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Aminohydroxyphosphine Ligand for the Copper-Catalyzed Enantioselective Conjugate Addition of Organozinc Reagents

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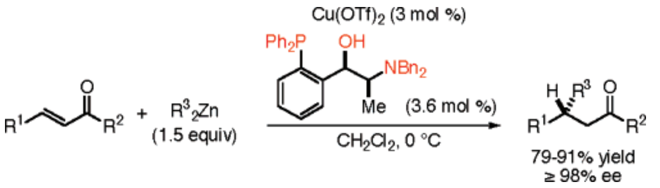
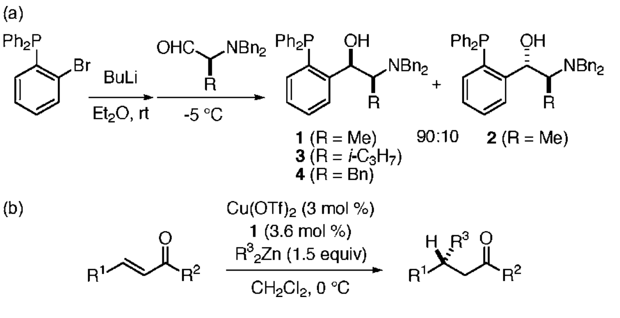
ABSTRACT



An alanine-derived aminohydroxyphosphine ligand was developed for copper-catalyzed asymmetric conjugate addition of organozinc reagents to α,*β*-unsaturated carbonyl compounds. This new tridentate ligand induces consistently high enantioselectivity in reactions of a variety of acyclic substrates. Theoretical mechanistic analysis suggests that the C–C bond formation takes place through a highly ordered transition state by the coordination of the phosphorus and nitrogen atoms to the copper(III) and zinc(II) atoms, respectively, and of the oxygen anion to both the metal centers.

Copper-catalyzed conjugate addition of a main group organometallic reagent to an enone is an illustrative example of the intricacy of multimetallic catalysis.[1] It is this complexity that has hampered the development of catalytic enantioselective additions until recently.[2,3] A common feature of the chiral ligands developed in the past is their multiligation ability,[2] but its function remained rather unclear. We suggested some time ago that an effective ligand must effectively coordinate to the copper(III) center on one hand and to the main group metal center on the other.[4] We report here a new tridentate ligand **1** for the enantioselective conjugate addition of an organozinc reagent to a variety of α,*β*-unsaturated carbonyl compounds (Scheme 1b) developed on the basis of this guiding principle. The ligand **1** was synthesized in one step by addition of lithiated triphenylphosphine to *N*,*N*-dibenzylalaninal (Scheme 1a).[5] The modular synthesis is a useful feature of this ligand design. A working model of the ligand acceleration of the reaction is also provided (Figure 1).

Scheme 1



We recently reported a Ni-catalyzed cross-coupling reaction of a Grignard reagent where a hydroxyphosphine ligand was employed to promote synergy between nickel and magnesium atoms.[6] On the basis of these experiments and a series of theoretical studies on organocopper reactions,[7] we modeled computationally C−C bond forming transition states

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(1) *Multimetallic Catalysts in Organic Synthesis*; Shibasaki, M., Yamamoto, Y., Eds.; Wiley-VCH: Weinheim, 2004.

(2) (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221−3236. (b) Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: Weinheim, 2002; pp 224−258. (c) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171−196.

10.1021/ol0618306 CCC: $33.50

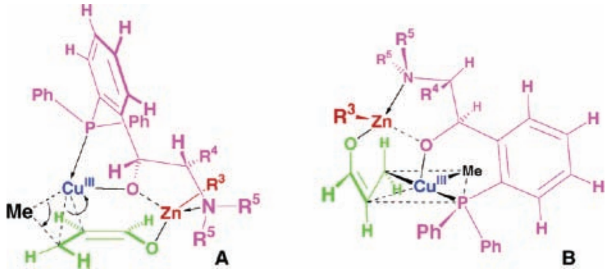

Figure 1. Schematic representations of a C−C bond formation TS (**A**) and a π-complex (**B**) in the conjugate addition reaction based on density functional calculations of a simplified model (R^3 = Me or Cl, R^4 = H, R^5 = Me).

(TSs) of the organocopper conjugate addition (cf. Figure 1) and conceived a variety of possible ligand structures that form rigid Cu/Zn bimetallic complexes. After experimental screening of several practical candidates, the aminohydroxyphosphine **1** emerged as a promising ligand.

Representative results of the screening of the ligand and the reaction conditions as studied for the addition of Et_2Zn to *trans*-3-nonen-2-one are summarized in Table 1. The ligand **1** gave an enantioselectivity of up to 98% ee at 0 °C (entries 1, 6, 7, and 10−12), whereas its diastereomer **2** gave virtually no selectivity with a much slower reaction rate (entry 2). This is a practical merit of the use of **1** because a 90:10 mixture of diastereomers **1** and **2** as synthesized (Scheme 1a) gives essentially the same enantioselectivity as pure **1** (entry 3). Ligands derived from bulkier aminoaldehydes gave lower selectivity (entries 4 and 5). Choice of solvent is important.[2] Noncoordinating solvents are superior to coordinating solvents including bidentate 1,2-dimethoxyethane (DME, entries 6−9). The enantioselectivity is also sensitive to the countercation of the copper source. Oxygen anions are uniformly better than halide anions (entries 10−14). The slower reaction rate and the inferior enantioselectivity by CuBr·Me_2S than by CuBr suggest that Me_2S competes with the ligand **1**. On the basis of these results, we employed $Cu(OTf)_2$ and CH_2Cl_2 at the synthetically convenient temperature of 0 °C in the following studies, and some other choices may also be effective.

Table 1. Enantioselective Conjugate Addition to *trans*-3-Nonen-2-one[a]

entry	ligand	Cu salt	solvent	time/h	yield/%	ee/%
1	**1**	$Cu(OTf)_2$	CH_2Cl_2	3	91	98 (*S*)
2	**2**	$Cu(OTf)_2$	CH_2Cl_2	11	80	−3
3^b	**1 + 2**	$Cu(OTf)_2$	CH_2Cl_2	3	90	96
4	**3**	$Cu(OTf)_2$	CH_2Cl_2	3	87	23
5^c	**4**	$Cu(OTf)_2$	CH_2Cl_2	3	86	30
6	**1**	$Cu(OTf)_2$	toluene	2	90	88
7	**1**	$Cu(OTf)_2$	Et_2O	2	85	87
8	**1**	$Cu(OTf)_2$	THF	12	55	66
9	**1**	$Cu(OTf)_2$	DME	12	15	3
10	**1**	Cu(OTf)	CH_2Cl_2	3	90	95
11	**1**	$Cu(OAc)_2$	CH_2Cl_2	5	85	96
12	**1**	CuI	CH_2Cl_2	12	78	93
13	**1**	CuBr	CH_2Cl_2	12	39	71
14	**1**	CuBr·Me_2S	CH_2Cl_2	12	45	56

[a] Conditions: 3 mol % of Cu salt, 3.6 mol % of ligand, 1.5 equiv of Et_2Zn, 0 °C. [b] A 9:1 mixture of **1** and **2** was used. [c] Ligand **4** was used as a diastereomeric mixture (86:14).

Table 2 illustrates representative results of the addition of Me_2Zn and Et_2Zn to a variety of α,β-unsaturated carbonyl compounds. The substrate scope of the present catalytic system has proven to be very wide. Acyclic enones reacted in uniformly high enantioselectivity (≥98% ee) and good yield (79−91%); they are known as poor substrates for this class of reactions, and enantioselectivities of >95% are rare.[2,3a,b,d−h,k,l] The reaction was applicable to chalcone (entry 1) and aliphatic enones with β-aryl (entries 2−7) and alkyl (entries 8−11) substituents. The electronic (entries 3−5) and steric (entries 9 and 11) properties of the β-substituents did not affect the selectivity. Furyl and thienyl substituents did not show any adverse effect on the reaction (entries 6 and 7). The two organozinc reagents showed the same level of selectivity of 98% ee: Me_2Zn was less reactive but still gave good yields (entries 2, 3, 8, and 9).[3f] The reaction can be carried out on as much as a 10-mmol scale without significant decrease of enantioselectivity (entry 10). The reaction of a trisubstituted cyclic enone proceeded in excellent selectivity of >98% ee (entry 12).[3d] Cyclic enones are poorer substrates for the ligand **1** suggesting in turn that s-cis conformers take part in the reaction of acyclic enones: 2-cyclohexenone was only moderately selective (82% ee, entry 13), and 2-cycloheptenone was poorly selective (16% ee, see Supporting Information). α,β-Unsaturated esters are unreactive, but the corresponding imide took part in the reaction smoothly and gave excellent selectivity of 98.7% ee (entry 14).[3e]

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(6) Yoshikai, N.; Mashima, H.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 17978−17979.

(7) Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750−3771.

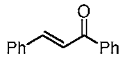
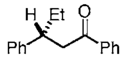
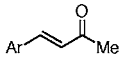
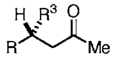
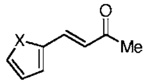
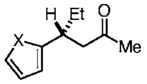
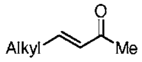
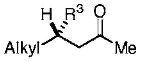
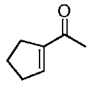
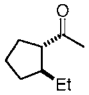
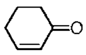
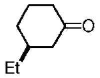
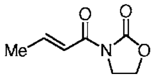
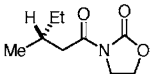
(8) (a) Yamanaka, M.; Nakamura, E. *Organometallics* **2001**, *20*, 5675−5681. (b) Canisius, J.; Gerold, A.; Krause, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 1644−1646. (c) Frantz, D. E.; Singleton, D. A.; Snyder, J. P. *J. Am. Chem. Soc.* **1997**, *119*, 3383−3384. (d) Woodward, S. *Chem. Soc. Rev.* **2000**, *29*, 393−401.

Being aware of the complexity of the conjugate addition of lithium organocuprates[7−9] and, especially, that of copper-catalyzed addition of organozinc and magnesium reagents,[10] we consider it premature to discuss details of the mechanism of the whole catalytic cycle. Therefore, we only discuss the C−C bond forming stage of the reaction, which most likely comprises the step where the enantioselectivity is determined. Figure 1 shows a TS model of the addition of a heterocuprate complex of MeCu and **1** to an *s-cis*-acrolein (**A**, focused on the substrate) based on a computational modeling of a simplified model (R^3 = Me or Cl, R^4 = H, R^5 = Me; B3LYP/6-31G(d) and equivalent basis sets).[11] The structure of the π-complex (**B**, focused on the Cu atom) preceding the TS is essentially the same as the TS structure.

The first important common structural feature is that the Lewis acidic zinc atom and the nucleophilic copper atom are properly located to effect ligand acceleration of the conjugate addition. The central oxygen anion plays the role of a counteranion for the zinc atom and that of a basic ligand to the copper atom to form a reactive cuprate complex. *S-trans*-Acrolein where the molecule is in its extended conformation does not fit into this rigid coordination environment. The large difference between **1** and **2** can be rationalized on the basis of the positioning of the R^4 methyl group that controls the relative orientation between the nearby benzene group and the nitrogen substituent.

The second important feature is that the zinc(II) geometry is tetrahedral and the copper(III) geometry is square-pyramidal (cf. **B**): one Me group, a β-carbon atom, a phosphorus atom, and the zinc enolate occupy the equatorial positions, and the alkoxide coordinates from the apical site. The activation energy of reductive elimination is quite low (ca. 11 kcal/mol) because of the relatively weak donating ability of the ligands.[12]

Table 2. Enantioselective Conjugate Addition to α,β-Unsaturated Carbonyl Compounds[a]

entry	substrate	R^3	product	time/h	yield/%[b]	ee/%[c]
1		Et		4	90	> 98 (*R*)
						
2[d]	Ar = Ph	Me		16	83	> 98 (*R*)
3	Ar = Ph	Et		3	91	> 98 (*R*)
4	Ar = 4-$NO_2C_6H_4$	Et		5	79	> 98 (–)
5	Ar = 4-$MeOC_6H_4$	Et		5	91	> 98 (–)
						
6	X = O	Et		3	89	98.9 (–)
7	X = S	Et		3	90	98.1 (–)
						
8[d]	Alkyl = *n*-C_5H_{11}	Me		12	90	98.1 (*S*)
9	Alkyl = *n*-C_5H_{11}	Et		3	91	97.9 (*S*)
10[e]	Alkyl = *n*-C_5H_{11}	Et		5	93	97 (*S*)
11[f]	Alkyl = *i*-C_3H_7	Et		12	81	98.1 (–)
12		Et		3	86	> 98 (–) (*dr* = 62:38)
13		Et		1.5	92	82 (*S*)
14		Et		3	91	98.7 (*R*)

[a] The reaction was carried out on a 1-mmol scale as described in Scheme 1b unless otherwise noted. [b] Isolated yields. [c] The selectivity was determined by chiral HPLC (entries 1−5), GLC (entries 6−12 and 14), or NMR analysis after derivatization to diastereomeric ketals (entry 13). [d] 2 equiv of Me_2Zn was used. [e] The reaction was carried out on a 10-mmol scale. [f] 5 mol % of $Cu(OTf)_2$ and 6 mol % of **1** were used.

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Supporting Information Available: Details of experimental and computational procedures, spectral data for new compounds, and Cartesian coordinates for optimized structures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) A square planar geometry has been described for the intermediate of the conjugate addition of a lithium organocuprate (Me_2CuLi),[8a] and the four ligands on the copper atom consist of two Me groups, a β-carbon atom, and a lithium enolate moiety. These σ-donating ligands stabilize the high oxidation state of the copper atom, and therefore, the activation energy of reductive elimination is rather high (15[8a]−18[8b] kcal/mol with 4,4-dimethylcyclohexenone).