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Bis(oxazoline)-Copper Catalyzed Enantioselective Hydrophosphonylation of Aldehydes

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A highly enantioselective copper-catalyzed hydrophosphonylation of aldehydes in the presence of bis(oxazoline) ligand is presented. The reaction proceeded smoothly under mild conditions. The resulting α-hydroxyphosphonates were obtained with high yields as well as enantioselectivities (up to 98% *ee*).

Chiral bis(oxazoline) (BOX) ligands were first used in 1991[1,2] and since that time, a large number of such ligands have been reported.[3] BOX ligands have been applied to the asymmetric catalysis of a wide variety of key organic reactions, such as Friedel-Crafts reaction,[4] Mukaiyama-Michael reaction[5] and so on. In general, the BOX ligands reported to date are predominantly based around the same ligand backbone with variation in the pendant groups at the two available positions in the oxazoline ring or on the bridgehead atom. Hence, a variety of bisoxazoline derivatives have been prepared and extensively utilized in asymmetric catalysis, in addition to other chiral ligands.[6]

Phosphonic acids and their phosphonate derivatives are of immense interest in organic chemistry due to their biological activities.[7] These molecules, such as α-aminophosphonates, α-hydroxyphosphonates, have found a wide range of applications in the areas of fine chemical, biological, and medicinal chemistry, as inhibitors of synthase, HIV protease, antibiotics, enzyme inhibitors, anti-thrombotic agents, herbicides, fungicides, insecticides, plant growth regulators and as substrates in the synthesis of phosphonopeptides.[8] The addition of dialkyl phosphites to carbonyl compounds, known as Pudovik reaction, is a direct and atom-economical method for the synthesis of α-hydroxyphosphonates and for C-P bond formation.[9] Since the pioneering chiral organocatalytic example appeared in 1983,[10] in which a limited number of aldehydes (only two) was disclosed, much attention has been paid to developing enantioselective catalysts for the synthesis of chiral α-hydroxyphosphonates.[11] Chiral aluminium complexes (e.g. Al(salen) and Al(salcyen) catalysts, Al-Schiff base) are the most successful among the chiral catalysts[12]. During the last decade, Feng and co-workers reported the first highly efficient Lewis-acid-catalyzed hydrophosphonylations in the presence of $Ti(OiPr)_4$ or Et_2AlCl as catalysts. Then it was found that $Ln(OTf)_3$ species (Ln=Sc, La, Yb) exhibited catalytic activities for hydrophosphonylations of acetophenones.[13] Very recently, Herrera and co-workers reported the results concerning the first asymmetric squaramide-organocatalyzed Pudovik reaction.[14]

Although the asymmetric addition of dialkyl phosphites to aldehydes has been successfully studied by different groups, strong bases have been the most general reagents for the synthesis of α-hydroxyphosphonates until now. However, the yields were not always good and complex mixtures were sometimes obtained, due to side reactions.[15] These results showed that new and more effective catalysts need to be developed for highly enantioselective dialkyl phosphite additions to aldehydes. Following our interest in asymmetric synthesis using bis-oxazoline ligands,[16] we hypothesized that this bis(oxazoline) ligand would afford a high level of chiral induction in the hydrophosphonylation reactions of aldehydes because of the presence of steric hindrance. Herein, we report the results of the copper-catalyzed hydrophosphonylation of aldehydes in the presence of bis(oxazoline) ligands.

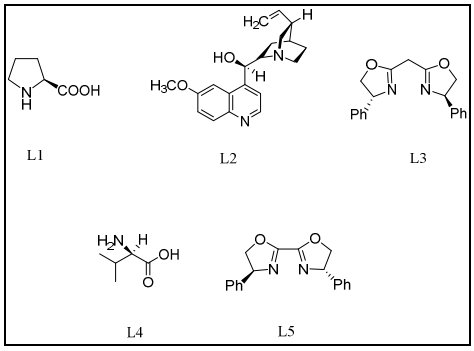
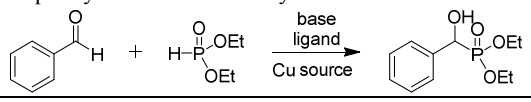


Figure 1 Selected examples of chiral ligands examined

Firstly, a preliminary screening of different privileged ligands (Figure 1), such as L-proline (L1), quinine (L2), D-valine (L4) and bis(oxazoline) (L3 and L5), was carried out with $CuBr_2$ using methanol as solvent and K_3PO_4 as base. Good enantioselectivities at room temperature were obtained only with the BOX-type ligands (L3, L5), the best result being those obtained with Ph-BOX (L3) (Table 1, entry 3). Copper complexes based on other chiral ligands were found to catalyze the reaction in low yields with moderate enantiomeric excess.

Table 1 Optimization of the conditions for the hydrophosphonylation of benzaldehyde[a]



Entry	L	Cu source	Base	Solvent	Yield[b]/%	*ee*[c]/%
1	L1	$CuBr_2$	K_3PO_4	MeOH	37	58
2	L2	$CuBr_2$	K_3PO_4	MeOH	53	64
3	L3	$CuBr_2$	K_3PO_4	MeOH	41	94
4	L4	$CuBr_2$	K_3PO_4	MeOH	48	76
5	L5	$CuBr_2$	K_3PO_4	MeOH	45	88
6	L3	$CuBr_2$	K_3PO_4	hexane	nr	--
7	L3	$CuBr_2$	K_3PO_4	toluene	nr	--
8	L3	$CuBr_2$	K_3PO_4	DMSO	nr	--
9	L3	$CuBr_2$	K_3PO_4	MeCN	nr	--
10	L3	$CuBr_2$	K_3PO_4	CH_2Cl_2	71	86
11	L3	$CuBr_2$	K_3PO_4	DMF	33	64
12	L3	$CuBr_2$	K_3PO_4	Et_2O	67	90
13	L3	$CuBr_2$	K_3PO_4	dioxane	49	92
14	L3	$CuBr_2$	K_3PO_4	THF	76	96
15	L3	$CuBr_2$	Na_2CO_3	THF	67	84
16	L3	$CuBr_2$	K_2CO_3	THF	53	94
17	L3	$CuBr_2$	DBU	THF	33	28
18	L3	$CuBr_2$	DABCO	THF	38	72
19	L3	$CuBr_2$	TEA	THF	29	66
20	L3	$CuBr_2$	NaOEt	THF	nr	--
21	L3	$CuBr_2$	t-BuOK	THF	nr	--
22	L3	$Cu(TFA)_2$	K_3PO_4	THF	63	94
23	L3	$Cu(OTf)_2$	K_3PO_4	THF	37	82
24	L3	$CuCl_2$	K_3PO_4	THF	nr	--
25	L3	$Cu(OAc)_2$	K_3PO_4	THF	81	96

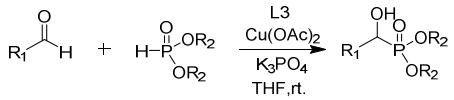
[a] Unless otherwise specified, all reactions were carried out at room temperature with benzaldehyde (1.0 mmol), diethyl phosphite (1.2 mmol), base (0.2 mmol), Cu source(0.1 mmol) and ligand(0.1 mmol) in the solvent (1 mL) for 24 hours.[b] Isolated yields after column chromatography.[c] The *ee* values were determined by chiral HPLC using a Ultron ES-OVM column.

Next, solvents were evaluated for this reaction (Table 1, entries 6-14). Tetrahydrofuran gave the best result in terms of both yield and enantioselectivity (76% yield, 96% *ee*, Table 1, entry 14). In the case of using hexane, toluene, dimethyl sulfoxide and acetonitrile as solvent, no reaction occured.

Subsequently, we focused on optimizing the base for the hydrophosphonylation. Inorganic bases have been considered to facilitate the hydrophosphonylation reaction without eroding the enantioselectivity because they exhibit a relatively weak basicity and a low solubility in THF. The results of the base screening (Table 1, entries 14-21) showed that 0.1 equivalent of inorganic bases, such as Na_2CO_3, K_2CO_3, K_3PO_4, produced hydroxyphosphonates with higher *ee* values (84%, 94% and 96%, respectively) than that of organic bases, such as TEA, DBU and DABCO. NaOEt and t-BuOK afford only traces of product, and the non-nucleophilic organic base DBU affords almost racemic phosphonate (only 28% *ee*).

Additionally, we explored other copper sources, such as $Cu(TFA)_2$, $Cu(OTf)_2$, $CuCl_2$, $Cu(OAc)_2$, and $Cu(OAc)_2$ was found to be the best choice for the hydrophosphonylation of benzaldehyde to obtain good yields and enantioselectivity (Table 1, entry 25). In the case of using $Cu(TFA)_2$ or $Cu(OTf)_2$, low conversion and enantioselectivity were obtained (Table 1, entries 22, 23). The reaction did not occur with $CuCl_2$ as copper source (Table 1, entry 24).

Table 2 Enantioselective hydrophosphonylation of various aldehydes[a]



Entry	R1	R2	Product	Yield[b]/%	*ee*[c]/%
1	Ph	Et	**1a**	81	96(S)[d]
2	4-$MeOC_6H_4$	Et	**2a**	75	98(S)[d]
3	3-$NO_2C_6H_4$	Et	**3a**	67	96(S)[d]
4	4-MeC_6H_4	Et	**4a**	76	97(S)[d]
5	4-ClC_6H_4	Et	**5a**	73	94(S)[d]
6	4-$CF_3C_6H_4$	Et	**6a**	91	74
7	3-$CF_3C_6H_4$	Et	**7a**	86	95(S)[d]
8	2-$CF_3C_6H_4$	Et	**8a**	83	88
9	4-CNC_6H_4	Et	**9a**	69	91(S)[d]
10	2-$NO_2C_6H_4$	Et	**10a**	42	96
11	2-furyl	Et	--	nr	--
12	2-thienyl	Et	--	nr	--
13	2-pyridinyl	Et	**11a**	71	79
14	Ph	iPr	--	nr	--
15	1-naphthyl	Et	**12a**	84	69(S)[d]
16	(E)-PhCH=CH	Et	**13a**	53	67(S)[d]

[a] Unless otherwise specified, all reactions were carried out at room temperature with aldehyde (1.0 mmol), diethyl phosphite (1.2 mmol), K_3PO_4 (0.2 mmol), $Cu(OAc)_2$ (0.1 mmol) and L3 (0.1 mmol) in the THF (1 mL) for 24 hours.[b] Isolated yields after column chromatography.[c] The *ee* values were determined by chiral HPLC using a Ultron ES-OVM column. [d] The absolute configurations were determined by comparison with literature data.

Table 2 shows the result of the hydrophosphonylation of various aldehydes under the optimal conditions. Most of the aldehydes rendered moderate to excellent yields (up to 91%) and *ee* values (up to 98%) of α-hydroxyphosphonates. The aromatic aldehydes possessing a strong electron-donating group at the *para*-position showed a high enantioselectivity; for instance, 4-methoxybenzaldehyde and 4- methylbenzaldehyde formed **2a** and **4a** with 98% *ee* and 97% *ee*, respectively (Table 2, entries 2 and 4). Electron-withdrawing halogen substituent slightly reduced the enantioselectivity (Table 2, entry 5). With strong electron-withdrawing groups on the phenyl ring led to lower yields and enantioselectivities (Table 2, entries 3, 6-10). Regardless of the electronic nature of the substituents on the aryl groups, it was also found that the steric hindrance of the substrates had an effect on the reactivities of hydrophosphonylation of aldehydes, with the corresponding products being obtained in higher yields but with obvious loss of *ee* values (Table 2, entries 6-8). The addition of diethyl phosphite to 4- trifluoromethyl benzaldehyde, for example, afforded the product 6a in 91% yield and 74% *ee* (Table 2, entry 6), the addition to 2- trifluoromethyl benzaldehyde gave **8a** in 83% yield and 88% *ee* (Table 2, entry 8). However, the addition to 3-trifluoromethyl benzaldehyde afforded **7a** in an excellent *ee* of 95% (Table 2, entry 7). For heterocyclic aldehydes, 2-

pyridinecarboxaldehyde was also converted to the α-hydroxyphosphonate **11a** with 79% *ee* in 71% yield (Table 2, entry 13), while no desired α-hydroxyphosphonates were obtained for furfural and 2-thienaldehyde (Table 2, entries 11 and 12). Unfortunately，we found that no desired product was obtained with bulky diisopropyl phosphite due to side reaction (Table 2, entry 14). While the condensed-ring aldehydes (1-naphthaldehyde) reacted smoothly with diethyl phosphite, giving the product with 69% *ee* (Table 2, entry 15), the α,β-unsaturated aldehyde (cinnamaldehyde) showed a slightly reduced reactivity and enantioselectivity (Table 2, entry 16).

Conclusions

In summary, we have demonstrated for the first time that $Cu(OAc)_2$ paired with Ph-BOX (L3) turned out to be a good catalytic system to accomplish the asymmetric hydrophosphonylation of aldehydes with diethyl phosphite. This process was applied to a wide variety of aldehydes and in most of the cases good yields and enantioselectivities were achieved. Our work in this area is currently ongoing particularly in the application of metal complexes of the bis(oxazoline) ligands to the catalysis of different reactions.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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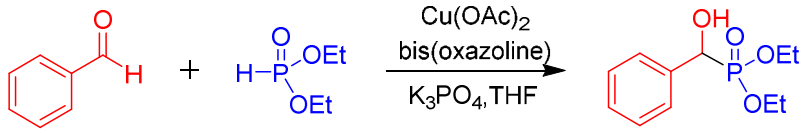
Graphical Abstract



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