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Cu(I)-catalyzed asymmetric allylation of ketones and ketimines*

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Abstract: Chiral CuF-catalyzed asymmetric allylation of ketones and ketimines is described. Nucleophile activation via transmetallation (allylboronate to allylcopper), which is facilitated by a cocatalyst [$La(O^iPr)_3$ or LiO^iPr], is key for these reactions. A CuOTf–3KO^tBu–DUPHOS complex is a comparably effective catalyst that reduces the required amount of chiral phosphines.

Keywords: asymmetric catalysis; copper; allylation; tetrasubstituted carbon; ketones; ketimines.

INTRODUCTION

Catalytic asymmetric allylation of carbonyl compounds and imines is a powerful method for synthesizing enantiomerically enriched homoallylic alcohols and amines [1]. Although there are many successful examples of this transformation using aldehydes and aldimines as substrates [2], the substrate scope was only recently extended to ketones [3–7] and ketimines [8]. This is due to both the lower reactivity and the inherent difficulty in differentiating the enantiotopic faces of ketones and ketimines compared to aldehydes and aldimines. The products, homoallylic tertiary alcohols and α-tertiary amines, are important chiral building blocks in organic synthesis. The development of new catalytic asymmetric methods to access chiral tetrasubstituted carbon-containing building blocks is an important frontier in the field of asymmetric catalysis. Here, we describe the Cu(I)-catalyzed asymmetric allylation of ketones and ketimines, including an improved catalyst preparation method.

CATALYTIC ASYMMETRIC ALLYLBORATION OF KETONES

Two main problems in catalytic asymmetric allylation of ketones existed prior to our contribution [3]; first, the use of stoichiometric amounts of toxic allyltin as an allylating reagent; and second, the requirement for high catalyst loading (20–30 mol %). In 2004, we developed a catalytic asymmetric allylation of ketones using allylboronates as nucleophiles, CuF–^{i}Pr-DUPHOS complex [generated by reducing $CuF_2 \cdot H_2O$ with 2 equiv (to Cu) of the chiral phosphine] as an asymmetric catalyst, and $La(O^iPr)_3$ as a cocatalyst (Scheme 1) [4]. Products were obtained with moderate to high enantioselectivity from aromatic and aliphatic ketones. Our methodology was the first to overcome the abovementioned problems in the previous methodologies. Moreover, high catalyst activity allowed us to ex-

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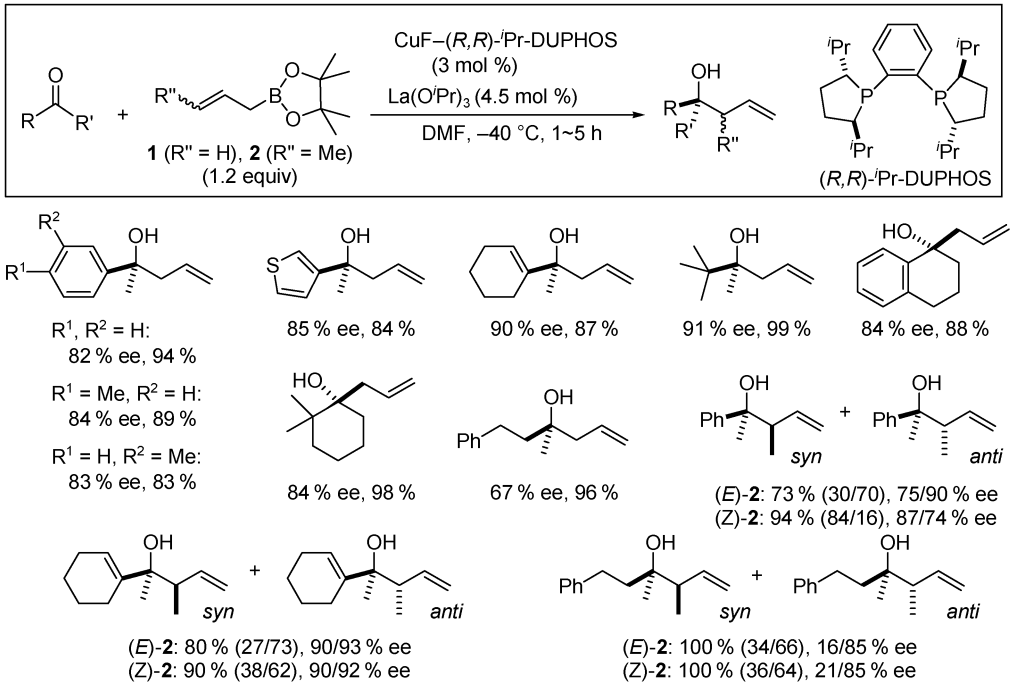
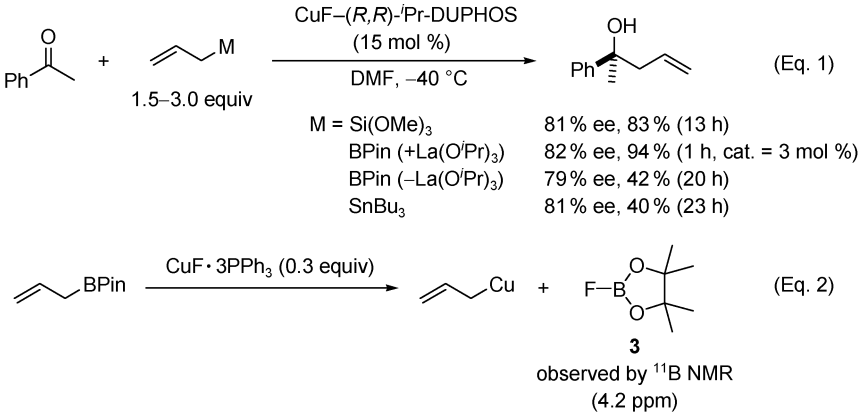


Scheme 1 Catalytic asymmetric allylation of ketones.

tend this method to realize the first catalytic asymmetric crotylation of ketones. Although the diastereoselectivity requires further improvement, products containing contiguous tetrasubstituted–trisubstituted carbons were obtained with excellent enantioselectivity. The geometry of crotylboronate **2** was transferred to the relative stereochemistry of the products in the case of aromatic ketones, whereas *anti*-products were the major products using both (*E*)- and (*Z*)-crotylboronate in the case of aliphatic ketones (Scheme 1).

There are two novel mechanistic issues in this reaction. First, the active nucleophile is an allylcopper species, which is generated through transmetallation from B to Cu. Identical enantioselectivity was produced using allylboronate **1**, allyltrimethoxysilane, or allyltributyltin as an allylating reagent (Scheme 2, eq. 1). This result strongly suggests that an identical species, most probably allylcopper, acts

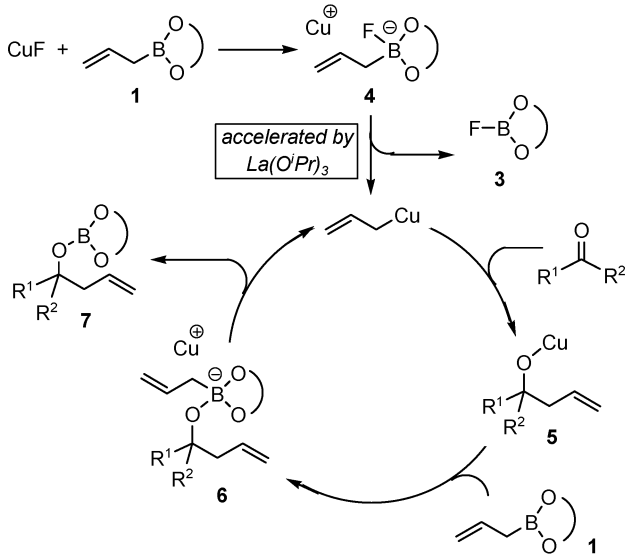


Scheme 2 Mechanistic support for allylcopper acting as the active nucleophile.

as the active nucleophile. The generation of allylcopper from **1** in the presence of the CuF catalyst was also spectroscopically supported; fluoroboronate **3** was observed in ^{11}B NMR of **1**+CuF·3PPh$_3$ [9] [Scheme 2, eq. 2 and Fig. 1, (a)] [10].

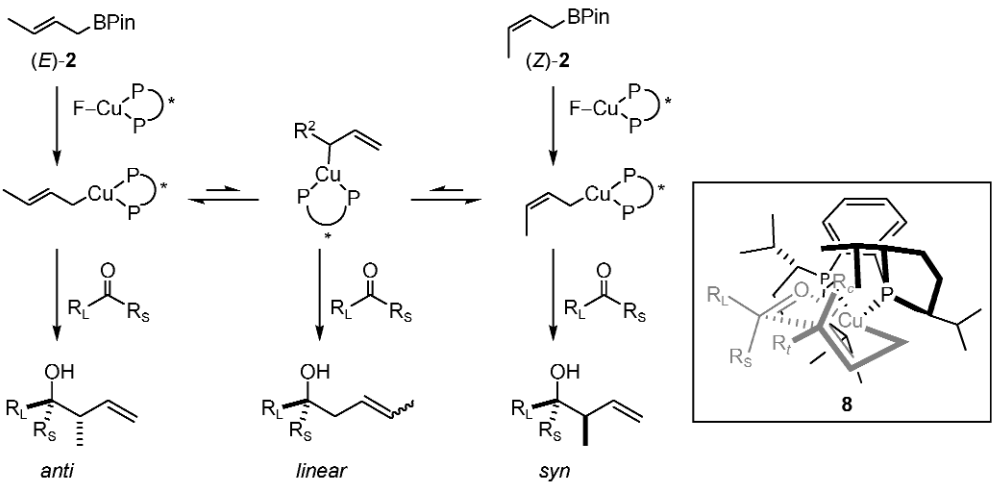
Second, the cocatalyst La(O^{i}Pr)$_3$ accelerates the transmetallation step without affecting the enantiodifferentiation step (the addition step of allylcopper to ketones). Results of kinetic studies in the absence of La(O^{i}Pr)$_3$ (1.4th order to [CuF], 1st order to [allylboronate], and 0th order to [ketone]) indicate that transmetallation is the rate-determining step. Therefore, the dramatic rate acceleration in the presence of La(O^{i}Pr)$_3$ is due to acceleration of the transmetallation step. A possible mechanism of the cocatalyst-induced acceleration of the transmetallation step was proposed after more detailed mechanistic studies of the catalytic enantioselective allylation of ketimines (see below).

On the basis of these experimental results, we propose the catalytic cycle shown in Scheme 3. CuF is a mismatched catalyst with a soft metal and a hard anion conjugated with each other. Facile transfer of hard fluoride onto hard boron affords copper borate **4**. The soft allyl ligand on B is then transferred back to the soft Cu, generating the active nucleophile, allylcopper. This transmetallation is not very efficient in the absence of La(O^{i}Pr)$_3$ (see below). Once allylcopper is generated, it rapidly reacts with ketones. This addition step defines the enantioselectivity, but is not rate-determining. The resulting copper alkoxide **5** again has mismatched characteristics, and it can quickly transfer the alkoxide ligand on B of **1**. Through the ate complex **6**, allylcopper is regenerated with liberating product **7**.



Scheme 3 Proposed catalytic cycle of Cu(I)-catalyzed allylation of ketones.

We also proposed a cyclic transition-state model **8** for the addition of allylcopper to ketones (Scheme 4). This model was based on the fact that the geometry of crotylboronates **2** reflects the relative stereochemistry of the products in the case of aromatic ketones (Scheme 1). In contrast, *anti*-isomers were the major products irrespective of the geometry of **2** in the case of aliphatic ketones (Scheme 1). This difference, which depends on the substrate ketones, is due to differences in the relative rate of metallotropic equilibrium [11] vs. addition to ketones. Allylic metal compounds with ionic characteristics (such as allyllithium, magnesium, and zinc reagents) are configurationally unstable, existing as mixtures of rapidly equilibrating (*E*)- and (*Z*)-isomers through 1,3-metal transposition. Allylcopper is in this category (Scheme 4) [12]. The rate of the crotylcopper addition step to aromatic ketones might be faster than that to aliphatic ketones [13]. Therefore, the addition could proceed before

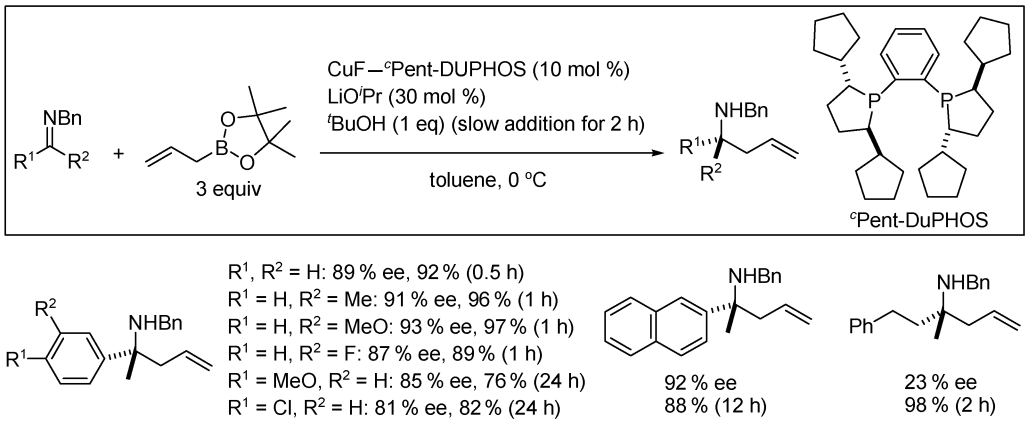


Scheme 4 Proposed model explaining enantio- and diastereoselectivity.

(*E*)/(*Z*) equilibrium of crotylcopper in the case of aromatic ketones, whereas the addition proceeded after equilibrium in the case of aliphatic ketones. Model **8** also rationalizes the absolute configuration of the products.

CATALYTIC ENANTIOSELECTIVE ALLYLATION OF KETIMINES

The Cu-catalyzed allylation was extended to the first catalytic enantioselective allylation of ketimines [8]. To extend the reaction, tuning of three conditions was necessary: (1) sterically tuned cyclopentyl-DUPHOS afforded higher enantioselectivity than ^{i}Pr-DUPHOS; (2) slow addition (over 2 h) of ^{t}BuOH to the reaction mixture accelerated the reaction; (3) LiO^{i}Pr, rather than La$(O^{i}Pr)_3$, was the optimum co-catalyst. High enantioselectivity was produced from aromatic ketimines, but aliphatic substrates afforded unsatisfactory results (Scheme 5). The *N*-benzyl protecting group can be selectively cleaved in high yield through IBX oxidation to the corresponding *N*-benzylidene imine [14] followed by acid hydrolysis.



Scheme 5 Catalytic enantioselective allylation of ketimines.

Detailed NMR studies revealed a possible origin of the dramatic acceleration effect of the additive metal alkoxide cocatalysts [LiO^{i}Pr or La(O^{i}Pr)$_3$] (Fig. 1). When CuF·3PPh$_3$ was mixed with allylboronate **1** in a 1:3 ratio, the ^{11}B NMR peak intensity of fluoroboronate **3** (4.2 ppm, corresponding to the amount of allylcopper) was very weak (Fig. 1a). The major product was fluoroborate **4** (–13.4 ppm). In the presence of LiO^{i}Pr, however, the peak intensity of **3** markedly increased (Fig. 1b). This result indicates that LiO^{i}Pr significantly facilitates the transmetallation step and increases the concentration of the active nucleophile, allylcopper.

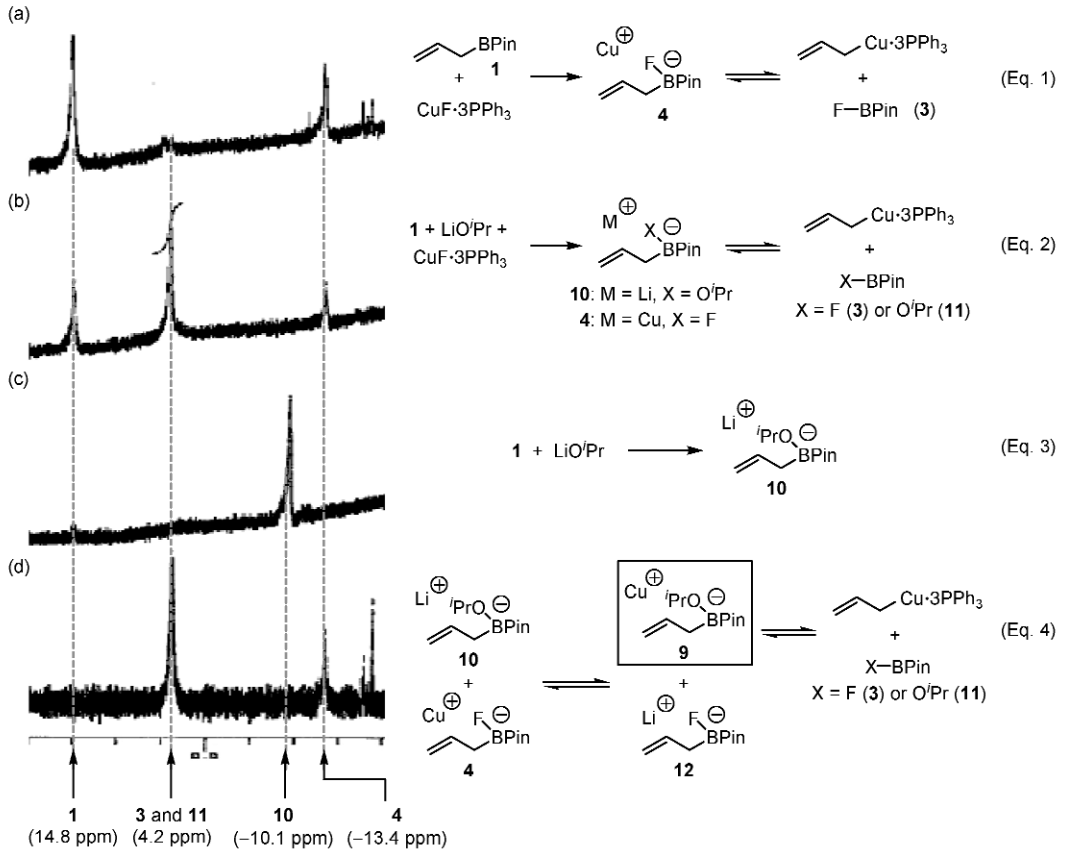
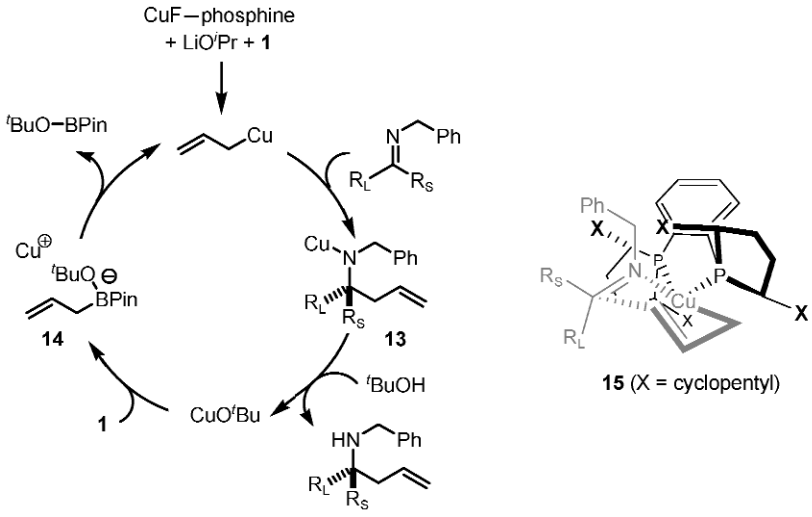


Fig. 1 ^{11}B NMR studies for the rate acceleration mechanism of LiO^{i}Pr.

The following results suggest that this LiO^{i}Pr effect is likely due to the generation of electron-rich copper alkoxyborate **9**, which apparently has greater transmetallation ability than fluoroborate **4**. First, when LiO^{i}Pr was mixed with **1** (1:1) in the absence of CuF·3PPh$_3$, clean formation of lithium alkoxyborate **10** (–10.1 ppm) was observed (Fig. 1c). No transmetallation (from B to Li) occurred in this case because there was no peak corresponding to alkoxyboronate **11** [15]. Next, **4** and **10** were separately generated and combined in a 1:1 ratio (Fig. 1d). The peak of alkoxyborate **10** then selectively disappeared, and a significant amount of **3** (or **11**, overlapping each other) was generated. These results can be explained by considering that the alkoxyborate **9** was produced via facile cation exchange between **4** and **10**, and that this reactive precursor (**9**), rather than fluoroborate **4**, was the major species transformed to allylcopper (eq. 4) [16].

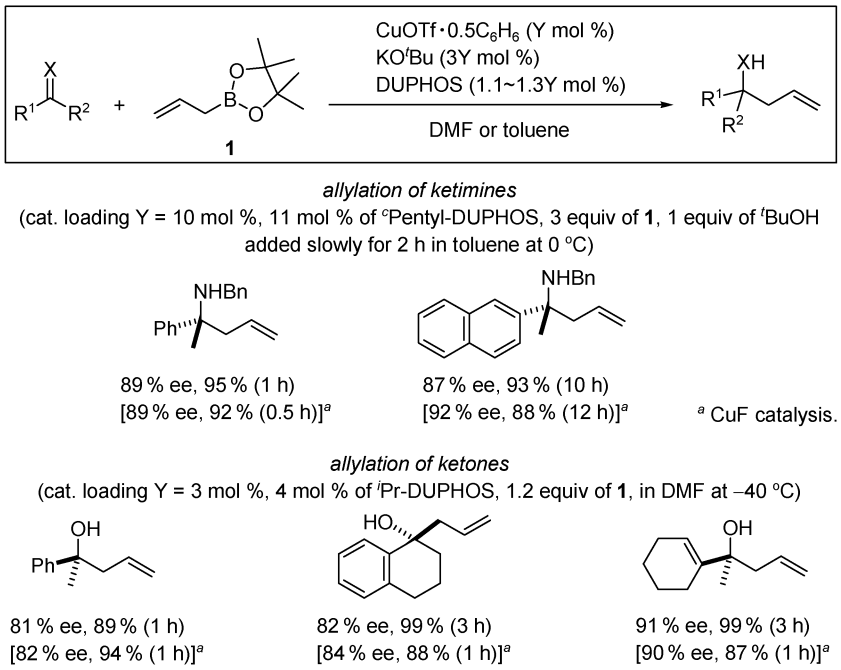
The proposed catalytic cycle is shown in Scheme 6. Allylcopper generated via transmetallation is sufficiently nucleophilic to facilitate addition to ketimines. Intermediate copper amide **13** should be protonated with ^{t}BuOH, giving the allylated product and CuO^{t}Bu. CuO^{t}Bu is catalytically active, and allylcopper is regenerated through alkoxyborate **14**. The cyclic transition state **15** explains the absolute configuration of the products.



Scheme 6 Proposed catalytic cycle of Cu-catalyzed allylation of ketimines (left) and transition-state model (**15**).

COPPER ALKOXIDE-CATALYZED ENANTIOSELECTIVE ALLYLATION OF KETONES AND KETIMINES

Because the catalytic cycle (Schemes 3 and 6) involves a copper alkoxide species (**5** in Scheme 3 and CuO^{t}Bu in Scheme 6) as an intermediate, the reaction can be initiated using a copper alkoxide catalyst. We previously developed a convenient method for in situ preparation of halide-free CuO^{t}Bu from CuOTf·0.5benzene and KO^{t}Bu [17,18]. The thus-prepared CuO^{t}Bu was used as a catalyst for enantioselective allylation of ketimines in the presence of various amounts of alkali metal alkoxide [19]. Optimum enantioselectivity, comparable to that produced using the CuF–3LiO^{i}Pr catalyst system, was obtained using CuOTf·0.5benzene–3KO^{t}Bu (Scheme 7). This new catalyst system was also effective for catalytic enantioselective allylation of ketones (Scheme 7) [20]. In the previous system, chiral CuF catalyst was prepared through the reduction of CuF_2 with an excess amount (2 equiv to Cu) of chiral phosphine. When using a copper alkoxide catalyst, the amount of chiral phosphines can be reduced to levels approximately equimolar to Cu. This new method is advantageous, especially when applied to a large-scale synthesis. Efforts are ongoing to extend these methodologies to the synthesis of complex molecules.



Scheme 7 CuO^{t}Bu-catalyzed enantioselective allylation of ketones and ketimines.

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16. Although no interaction between La(O^{i}Pr)$_3$ and **1** was observed in ^{11}B NMR, it is reasonable to assume that La(O^{i}Pr)$_3$ accelerates the reaction by the same mechanism as LiO^{i}Pr.
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20. A representative procedure for CuO^{t}Bu-catalyzed asymmetric allylation of ketones: CuOTf·0.5benzene (4 mg, 0.016 mmol), (*R*,*R*)–^{i}Pr-DUPHOS (9 mg, 0.021 mmol), and KO^{t}Bu (5 mg, 0.048 mmol) were dissolved in DMF (0.18 mL), and the mixture was stirred at room temperature for 15 min. After cooling to –40 °C, allylboronate (121 μL, 0.64 mmol) and a ketone (0.533 mmol) were added successively. The reaction was monitored by TLC, and quenched with 10 % citric acid after the starting material was completely consumed.