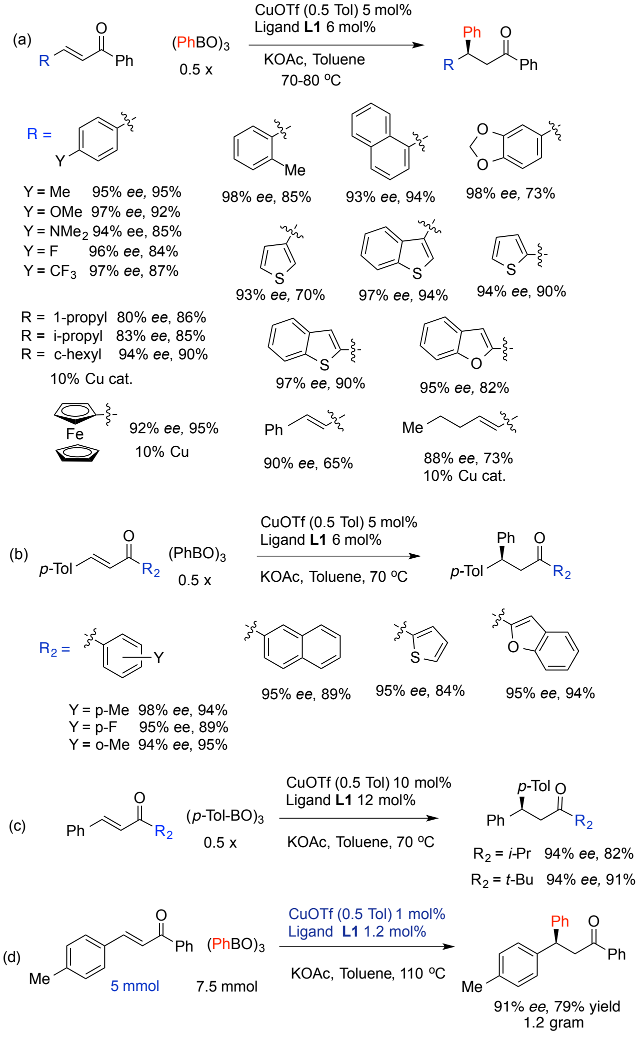


Table 1. Ligand screening for conjugate addition to a model chalcone

In the beginning, we found that a commercially available spiro–phosphoramidite **L2**[17] afforded promising results with 87% *ee* (Table 1). Changing its phenethyl group to a tetralinyl ring (**L3**) helped to improve the *ee* to 91%. Subsequent alteration of the other phenethyl group to cyclohexylethyl led to our optimal ligand **L1**. Notably, ligand

L4 bearing a cyclododecyl group was also very stereoselective. Later, we tried to "invert" the configuration of cyclohexylethylamine in **L1**, and the resulting ligand **L1a** was slightly less selective (88% *ee*). We also tried to "mutate" the spiro chirality in **L1**. The new ligand **L1b** led to the opposite enantiomer as the major product in the model reaction. Thus, the spiro chirality had dominant influence on the stereoselectivity. In comparison, Feringa ligand **L5** built on a binaphthyl skeleton gave only 38% *ee*.

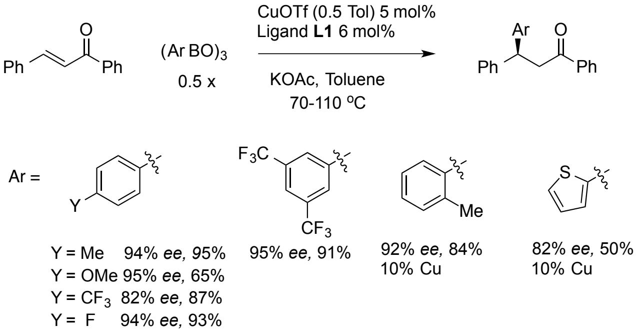
When 1:1 or 1:2 molar ratios of the CuOTf complex and **L1** were added, almost the same reaction rates and *ee* values were seen in the model reaction, (at 5% Cu loading). However, when the ratio was reduced to 1:0.5, the reaction rate decreased significantly, although the *ee* remained constant (see the Supporting Information). Therefore, the 1:1 complex of (**L1**)arylcopper(I) is most likely the active species during insertion. We noticed that other copper salts (e.g., CuCl, CuBr and CuOAc) led to slightly slower conversion in comparison.



Scheme 1 Examples of copper–catalyzed conjugate addition of phenylboroxine.

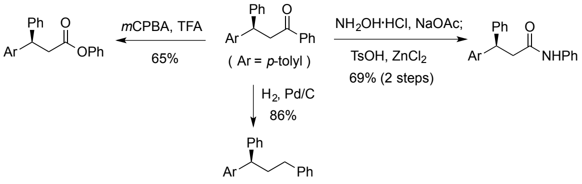
The copper/**L1** catalyst was applicable to chalcones carrying β aryl and heteroaryl groups with diverse electronic properties (Scheme 1a). Enones bearing β aliphatic groups were less reactive and needed 10% copper catalyst to reach good conversion. In reactions of two dienones, only 1,4–adducts were detected without any trace amount of 1,6–adducts. Moreover, enones carrying both α′ aryl and heteroaryl groups reacted very efficiently (Scheme 1b). Those carrying α′ alkyl groups, however, required 10% catalyst loading to give good conversion (Scheme 1c). A model reaction was easily scaled up to give more than one gram of a product at 1 % copper loading (Scheme 1d). Notably, the reaction was not very sensitive to air. It still gave 70% yield and 91% *ee* even after the mixture was exposed to air for 5 minutes before heating (see Supporting Information). α,β-Unsaturated esters and aldehydes remained unreactive. We also tested α-cyanocinnamates and *N*-methyl-2-acroylimidazole. The former afforded very low conversion (<10%) while the latter gave 30% yield and 13% *ee*.

Other arylboroxines with diverse electronic demands and a thienyl derivative reacted smoothly (Scheme 2). We found that alkenylboroxines gave only partial conversion under similar conditions.



Scheme 2 Examples of copper–catalyzed conjugate addition of other organoboroxines.

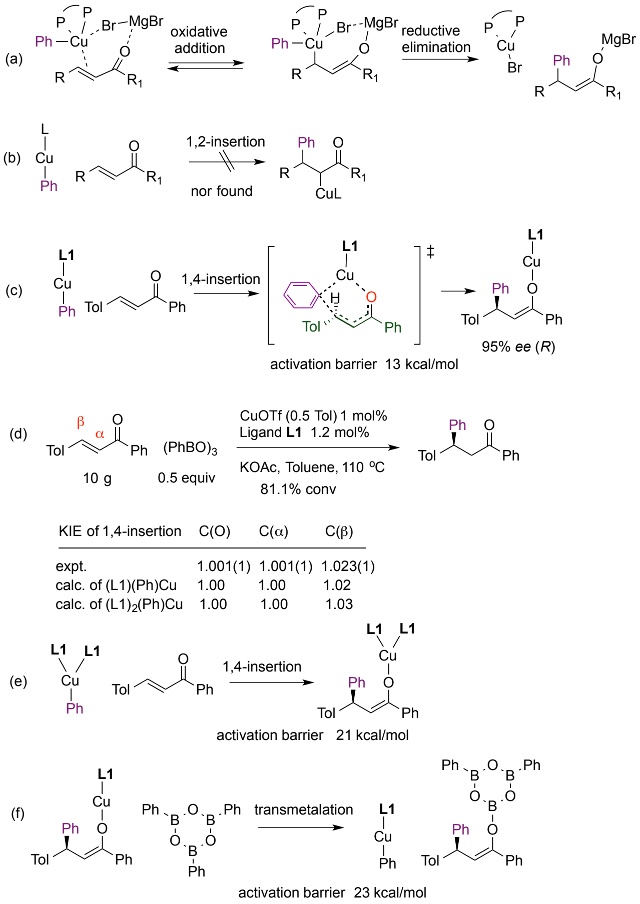
The ketone group in a product was readily converted to an ester and an amide by simple manipulation (Scheme 3). It was also readily deoxygenated by Pd/C catalyzed hydrogenolysis. No erosion of 99% *ee* was seen in all cases.



Scheme 3 Product derivatization

We have considered a few possible pathways for the key C–C bond formation in the conjugate addition. Classical conjugate addition of diorganocuprates involved a sequence of oxidative addition and reductive elimination at β position of enones.[18] In 2006, Feringa *et al.* proposed a similar mechanism involving (bisphosphine)arylcopper(I) in conjugate additions of Grignard reagents (Scheme 4a).[19] Importantly, Lewis acidic metal ions such as lithium, magnesium and zinc ions played a key role in stabilizing enolate structures during oxidative addition. Potassium ion is insufficiently Lewis acidic to serve this role to stabilize enolates. Furthermore, reversible oxidative addition can lead to cis–to–trans isomerization of unreacted starting material, which was not detected under our conditions.

We then conducted DFT calculations[20] to simulate insertion of (**L1**)phenylcopper(I) to *p*–methylchalcone. To our surprise, classical 1,2–insertion was not found (Scheme 4b). Instead, rare 1,4–insertion pathway was identified, in which a 6–membered transition state led directly to an *O*–bound copper enolate (Scheme 4c).[21] During insertion, we believe the Cu–O coordination helped to dissipate the negative charge of enolates. The energy gap of two transition states TS–R and TS–S was determined to be 2.3 kcal/mol, in good agreement with the observed 95% *ee* (*R*) from the model reaction. The overall insertion barrier leading to the major (*R*)–enantiomer was 13 kcal/mol, as the two ground state structures can interconvert easily.



KIE of 1,4-insertion	C(O)	C(α)	C(β)
expt.	1.001(1)	1.001(1)	1.023(1)
calc. of (L1)(Ph)Cu	1.00	1.00	1.02
calc. of (L1)$_2$(Ph)Cu	1.00	1.00	1.03

Scheme 4 Mechanistic studies

In 1,4–insertion, the enones must assume an *s*–cisoid reactive conformation, which is consistent with the fact that cyclic enones, e.g., 2-cyclohexene and indenone, did not react under this condition. Furthermore, 1,4–insertion predicted a C12/C13 KIE value of 1.02 at β carbon of the chalcone, which was confirmed by natural–abundance C13 KIE experiments (Scheme 4d).[22]

We also modeled 1,4–insertion pathways of (**L1**)$_2$(phenyl)copper (Scheme 4e),[23] but the insertion barriers were too high, around 21– 25 kcal/mol, to be considered as the main pathways.

The calculated transition structures revealed how a monoligated copper complex formed a good chiral pocket around the copper center. **L1** assumed a specific conformation to minimize steric repulsion between two large groups on the nitrogen (Fig 1). The cyclohexylethyl group pointed up and shielded the top–right quadrant, while an indanyl ring extended out in the bottom–left space. Consequently, the top–left quadrant was left widely open for the C–C bond formation. In comparison, the bottom–right space was slightly more congested and thus the C–C bond formation thereby had higher barriers.

Interestingly, we identified that in TS–R leading to the major enantiomer, there was weak hydrogen bonding between two aromatic C–H bonds of ligand **L1** and the oxygen atom of the chalcone, which was absent in TS–S. Each of the CH hydrogen atoms had a partial charge of +0.2. Thus, weak attractive interactions provided additional charge stabilization of the developing enolate during insertion. The CH···O hydrogen bonding can provide stabilizing energy of 0.5–4 kcal/mol depending on the acidity of CH bonds and the topology of bonds.[24] Recently, examples of this kind are emerging in transition metal catalysis.[25]

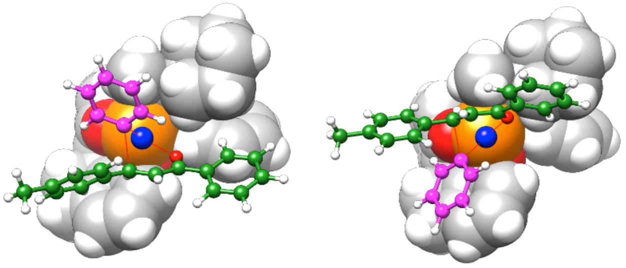


Figure 1. Transition states TS–R (left) and TS–S (right) for 1,4–insertion of (**L1**)phenylcopper(I) to *p*–methylchalcone. **L1** is shown in a space–filling model and reacting ligands and copper are in ball–and–stick. Copper is in blue while Cu–bound phenyl ring is in pink. The carbon atoms of chalcone are in green while its oxygen is in red.

Mechanistic studies on transmetalation from copper complexes of enolates to organoboron reagents have not been reported.[26] We conducted DFT calculation on transmetalation from (**L1**)Cu(enolate) to phenylboroxine (Scheme 4f). Relatively high activation barriers were identified (23–25 kcal/mol), indicating that the transmetalation was rate–limiting in a catalytic cycle. Modeling of transmetalation using phenylboronic acid, however, suggested even higher barriers (27–30 kcal/mol). Moreover, metathesis of (**L1**)Cu(enolate) and KOAc was not found due to the formation of highly basic potassium enolate. Putting all the results together, we conclude that phenylboronic acid and boron ester derivatives did not react, due to prohibitively slow transmetalation. Moreover, NaOH and other strong bases inhibited the addition reaction, presumably because they reacted with organoboroxines and formed ate complexes. The latter were inactive in transmetalation.

In summary, we report here copper catalysts ligated by phosphoramidites for asymmetric addition of organoborons to common enones. Compared to copper/NHC catalysts as previously reported by Hayashi and Sawamura, weak donation from phosphoramidites reduced the electron density on copper centers and thus accelerated the insertion step. DFT calculations and natural–abundance C13 KIE experiments supported the 1,4–insertion mechanism. The pathway explained why cyclic enones were unreactive. The new pathway is different from 1,2–insertion, which operated in palladium and rhodium catalysis. It is also different from oxidative addition/reductive elimination of arylcopper(I). In the latter case, Lewis acidic metal ions were intimately involved in stabilizing the developing charge of enolate intermediates and were indispensible.

ASSOCIATED CONTENT

Supporting Information. Procedures for conjugate addition, characterization of products, NMR spectra of products and DFT calculation of insertion pathways. This material is available free of charge via the Internet at http://pubs.acs.org.

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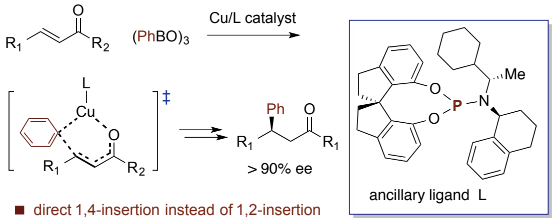
Cu/L catalyst
R1
R2
(PhBO)3
L
Cu
O
‡
Ph
R1
> 90% ee
O
P
N
Me
ancillary ligand L
■ direct 1,4-insertion instead of 1,2-insertion