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[2,2]Paracyclophane-Based *N*,*O*-Ligands in Alkenylzinc Additions to Aldehydes

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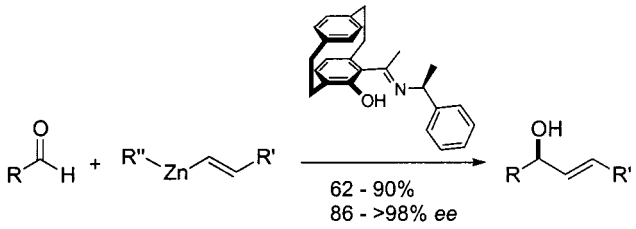
ABSTRACT



The application of planar and central chiral [2,2]paracyclophane-based *N*,*O*-ligands in asymmetric alkenylzinc additions to various aldehydes is described, which gives rise to very high ee's especially for difficult substrates. A fine-tuning of the alkenylzinc species by employing different transmetalation reagents is reported, allowing control of the steric bulk of the alkenylzinc species and thus the selectivity of the catalysis.

Asymmetric organozinc additions to carbonyl compounds are among the most extensively studied catalytic reactions in modern organic synthesis. In a recent review, Pu and Yu summarized the results of diethylzinc additions carried out with approximately 600 individual catalysts in the past decade.[1] Very recent developments in this field are asymmetric arylation reactions, namely, the addition of phenylzinc reagents to carbonyl compounds, which gives rise to diphenylmethanols and related compounds.[2]

However, the application of alkenylzinc reagents in asymmetric catalysis has so far been limited to very few examples, and the methodology is far from being general. The addition of alkenylzincs to carbonyl compounds affords the synthetically very useful chiral allyl alcohols, which are key intermediates in various reactions.[3]

Generally, alkenylzinc reagents are not temperature-stable and are therefore prepared in situ using transmetalation protocols. Oppolzer and Radinov prepared diethenylzinc by the reaction of ethenyl Grignard reagents with $ZnCl_2$ and alkenylzinc bromides from alkenyllithium and $ZnBr_2$.[4] Later, the same authors reported the preparation of alkenylzinc reagents for the asymmetric addition to aldehydes by reaction of terminal alkynes with dicyclohexylborane followed by boron−zinc exchange. By using Noyori's DAIB ligand,[5] good enantioselectivities were achieved for certain aromatic and aliphatic aldehydes.[6,7] In the same paper,[6] the authors also screened a couple of amino alcohols, which are usually successfully applied in diethylzinc additions to aldehydes,

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(1) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757.

(2) For a recent review, see: Bolm, C.; Hildebrand, J. P.; Muniz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284.

(3) Allyl alcohols are substrates for, e.g., cyclopropanation reactions, aziridination reactions, ene-reactions, epoxidations, dihydroxylations, methoxy selenations, iodo hydroxylations, brominations, and allylic substitution reactions.

(4) (a) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1988**, *29*, 5645. (b) Oppolzer, W.; Radinov, R. N. *Tetrahedron Lett.* **1991**, *32*, 5777.

(5) (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. (b) Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6071.

(6) (a) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*. 10. This reaction was recently extended to intramolecular cyclization reactions: (b) Oppolzer, W.; Radinov, R. N.; El-Sayed, E. *J. Org. Chem.* **2001**, *66*, 4766.

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but with these ligands, only moderate selectivities were obtained.

Wipf et al. developed a method to prepare alkenylzinc reagents by in situ transmetalation of alkenylzirconocenes synthesized by hydrozirconation of alkynes using Cp_2ZrHCl (Schwartz reagent).[8] However, relatively large amounts of ligand had to be employed (10%) to suppress the background reaction catalyzed by zirconocene byproducts.

During a ligand screening employing various hydroxy imine, hydroxy ketimine, and amino alcohol ligands based on the [2,2]paracyclophane backbone, we discovered that ketimines such as **1** and **2** (Figure 1) showed superior

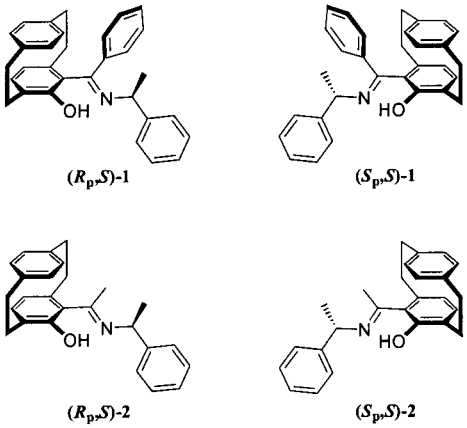


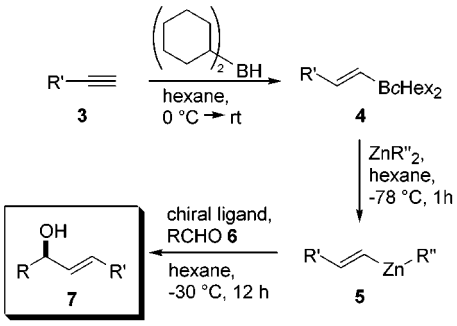
Figure 1. [2,2]Paracyclophane-based ketimine ligands.

selectivity and activity in the diethylzinc addition to benzaldehyde and revealed cooperative effects arising from the combination of the different chirotopic elements of the ligands (chiral cooperativity). The ketimines **1** and **2** have first been synthesized by Rozenberg and Belokon, who used them for the resolution of the corresponding racemic hydroxyketones.[9] Here, we will report on the application of these ligands in the asymmetric alkenylzinc addition to aldehydes.

The protocol we used relies on the method initially developed by Oppolzer et al.[6] Hydroboration of alkynes with dicyclohexylborane, prepared in situ from borane dimethyl sulfide complex and cyclohexene, gives rise to the [(*E*)-1-alkenyl]boranes **4**, which were directly treated with diethylzinc (Scheme 1). The transmetalation to give the alkenylzinc species **5** takes place even at −78 °C and is complete within a couple of minutes (vide infra).

As Oppolzer et al.[6] and Wipf et al.[8] did not find significant differences between the use of diethyl- or dimethylzinc, we

Scheme 1. Generation and Reaction of Alkenylzinc Reagents

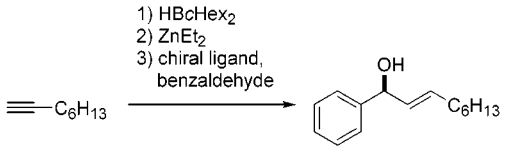


initially only employed diethylzinc as a 1 M stock solution in hexane. Addition of the ligand and the aldehyde furnishes the chiral allyl alcohol product **7**.

Although the original Oppolzer protocol essentially employing equimolar amounts of borane, alkyne, diethylzinc, and aldehyde gave rise to the correct products, in our hands the yields were poor (usually below 50%). Increasing the amount of borane **4** to 1.5 equiv and employing an excess of diethylzinc (2 equiv with regard to the aldehyde) substantially improved the isolated yield to around 80%. Also, addition of 1 mL of toluene was beneficial, as it obviously improves the solubility of certain substrates at low temperatures.[10]

The four paracyclophane ligands depicted in Figure 1 were tested using these optimized conditions with 1-octyne as the alkenylzinc precursor and benzaldehyde at −10 °C (Table 1, entries 1−4). At 2% catalyst loading, good enantioselectivities ranging from 68% to 86% were obtained. The diastereomers **2** gave essentially the same selectivities while producing the opposite enantiomers. The level of selectivity

Table 1. Optimization of Reaction Conditions and Ligand Screening



entry	ligand (mol %)	temp (°C)	yield (%)	ee (%)[a]
1	(R_p,S)-**1** (2)	−10	64	68 (*S*)
2	(S_p,S)-**1** (2)	−10	70	81 (*R*)
3	(R_p,S)-**2** (2)	−10	62	86 (*S*)
4	(S_p,S)-**2** (2)	−10	69	85 (*R*)
5	(R_p,S)-**2** (5)	−20	57	90 (*S*)
6	(R_p,S)-**2** (2)	−30	71	86 (*S*)

[a] Determined by HPLC (Chiracel OD). See ref 12.

(7) The addition of vinylzinc has also been studied: (a) von dem Bussche-Hünnefeld, J. L.; Seebach, D. *Tetrahedron* **1992**, *48*, 5719. (b) Soai, K.; Takahashi, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1257. (c) Shibata, T.; Nakatsui, K.; Soai, K. *Inorg. Chim. Acta* **1999**, *296*, 33.

(8) (a) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197. (b) Wipf, P.; Xu, W. *Org. Synth.* **1996**, *74*, 205. (c) Wipf, P.; Ribe, S. *J. Org. Chem.* **1998**, *63*, 6454.

(9) Rozenberg, V.; Danilova, T.; Sergeeva, E.; Vorontsov, E.; Starikova, Z.; Lysenko, K.; Belokon, Y. *Eur. J. Chem.* **2000**, 3295.

(10) Using these modifications, the aldehyde could be added in one portion, which is a significant practical improvement over the original Oppolzer protocol, where the aldehyde had to be added over a period of 20 min to obtain high enantioselectivities.

achieved for the benzaldehyde substrate with the ligands **2** is comparable to the results of the diethylzinc addition to benzaldehyde with these ligands.[11] Despite the use of excess diethylzinc, no 1-phenylpropanol, the product of the diethylzinc addition to benzaldehyde, was observed, which is consistent with the findings in the literature.[6,8] The conditions for the best ligand (R_p,*S*)-**2** were further optimized by varying reaction temperature and catalyst loading (Table 1).

Decreasing the reaction temperature to −20 or −30 °C did not change the enantioselectivity of the catalysis. However, at −20 °C using 5 mol % of ligand (R_p,*S*)-**2**, selectivity rose to 90% ee but with a diminished isolated yield of 57% (Table 1, entry 5). Hence, all further catalyses were carried out at −30 °C with 2 mol % of ligand as a compromise between selectivity and yield.

The scope of the asymmetric addition of alkenylzinc reagents to aldehydes with 2 mol % of ligand (R_p,*S*)-**2** is illustrated in Table 2. Electron-withdrawing substituents on aromatic aldehydes are well tolerated and lead to increased enantioselecivity of 97% ee for *p*-chlorobenzaldehyde (entry 2). The electron-rich *p*-methoxybenzaldehyde, which is a difficult substrate for many ligands in the diethylzinc[1] as well as alkenylzinc[8c] addition, also provides a very good ee of 91% although with a diminished yield of 62% (entry 3).

Aliphatic and especially α-branched aliphatic aldehydes belong to the most problematic substrates for nearly all ligand systems. To the best of our knowledge, in the alkenylzinc addition to aldehydes there has been no report of a highly enantioselective addition to these substrates. However, these aldehydes are excellent substrates for the paracyclophane ligands, giving virtually complete enantioselection for cyclohexylcarbaldehyde and pivalaldehyde (entries 4 and 5).

Bulky alkynes were examined next, and at first glance they seemed to limit the wide applicability of the paracyclophane ligands. Thus, with the internal alkyne 3-hexyne only 75% ee was obtained (entry 6) and the sterically even more demanding *tert*-butyl ethyne lead to the desired product in a disappointing 64% ee (entry 7).

At this point, the other ligands (Figure 1) were reexamined with the sterically demanding *tert*-butyl ethyne, but no improvement could be made (entries 8−10). Obviously, the greater steric bulk of the zinc species resulting from *tert*-butyl ethyne substantially diminishes the stereoselection of the catalyst. In a final attempt to decrease the steric demand of the zinc species, dimethylzinc (3 equiv) was employed as the transmetalation reagent. This should result in the formation of the somewhat less demanding zinc species **5** (R″ = methyl in Scheme 2). Gratifyingly, this brought the breakthrough for bulky alkynes. For *tert*-butyl ethyne now 89% ee was achieved with ligand (R_p,*S*)-**2** (entry 11), and also for the symmetrical internal alkyne 3-hexyne 88% ee could be obtained under the changed reaction conditions (entry 12).

However, the use of dimethylzinc was only beneficial for the aforementioned bulky alkynes. Its application in the reaction of the hydroborated 1-octyne with benzaldehyde lead to diminished enantioselectivity and yield (76% ee and 48% isolated yield, entry 13) as compared to the already mentioned results with diethylzinc (Table 1 and Table 2, entry 1).

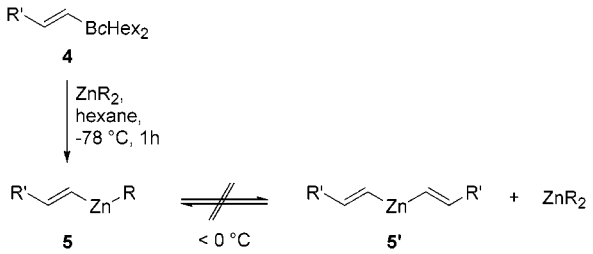
We rationalize these results with the slow equilibration of zinc species at temperatures below 0 °C. Oppolzer et al. already mentioned ^{1}H NMR studies of the species formed by reaction of hydroborated alkynes with dimethylzinc.[6a] Although the transmetalation proceeds quickly at −65 °C to give two equilibrating alkenylzinc species (which they assigned as monomeric and dimeric species), no equilibrium between mixed (**5** in Scheme 2) and symmetrical species (**5′** in Scheme 2) was observed up to 0 °C, where the zinc species begin to decompose. Thus, the active zinc species **5** can be tuned by the choice of the transmetalation reagent.

Table 2. Alkenylzinc Addition to Various Aldehydes to Give the Allyl Alcohols **7** According to Scheme **1**[a]

entry	alkyne **3**	aldehyde **4**, R =	yield (%)	ee (%)[b]
1	1-octyne	phenyl	71	86 (*S*)
2	1-octyne	4-Cl-phenyl	88	97 (*S*)
3	1-octyne	4-MeO-phenyl	62	91 (*S*)
4	1-octyne	cyclohexyl	80	>98 (*R*)[c]
5	1-octyne	*tert*-butyl	89	>98 (*R*)[d]
6	3-hexyne	phenyl	86	75 (*S*)
7	*tert*-butyl ethyne	4-Cl-phenyl	78	64 (*S*)
8	*tert*-butyl ethyne	4-Cl-phenyl	90	62 (*R*)[e]
9	*tert*-butyl ethyne	4-Cl-phenyl	88	67 (*R*)[f]
10	*tert*-butyl ethyne	4-Cl-phenyl	83	54 (*S*)[g]
11	*tert*-butyl ethyne	4-Cl-phenyl	88	89 (*S*)[h]
12	3-hexyne	phenyl	84	88 (*S*)[g]
13	1-octyne	phenyl	48	76 (*S*)[g]

[a] In the presence of 2 mol % of chiral ligand (R_p,*S*)-**2** (unless otherwise stated) at −30 °C. [b] Determined by HPLC (Chiracel OD column, entries 1−3, 13; Chiracel AD column entries 7−11; (*S*,*S*)-Welk-O 1 column entries 6, 12). See ref 12. [c] Determined by GC (Chirasil-dex). The other enantiomer was not observed. [d] Determined by NMR of the camphanic ester derivative. The other enantiomer was not observed. [e] (S_p,*S*)-**1** was used as ligand. [f] (S_p,*S*)-**2** was used as ligand. [g] (R_p,*S*)-**1** was used as ligand. [h] Dimethylzinc was used instead of diethylzinc.

Scheme 2. Equilibrium of Zinc Species



(11) Dahmen, S.; Bräse, S. *Chem. Commun.* **2001**, in press.

(12) The absolute configuration was assigned by comparison of the optical rotation with the literature known compounds (*S*)-1-(4-chlorophenyl)-hept-2-en-1-ol [ref c, Supporting Information] and (*S*)-1-phenyl-non-2-en-1-ol [ref a], respectively, and the assumption of a unanimous reaction pathway for all other aldehyde substrates. The absolute configuration of the allyl alcohol products **7** is consistent with the induction observed in the diethylzinc addition to aldehydes with the ligands **1** and **2**.

In the case of the paracyclophane ligands, a smaller R-group is obviously beneficial when sterically demanding alkynes are employed.

The ruling out of an equilibrium as depicted in Scheme 2 is not self-evident. At room temperature, mixed organozinc compounds ZnR^1R^2 with similar R^1 and R^2 groups are in equilibrium with the corresponding symmetrical species ZnR^1_2 and ZnR^2_2.[13] The same applies for dialkyl- and diarylzinc species.[14] Organozincates, however, do not interchange at low temperatures.[15]

In conclusion, we have demonstrated the successful application of [2.2]paracyclophane-based *N,O*-ligands in the alkenylzinc addition to aldehydes. The use of these ligands substantially extends the scope of this reaction, as aliphatic and especially α-branched aliphatic aldehydes can now be applied with very high levels of enantioselection. In contrast to the prior results in this field,[6,8] we could observe a severe influence of the applied transmetalation agent on the selectivity of the catalysts, especially with sterically demanding substrates. A fine-tuning of enantioselectivity, depending on the steric demand of the substrates was successfully carried out by varying the transmetalation agent.

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Supporting Information Available: Experimental procedures and characterizations for the compounds **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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