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Enantioselective Copper-Catalyzed Allylic Substitution Reaction with Aminohydroxyphosphine Ligand

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Dedicated to Prof. Armin de Meijere on the occasion of his 70th birthday.

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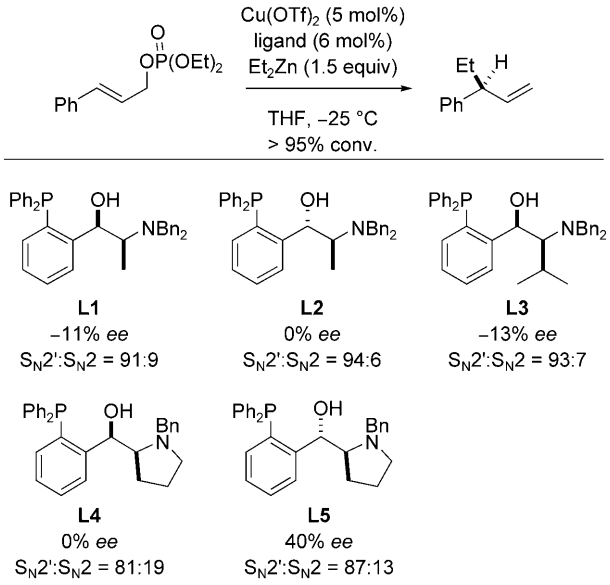
Abstract: A proline-derived aminohydroxyphosphine ligand induced excellent regio- and enantioselectivities ($S_N2':S_N2 > 94:6$, 94–97% *ee*) in the copper-catalyzed substitution reaction of cinnamyl phosphates with Et_2Zn. A computational modelling study of the reaction pathway suggests that the displacement of the leaving group takes place in an ordered, *anti*-fashion through simultaneous copper–olefin and zinc–oxygen interactions, which is critical for the enantioselection.

Keywords: allylic substitution; C–C bond formation; copper; organozinc reagents; phosphane ligands

Chiral copper complex-catalyzed reactions of organometallic reagents with electrophiles such as α,β-unsaturated carbonyl compounds and allylic halides and pseudohalides provide powerful methods for the stereoselective construction of carbon-carbon bonds.[1] While the past decade has seen significant advances in this area, the intrinsic mechanistic complexity of these reactions involving multimetallic catalysis has hampered an understanding of the origin of the enantioselectivity and hence the rational design of the ligands and the catalysts.[2–6]

Through our theoretical mechanistic studies on organocopper transformations,[2] we suggested that an effective chiral ligand would need to coordinate to the nucleophilic copper atom on the one hand, and to the Lewis acidic main group metal atom on the other.[7] The validity of this suggestion was supported by a tridentate aminohydroxyphosphine ligand **L1** (Scheme 1) that effected the highly enantioselective conjugate addition of a dialkylzinc to an acyclic α,β-unsaturated carbonyl compound.[5] The multidentate structure of the aminohydroxyphosphine ligand and the modular character of the synthesis[8] readily allow us to modify the ligand to make it suitable for other types of asymmetric copper catalysis. We report here that this ligand design is effective for the enantioselective allylic substitution reaction. Thus, a proline-derived ligand **L5** was found to show excellent regio- and enantioselectivities in the copper-catalyzed substitution of allylic phosphates with Et_2Zn. Theoretical working models for the asymmetric induction are also provided to account for the observed enantioselectivity.

We performed a preliminary examination of a variety of aminohydroxyphosphine ligands in the reaction



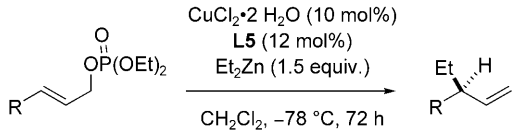
Scheme 1. Performance of aminohydroxyphosphine ligands in copper-catalyzed enantioselective allylic alkylation.

Table 1. Enantioselective allylic substitution of cinnamyl diethyl phosphate with Et_2Zn.[a]

Entry	Cu salt	Solvent	T [°C]	$S_N2':S_N2$[b]	*ee*[c] [%]
1	$Cu(OTf)_2$	THF	−25	87:13	40
2	$Cu(OTf)_2$	DME	−25	88:12	44
3	$Cu(OTf)_2$	Et_2O	−25	82:18	55
4	$Cu(OTf)_2$	Toluene	−25	81:19	46
5	$Cu(OTf)_2$	CH_2Cl_2	−25	86:14	60
6	$Cu(OTf)_2$	CH_2Cl_2	−40	88:12	64
7	CuOTf	CH_2Cl_2	−40	88:12	64
8	$Cu(OAc)_2$	CH_2Cl_2	−40	88:12	64
9	CuI	CH_2Cl_2	−40	93:7	65
10	$CuBr{\cdot}SMe_2$	CH_2Cl_2	−40	93:7	68
11	CuCl	CH_2Cl_2	−40	92:8	82
12	$CuCl_2{\cdot}2H_2O$	CH_2Cl_2	−40	91:9	88
13	$CuCl_2{\cdot}2H_2O$	CH_2Cl_2	−78	98:2	97
14	CuCN	CH_2Cl_2	−40	97:3	28

[a] *Reaction conditions:* 5 mol% of Cu salt, 6 mol% of **L5**, 1.5 equiv. of Et_2Zn, 20 h. Over 90% conversion of the starting material was attained except for entry 13 (60% conversion).
[b] Determined by GC analysis.
[c] Determined by chiral GC analysis.

Table 2. Enantioselective substitution of allylic phosphates with Et_2Zn.



Entry	R	$S_N2':S_N2$[a]	*ee*[b] [%]	Yield[c] [%]
1	Ph	97:3	96	53
2	4-MeC_6H_4	97:4	95	56
3	4-$NO_2C_6H_4$	96:4	97	64
4	4-ClC_6H_4	97:3	96	56
5	4-BrC_6H_4	97:3	96	36
6	4-$CF_3C_6H_4$	96:4	96	41
7	2-Naphthyl	94:6	94	59
8	EtO_2C	>99:1	84[d]	28
9	*c*-C_6H_{11}	95:5	53	<10[e]
10	$PhMe_2Si$	97:3	37	<10[e]

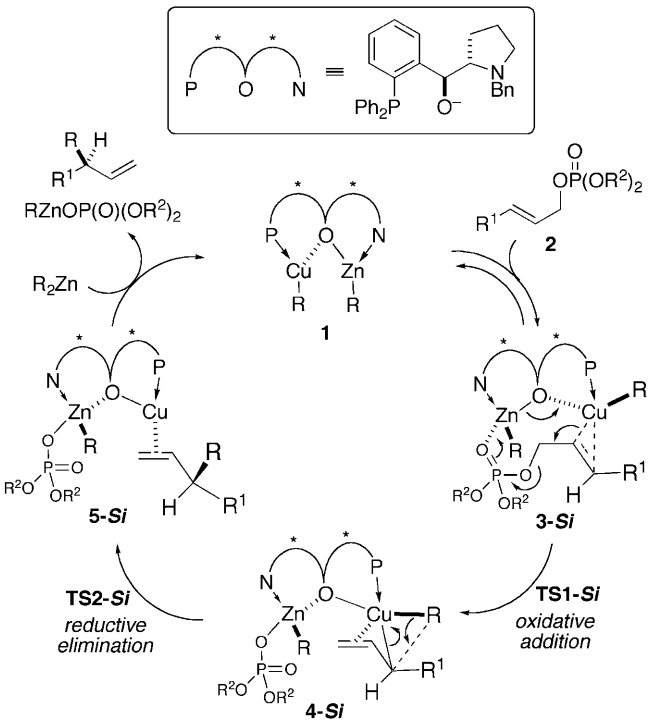
[a] Determined by GC analysis.
[b] Determined by chiral GC or HPLC analysis.
[c] Isolated yields unless otherwise noted.
[d] Determined for an alcohol obtained by $LiAlH_4$ reduction of the product.
[e] Estimated by GC analysis.

of cinnamyl diethyl phosphate and diethylzinc in THF at −25 °C using $Cu(OTf)_2$ (5 mol%) as a copper precatalyst (Scheme 1). For example, ligand **L1**, which gave excellent enantioselectivity in the conjugate addition reaction,[5,9] gave a poor enantioselectivity of 11% *ee*. No asymmetric induction was observed with its diastereomer **L2**. A bulkier analogue **L3** also gave poor selectivity. A proline-derived ligand **L5** gave moderate enantioselectivity of 40% *ee* with moderate regioselectivity (87:13), while its diastereomer **L4** did not induce any enantioselectivity. Cinnamyl halides were found to be poorly selective and cinnamyl acetate unreactive.

With these results in hand, we carefully optimized the conditions for the ligand **L5** as summarized in Table 1. Entries 1–5 show the effect of solvent on the regio- and the enantioselectivity at −25 °C. Among ethereal solvents, Et_2O gave better enantioselectivity (55% *ee*) than the more strongly coordinating solvents THF and DME (40–44% *ee*) (entries 1–3). The polar non-coordinating solvent CH_2Cl_2 gave even better enantioselectivity (60% *ee*, entry 5), while nonpolar toluene gave only 46% *ee* (entry 4).

Using CH_2Cl_2, the effect of the copper precatalyst was examined (entries 6–14). Copper salts having oxygen counteranions (entries 6–8) gave identical results ($S_N2':S_N2$ ratio of 88:12, 64% *ee* at −40 °C). Iodide and bromide counteranions improved the regioselectivity (93:7), but had little effect on the enantioselectivity (65–68% *ee*) (entries 9 and 10). In contrast, the chloride counteranion proved to be beneficial. Thus, the use of CuCl and $CuCl_2{\cdot}2H_2O$ enhanced the enantioselectivity up to 82% and 88%, respectively, with a regioselectivity of >90:10 (entries 11, 12). By using $CuCl_2{\cdot}2H_2O$ at −78 °C, both the regio- and enantioselectivity reached to excellent levels ($S_N2':S_N2 = 98:2$, 97% *ee*, entry 13). The use of CuCN resulted in high regioselectivity (97:3), but considerably reduced the enantioselectivity (28% *ee*) (entry 14), perhaps because of uniquely strong coordination of the cyanide ion to the copper and zinc atoms.[10,11] On the basis of these results, we employed $CuCl_2{\cdot}2H_2O$ as the copper source and CH_2Cl_2 as the solvent in the following study.

Table 2 shows representative results of the enantioselective substitution of allylic phosphates with Et_2Zn. The reactions of the parent and substituted cinnamyl phosphates gave uniformly high regio- and enantioselectivities ($S_N2':S_N2 \geq 96:4$, ≥95% *ee*, entries 1–6). The reactions were rather sluggish at −78 °C and gave moderate yields (up to 64%) of substitution products. The rest of the starting materials were entirely recovered. Increased catalyst loading (up to 20%) and/or further addition of Et_2Zn (up to 3 equiv.) did not improve the yield very much. Me_2Zn was entirely unreactive. A substrate bearing a 2-naphthyl group also gave excellent regio- and enantioselectivities (entry 7). An allylic phosphate bearing an ethoxycarbonyl substituent resulted in an enantioselectivity at an acceptable level (84% *ee*) with perfect regioselectivity (>99:1), albeit in a low yield (entry 8).[12] Greatly reduced reactivity and enantioselecitivity were ob-



Scheme 2. Proposed catalytic cycle.

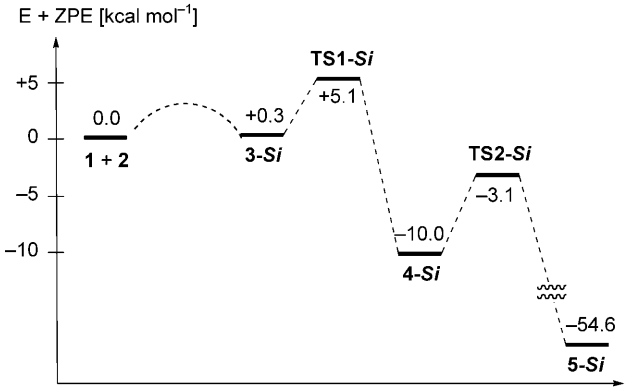


Figure 1. Energy profile (ZPE corrected) for the reaction of the Cu/Zn complex **1** (R = Me) and the allylic phosphate **2** (R^1 = Ph, R^2 = Me) at the level of B3LYP/SDD for Cu, Ahlrichs SVP for Zn, and 6-31G(d) for the rest.

served for aliphatic and silyl-substituted substrates (entries 9 and 10).[13]

While little is known about the detailed reaction pathway of copper-catalyzed allylic alkylation using organozinc reagents, we propose a catalytic cycle as outlined in Scheme 2 for the formation of the major enantiomer, on the basis of our previous mechanistic study on the allylic substitution of lithium organocuprates.[10,14] First, the aminohydroxyphosphine ligand forms, upon deprotonation by the organozinc reagent, a copper/zinc bimetallic complex **1**, where the phosphorus and the nitrogen atoms coordinate to the Cu and the Zn atoms, respectively, and the oxygen atom bridges the two metals.[5] The complex **1** gives, by copper–olefin and zinc–oxygen interactions with the allylic phosphate **2**, a π-complex ***3-Si***. The complex ***3-Si*** then undergoes oxidative addition (C–O bond cleavage) in a push-pull, *anti* manner to give an allylcopper(III) intermediate ***4-Si***. The C–C bond forming reductive elimination of ***4-Si*** gives a product-bound complex ***5-Si***, which regenerates the initial catalytic species **1** through transmetalation with R_2Zn.

A computational modelling study using DFT calculations on the reaction of **1** (R = Me) and **2** (R^1 = Ph, R^2 = Me) along the catalytic cycle gave a reasonable energy profile (Figure 1).[15] The formation of ***3-Si*** from **1** and **2** is almost thermoneutral ($\Delta E = +0.3$ kcal mol^{-1}), probably as the result of trade-off between the energy gain through the copper–olefin and zinc–oxygen interactions and the energy loss due to the structural deformation.[2] The oxidative addition step (***3-Si*** to ***4-Si*** *via* **TS1-*Si***) is very facile ($\Delta E^{\ddagger} = 4.8$ kcal mol^{-1}) and moderately exothermic ($\Delta E = -10.3$ kcal mol^{-1}). The subsequent reductive elimination requires an activation energy as low as 6.9 kcal mol^{-1} and is highly exothermic. The calculated energy profile does not give unambiguous information on the turnover-limiting step of the catalysis; nevertheless, in light of the entropy cost of bimolecular association, we presume that either the π-complexation step or the oxidative addition step is responsible for the slow turnover of the present catalysis.

The low activation energy for the reductive elimination indicates that the enantioselectivity of the product is determined prior to the C–C bond formation, i.e., in the π-complexation or the oxidative addition steps. In order to gain insights into the origin of the asymmetric induction, we analyzed the π-complex ***3-Si*** and the oxidative addition TS **TS1-*Si*** as well as their diastereomers (***3-Re*** and **TS1-*Re***) leading to the minor enantiomer (Figure 2).

An important common structural feature of ***3-Si*** and ***3-Re*** is the location of the nucleophilic copper atom and the Lewis acidic zinc atom. Thus, the copper atom interacts with the olefinic moiety (Cu–C: *ca.* 2.1 Å) while the zinc atom is coordinated by the Lewis basic P=O oxygen atom of the phosphate leaving group (Zn–O: *ca.* 2.3 Å). The alkoxide group in the ligand acts as a counteranion for the zinc atom (Zn–O: *ca.* 1.9 Å), and at the same time weakly coordinates to the copper atom (Cu–O: *ca.* 2.6 Å). In the oxidative addition transitions states, one can find that C–O bond cleavage (C–O: *ca.* 1.9 Å) is accompanied by tighter interactions between the zinc atom and the phosphate oxygen atom (Zn–O: *ca.* 2.1 Å) and between the copper atom and the bridging oxygen atom (Cu–O: 2.3–2.4 Å).

We consider that the high degree of structural organization of the π-complex and the oxidative addi-

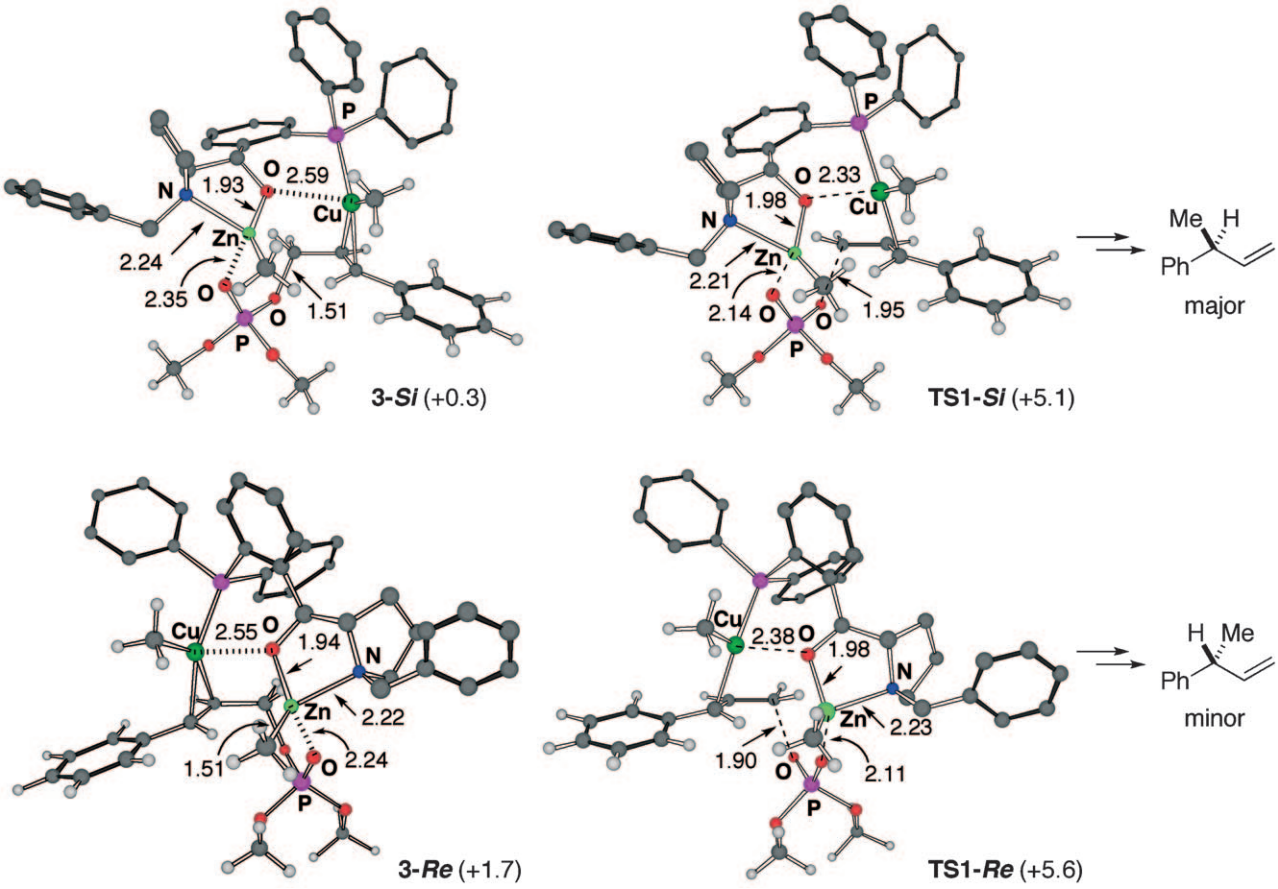


Figure 2. Structures of diastereomeric π-complexes and oxidative addition transition states. Color code: green, copper; light green, zinc; grey, carbon; white, hydrogen; red, oxygen; blue, nitrogen; pink, phosphorus. Hydrogen atoms on the ligand are omitted for clarity. Values indicate bond lengths (Å) and energies (kcal mol^{-1}) relative to [**1** + **2**] (in parenthesis).

tion TS are responsible for the high enantioselectivity. The experimental enantioselectivity of 96% *ee* at −78 °C corresponds to a small energy difference of 1.5 kcal mol^{-1}, which is rather difficult to reproduce at the current level of theory. Nonetheless, both **3-*Si*** and **TS1-*Si***, leading to the major enantiomer, were calculated to be preferred to their diastereomers by 1.4 kcal mol^{-1} and by 0.5 kcal mol^{-1}, respectively. It is notable that we do not find any particularly severe steric interactions in the complexes and the transitions states. For instance, the closest distances between the ligand and the phenyl group of the substrate in **3-*Si*** and **3-*Re*** are 2.74 Å and 4.41 Å, respectively. This subtlety of the selectivity control may be the reason for the rather high sensitivity of the enantioselectivity to the structure of the substrate (Table 2). This model did not provide us any insights on the low reactivity of Me_2Zn as opposed to Et_2Zn.

In summary, we have developed a proline-based P,O,N tridentate ligand for the copper-catalyzed asymmetric alkylation of allylic phosphates. The capability of the ligand to hold Cu and Zn atoms together in close proximity must be the driving force for the asymmetric induction. The calculated structures of the diastereomeric complexes and transitions states provide a pictorial illustration of the way that a multidentate ligand would hold many metal atoms together and exert cooperative effects.[3–5]

Experimental Section

Typical Procedure

A solution of $CuCl_2 \cdot 2H_2O$ (8.5 mg, 0.05 mmol) and **L5** (27.0 mg, 0.06 mmol) in CH_2Cl_2 (0.5 mL) was stirred for 1 h at room temperature. The solution was then cooled to −78 °C, and an allylic phosphate (0.5 mmol) was added dropwise. After stirring for 15 min, Et_2Zn (1.0 M in hexane, 0.75 mL, 0.75 mmol) was added over 3 min, and the reaction mixture was stirred for 3 d. The reaction was quenched by MeOH (0.3 mL) and saturated Rochelle salt solution (1 mL). After extraction with Et_2O (1 mL × 3), the combined organic layer was passed through a small plug of silica gel and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane) to obtain the desired allylation product.

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[15] For details of the computational method, see Supporting Information.

