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New Applications of Bis(oxazoline) Ligands in Catalysis: Asymmetric 1,2- and 1,4-Addition of ZnR_2 to Carbonyl Compounds

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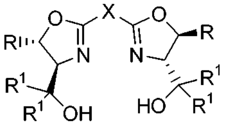
ABSTRACT



The enantioselective addition of ZnR_2 to aldehydes (1,2) and cyclic enones (1,4) was accomplished using bis(oxazolines) as chiral ligands. The requirement for hydroxymethylene side chains in the ligands strongly suggests that bimetallic catalysts are decisive for high enantiocontrol in these additions.

Conjugate additions of carbon nucleophiles to α,*β*-unsaturated carbonyl compounds are among the most useful transformations in organic synthesis.[1] Most prominently, this chemistry has been developed with organocuprates; nevertheless, the design of asymmetric variants for such processes has proved to be very difficult.[2]

The conjugate 1,4-addition of alkylzinc compounds to enones has found considerable attention because of the mild reaction conditions and high functional group tolerance zinc reagents offer.[3] This process could be rendered asymmetric by employing chiral nickel catalysts with amino, pyridinyl, or mercapto alcohols as chiral ligands.[4] Recently, phosphoramidites,[5] peptide-based phosphine ligands[6] and oxazoline-phosphite ligands[7] in combination with copper(I) or copper(II) salts have been found to be highly efficient chiral ligands, promoting especially the asymmetric 1,4-addition of organozinc reagents to cyclic enones.[8,9]

The common mechanism of the reaction calls for the transfer of an alkyl group from zinc to a chiral copper complex, which is subsequently capable of delivering the alkyl group to the enone enantioselectively. However, if this is the mode of action, it is surprising that many chiral copper catalysts fail to give useful asymmetric inductions in 1,4-addition processes. For example, bis(oxazolines) such as **1** form a superior chiral environment, for both copper(I) and copper(II), which has been applied to asymmetric cycload-

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[1] Perlmutter, P. In *Conjugate Addition Reactions in Organic Synthesis*, *Tetrahedron Organic Chemistry Series*; Pergamon Press: Oxford, 1992.

[2] Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Heidelberg, 1999; Vol. III, pp 1105−1120.

[3] Review: Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414−4435.

[4] (a) Yin, Y. W.; Li, X. S.; Lee, D. S.; Yang, T. K. *Tetrahedron: Asymmetry* **2000**, *11*, 3329−3333 and references therein. (b) Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. *J. Org. Chem.* **1988**, *53*, 4149.

[5] (a) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346−353. (b) Imbos, R.; Brilman, M. H. G.; Pineschi, M.; Feringa, B. L. *Org. Lett.* **1999**, *1*, 623−625.

[6] Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755−756.

[7] Escher, I. H.; Pfaltz, A. *Tetrahedron* **2000**, *56*, 2879−2888.

[8] Reviews: (a) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 711−806. (b) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033−8061. (c) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, *2*, 171−196 and references therein.

[9] Recent examples: (a) Dieguez, M.; Deerenberg, S.; Pamies, O.; Claver, C.; van Leeuwen, P.; Kamer, P. *Tetrahedron: Asymmetry* **2000**, *11*, 3161−3166. (b) Pamies, O.; Dieguez, M.; Net, G.; Ruit, A.; Claver, C. *Tetrahedron: Asymmetry* **2000**, *11*, 4377−4383. (c) Mandoli, A.; Arnold, L. A.; de Vries, A. H. M.; Salvadori, P.; Feringa, B. L. *Tetrahedron: Asymmetry* **2001**, *12*, 1929−1937.

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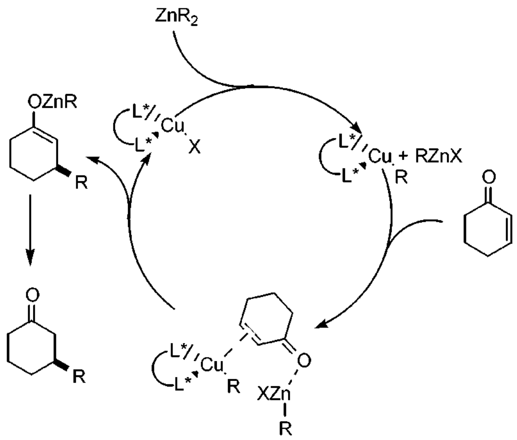
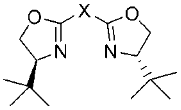
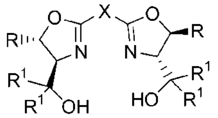
Scheme 1. Mechanism for the Copper-Catalyzed 1,4-Addition of Diorganozinc to 2-Cyclohexenone



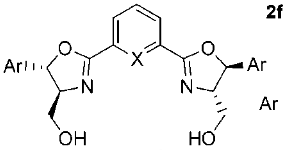
ditions, Mukaiyama aldol reactions, cyclopropanations, Michael reactions, carbonyl ene reactions or allylic oxidations with excellent results.[10]



1a: X = CMe$_2$
1b: X = NH

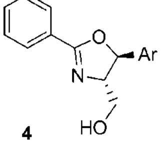


2a: X = CH$_2$, R = Ph, R^1 = H
2b: X = CMe$_2$, R = Ph, R^1 = H
2c: X = CMe$_2$, R = p-SMe-Ph, R^1 = H
2d: X = CMe$_2$, R = H, R^1 = Me
2e: X = CMe$_2$, R = H, R^1 = Ph
2f: X = (CH$_2$)$_2$, R = Ph, R^1 = H



3a: X = CH
3b: X = N

Ar = *p*-SMe-Ph



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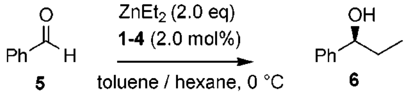
In contrast, the addition of diethylzinc to cyclohexenone in the presence of Cu(OTf)$_2$·**1a** or Cu(OTf)$_2$·**1b** proceeded well (>65% yield); however, we obtained only racemic product. Similar unsuccessful results were also reported by Pfaltz et al. using semicorrine ligands.[7,11] Very recently, the asymmetric 1,4-addition of Grignard reagents to enamidomalonates was achieved by Sibi et al. using an anionic bis(oxazoline). However, stoichiometric amounts of ligand were required.[12]

We were intrigued by the question whether both metals, zinc *and* copper, involved in this process need to reside in a chiral environment to achieve 1,4-additions enantioselectively. Amino alcohols are the ligands of choice in diethylzinc 1,2-additions to aldehydes,[13] and also oxazolines having hydroxymethylene side chains have been employed for this reaction, albeit enantioselectivities have been moderate.[14] We reasoned that bis(oxazolines) **2**, **3**, and **4**[15] are also suitable ligands for this process by coordinating zinc via one oxazoline and its adjacent alcohol functionality. Moreover, the bis(oxazoline) moiety should be able to coordinate copper, *therefore* **2** *could be able to provide two spatially separated coordination sites for zinc and copper*.

Table 1. Addition of ZnEt$_2$ to Benzaldehyde in the Presence of Ligands **1**−**4**



entry	ligand	time (h)	yield (%)	% ee
1	**1a**	40	60	20
2	**2a**	48	0	
3	**2b**	45	96	93
4	**2c**	96	56	83
5	(*ent*)-**2d**	48	0	
6	(*ent*)-**2e**	48	0	
7	(*ent*)-**2f**	52	5	0
8	**3a**	96	53	50
9	**3b**	96	19	0
10	**4**	96	31	49

To test this hypothesis we first carried out diethylzinc additions to benzaldehyde in the presence of catalytic amounts of various ligands **1**−**4** (Table 1). Again, **1a** promoted the reaction quite well, giving rise to **6** in 60% yield (entry 1), but the selectivity was low. With bis(oxazoline) ligands **2**−**4** bearing hydroxymethylene side chains, more promising results were obtained, which, however, varied greatly with the ligand structures. Compound **2a**, being the only anionic ligand in this series as a result of its methyleno bridge that is easily deprotonated, failed to catalyze the diethyl zinc addition at all (entry 2). In contrast, the *gem*-dimethyl-substituted ligands **2b** and **2c** are highly active promoters (entries 3 and 4). We attribute the lower yield and selectivity of **2c** to the decreased solubility in toluene/hexane compared to that of **2b**. Interestingly, the mono(oxazoline) **4** as well as the bis(oxazoline) **3a**, having the two oxazoline units spatially separated, promoted the

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[10] Representative examples*:* (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328−5329. (c) Johannnsen, M.; Jørgensen, K. A. *J. Org. Chem.* **1995**, *60*, 5757−5762. (d) Gokhale, A. S.; Minidis, A. B. E.; Pfaltz, A. *Tetrahedron Lett.* **1995**, *36*, 1831−1834. (e) Glos, M.; Reiser, O. *Org. Lett.* **2000**, *2*, 2045−2048.

[11] (a) Knobel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* **1997**, 1429−1431.

[12] Sibi, M. P.; Asano, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9708−9709.

[13] Reviews: (a) Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin Heidelberg, 1999; Vol. II, pp 911−922. (b) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824.

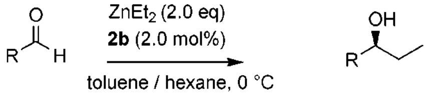
[14] Allen, J. V.; Frost, C. G.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1993**, *4*, 649−650.

[15] The syntheses of the following ligands have been reported before. **2a**: Hall, J.; Lehn, J.-M.; DeCian, A.; Fischer, J. *Helv. Chim. Acta* **1991**, *74*, 1−6. **2b**: Aggarwal, V. K.; Bell, L.; Coogan, M. P.; Jubault, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2037−2042. **4**: Schumacher, D. P.; Clark, J. E.; Murphy, B. L.; Fischer, P. A. *J. Org. Chem.* **1990**, *55*, 5291−5294.

formation of **6** with moderate but considerably decreased enantioselectivty (entries 8 and 10) compared to that of **2b**. Obviously, a second oxazoline unit plays a key role to achieve high selectivity, which might suggest that **2b** coordinates two zinc metals acting in a cooperative way. Increasing the steric bulk in the chiral pocket might therefore not be tolerated (entries 5 and 6), but also the introduction of a more flexible linker was detrimental for the catalysis of the reaction (entry 7).

Having identified **2b** as the best ligand, other aldehydes for diethylzinc addition were tested. Indeed, these reactions proceeded well, and high enantioselectivites could be obtained especially with aromatic aldehydes (Table 2, entries 1−6).

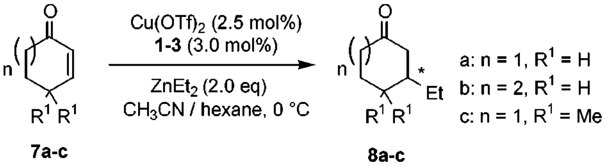
Table 2. Addition of $ZnEt_2$ to Aldehydes in the Presence of **2b** (2 mol %)



entry	R	*n*-BuLi (mol %)	time (h)	yield (%)	% ee
1	Ph	0	45	96	93
2	*p*-OMe-Ph	0	50	99	95
3	*p*-Cl-Ph	0	45	76	83
4	*p*-Cl-Ph	4	90	92	87
5	*p*-F-Ph	0	89	74	88
6	*p*-F-Ph	4	90	84	87
7	*n*-Hex	0	90	31	36
8	*n*-Hex	2	100	60	66
9	*n*-Hex	4	25	78	75
10	*n*-Hex	6	25	68	47
11	*n*-Hex	7	25	61	38

In the case of aliphatic aldehydes (entries 7−11) both yield and enantioselectivity could be considerably increased by the addition of catalytic amounts of butyllithium. This additive most likely causes the deprotonation of the alcohol functionality in **2b**, as was also observed when amino alcohols are used as chiral ligands.[16] A systematic variation of the added amount of butyllithium revealed that optimal results are obtained if the ratio of **2b** and the base is 1:2, thus indicating that deprotonation of both hydroxyl groups in the ligand is important. Likewise, the addition of butyllithium had a beneficial effect on the yield for aromatic aldehydes bearing electron withdrawing substituents (entries 3−6).

Table 3. 1,4-Addition of Et_2Zn (2 equiv) to Enones in the Presence of $Cu(OTf)_2$ (2.5 mol %) and **1**−**3** (3 mol %)



entry	ligand	enone	temp (°C)	time (h)	yield (%)	% ee
1	**1a**	**7a**	0	40	65	0
2	**1b**	**7a**	0	22	70	0
3	**2a**	**7a**	0	43	72	6 (*S*)
4	**2b**	**7a**	20	15	82	77 (*S*)
5	**2b**	**7a**	10	17	83	89 (*S*)
6	**2b**	**7a**	5	19	81	92 (*S*)
7	**2b**	**7a**	0	20	93	94 (*S*)
8	**2b**	**7a**	−18	40	80	67 (*S*)
9[a]	**2b**	**7a**	0	14	79	0
10[b]	**2b**	**7a**	0	50	81	32 (*S*)
11	**2c**	**7a**	0	48	81	90 (*S*)
12	(*ent*)-**2d**	**7a**	0	30	43	21 (*R*)
13	(*ent*)-**2e**	**7a**	0	28	52	8 (*R*)
14	(*ent*)-**2f**	**7a**	0	40	57	42 (*R*)
15	**3a**	**7a**	0	48	55	0
16	**3b**	**7a**	0	48	64	0
17	**2b**	**7b**	0	21	71	41[c]
18	**2b**	**7c**	0	140	42	8[c]

[a] Additive: 2.0 equiv of TMSCl. [b] Additive: 0.5 equiv of water. [c] Configuration not determined.

Encouraged by these results, we next attempted to apply **2** and **3** toward copper(II)-catalyzed conjugate additions of diethylzinc to enones (Table 3). In contrast to the 1,2-additions, all ligands promoted the addition of diethylzinc to cyclohexenone reasonably well (43−93% yield), although the enantioselectivities greatly varied (0−94% ee). The 1,4-addition in the presence of the anionic ligand **2a**—albeit requiring longer reaction times compared to the neutral analogue **2b**—proceeded smoothly (72% yield, entry 3), but virtually no enantioselectivity was induced. Again, **2b** and **2c** proved to be superior ligands, yielding (*S*)-**8a** in up to 94% ee (entries 4−11). In difference to the phosphoramidite ligands,[5] which work best at −30 °C, for our ligand system we determined the optimal reaction temperature between 0 and +10 °C, allowing this transformation to be carried out conveniently in an ice bath.

The importance of the interplay of zinc *and* copper in the coordination sphere of the ligand became apparent, in addition to the failure of **1a** and **1b** to induce selectivity (entries 1 and 2), with the sharp decrease of enantioselectivity in the presence of TMSCl[17] or water[18] (entries 9 and 10), being generally useful additives in 1,4-additions of diethylzinc. While TMSCl could serve to coordinate the carbonyl group of the enone instead of zinc or silylate the hydroxy groups of the ligand, water might compete as an external ligand with the hydroxy group in **2b** for a zinc atom. In both cases the communication of the ligand side chain with the

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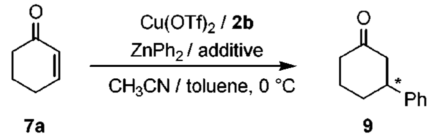
(16) Compare Corey, E. J.; Hannon, F. J. *Tetrahedron Lett.* **1987**, *28*, 5233.

(17) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368−3370.

(18) (a) Keller, E.; Maurer, J.; Naasz, R.; Schader, T.; Meetsma, A.; Feringa, B. L. *Tetrahedron: Asymmetry* **1998**, *9*, 2409−2413. (b) Delapierre, G.; Constantieux, T.; Brunel, J. M.; Buono, G. *Eur. J. Org. Chem.* **2000**, 2507−2511.

Table 4. 1,4-Phenylation of 2-Cyclohexenone (**7a**)



entry	ZnPh$_2$ (equiv)	additive (equiv)	Cu(OTf)$_2$/**2b** (mol %)	time (h)	yield (%)	% ee
1	1.5		3.0/4.1	90	0	
2	1.0	Et$_2$Zn (1.0)	3.0/4.1	20	53[a]	69 (S)
3	1.0	Me$_2$Zn (1.0)	11.0/14.9	18	53	59 (S)
4	1.06	Me$_2$Zn (3.2)	10.6/14.9	21	73	74 (S)

[a] In addition 41% (79% ee) **8a** was isolated.

enone would be disrupted. Also, separating the bis(oxazoline) units by a larger spacer (entries 15 and 16) results in a complete loss of selectivity.

The stringent requirement of two metals coordinating in the ligand sphere might be the cause for the high substrate specifity of the catalyst. Cycloheptenone (**7b**) already yielded the 1,4-adduct with diethylzinc with considerably diminished enantioselectivity (41% ee, entry 17), while substitution in the 4-position of the enone as seen with **7c** (entry 18) was not tolerated at all.

We were also able to achieve a 1,4-phenylation, marking to the best of our knowledge the first example of an asymmetric phenyl transfer to enones with diphenylzinc as a reagent.[19] Diphenylzinc alone proved to be not reactive enough (entry 1), whereas a mixture of diphenyl- and diethylzinc[20] resulted in a 1:1 mixture of ethylated and phenylated products **8a** and **9** (entry 2). However, with a mixture of diphenyl- and dimethylzinc, being optimal at a ratio of 1:3, an exclusive phenyl transfer was reached, giving **9** in 74% *ee*.

We reason that a bimetallic complex[21] such as **10** is decisive for 1,4-additions, in which the substrate is locked in a two-point binding mode via a zinc and a copper atom. Such restricted coordination would explain the high enantiocontrol in the alkyl transfer along with the limited substrate tolerance of the catalyst. Further studies to change the size of the chiral pocket by varying the ligand backbone and the geometry of the side chains are therefore under investigation in our laboratories.

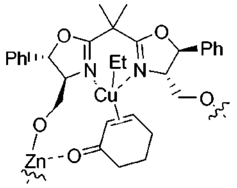


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Figure 1. Postulated binding mode between bifunctional catalyst and substrate.

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Supporting Information Available: Experimental procedures and analytical data of all new ligands, as well as ^{1}H NMR and HPLC data of all 1,2- and 1,4-addition products. This material is available free of charge via the Internet at http://pubs.acs.org.

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[19] Reviews: ref 8 and Bolm, C.; Hildebrand, J. P.; Muniz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284−3308.

[20] (a) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muniz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465. (b) Huang, W.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 4222−4223. (c) Bolm, C.; Muniz, K. *Chem. Commun.* **1999**, 1295−1296.

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