DOI: 10.1002/adsc.200606193

Second-Generation N,O-[2.2]Paracyclophane Ketimine Ligands for the Alkenylzinc Addition to Aliphatic and Aromatic Aldehydes: Scope and Limitations

Frank Lauterwasser,[a] Julia Gall,[a] Sebastian Höfener,[a] and Stefan Bräse[a,*]

[a] Institut für Organische Chemie, Universität Karlsruhe (TH), Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany
Fax: (+49)-721-608-8581; e-mail: braese@ioc.uka.de

Received: April 20, 2006; Accepted: August 21, 2006

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: Second generation N,O-[2.2]paracyclophane ketimine ligands were investigated for their ability to catalyze the 1,2-addition of alkenylzinc reagents to aliphatic and aromatic aldehydes with special focus on functionalized substrates. For aliphatic aldehydes, which have always been challenging in this field, remarkably high enantiomeric excesses could be determined (50–95% *ee*). However, alkenylzinc reagents bearing heteroatoms proved to be demanding substrates for this system.

Keywords: alkenylzinc reagents; asymmetric catalysis; chiral allylic alcohols; N,O ligands; paracyclophanes

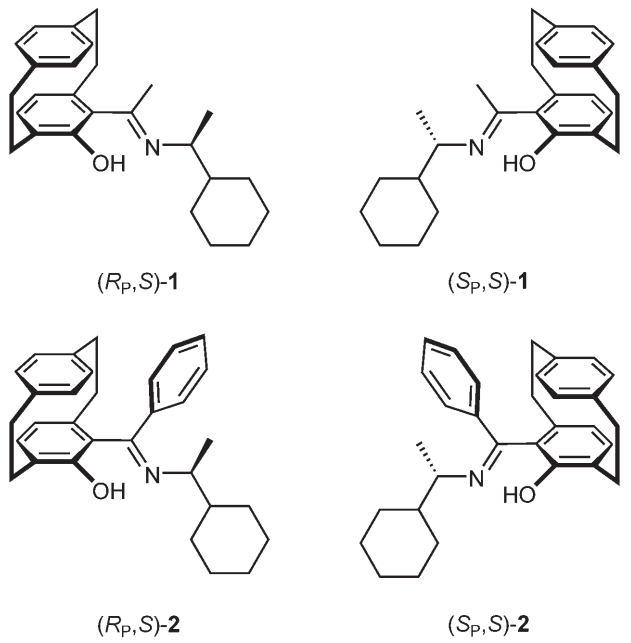
Chiral allylic alcohols are important targets in organic synthesis, especially in natural product synthesis. As intermediates they can be used in further reactions such as allylic substitution, dihydroxylation, ene reaction, cyclopropanation, bromination, or epoxidation. However, the lack of a powerful ligand system impedes the use of the 1,2-addition of alkenylzinc reagents to aldehydes as a key step in natural product synthesis because highly functionalized substrates must be tolerated and high enantiomeric excesses must be achieved.[1] The rare examples in the literature show mostly the use of divinylzinc and substrate-induced diastereoselectivity.[2]

In the case of substrate toleration, the catalyzed alkenylzinc addition could be an appropriate method because of the relatively low reactivity of zinc diorganyls towards aldehydes and ketones in comparison to other organometal compounds.[3] However, investigations in this field are few. In contrast, alkyl transfer to aromatic aldehydes is one of the most studied enantioselective catalytic reactions, yet there are only a few examples with high enantiomeric excesses for aliphatic aldehydes.[4] The alkenylzinc transfer is even less investigated; however, interest in this reaction has increased throughout the last years.[5–12]

One method elaborated by Oppolzer and Radinov produces mixed alkyl-alkenylzinc species *in situ* using a transmetalation protocol involving hydroboration of alkynes.[5] Dahmen et al. showed that N,O-[2.2]paracyclophane-based ligands produce results ranging from good to excellent for this type of reaction, whereas the scope is limited to aromatic aldehydes and fully branched aliphatic aldehydes.[11] Wipf et al. also reported the preparation of alkenylzinc reagents *via* transmetalation but using zirconium as metal.[9]

A comprehensive survey of [2.2]paracyclophane-based ligands can be found in recent reviews.[13] The use of planar-chiral and central-chiral ligands based on paracyclophane systems has emerged *en masse* since the disclosures by Belokon, Rozenberg et al.,[14,15] the Berkessel group,[16] and most notably the Hopf group.[17] Within the last years, various new paracyclophane ligands have been used for asymmetric catalysis.[18–20] In particular, the asymmetric 1,2-addition reaction of organozinc compounds such as alkyl-,[21] alkenyl-,[11] and alkynylzinc[22] reagents with aldehydes or imines,[21] respectively, can be efficiently controlled by the use of hydroxy[2.2]paracyclophane ketimine ligands. We recently reported the synthesis of the N,O-[2.2]paracyclophane-based ligands (R_p,*S*)-**1**, (S_p,*S*)-**1**, (R_p,*S*)-**2**, and (S_p,*S*)-**2** (Figure 1) and their application in asymmetric catalysis.[23,24] In addition, we carried out non-linear-like effect and activity studies for this class of ligands.[25]

Here we present an extension on the highly selective alkenyl transfer onto aliphatic and aromatic aldehydes using the second generation of these N,O-[2.2]paracyclophane-based ligands **1** and **2**. Our goal was to investigate whether our ligands which showed the best activity and selectivity in the diethylzinc addition[23,24] also catalyze the alkenylzinc addition and to investigate which substrates are tolerated. There-



(R_P,S)-**1** (S_P,S)-**1**

(R_P,S)-**2** (S_P,S)-**2**

Figure 1.

fore, we used various functionalized aldehydes as well as alkynes bearing a heteroatom to generate the alkenyl species.

The active alkyl-alkenylzinc species was generated *via* transmetalation by following the Oppolzer protocol.[5] Starting from borane-dimethyl sulfide complex and cyclohexene which *in situ* gave the dicyclohexylborane, followed by treatment with a 1-alkyne, the [(*E*)-1-alkenyl]borane was obtained. Transmetalation occurred after addition of diethylzinc at −78 °C to yield the alkyl-alkenylzinc species. The ratio of the aldehyde to the active alkenylzinc species (2:3) was adapted to the modified Oppolzer protocol introduced by Dahmen et al.[11]

The first investigation focused on the scope of substrates for aliphatic aldehydes using an [(*E*)-1-octenyl]borane. It is important to note that both enantiomers of the resulting allylic alcohols can be generated with similar enantiomeric excesses by using diastereomers of the AHPC-based ketimines **1** with a different planar-chiral type stereochemistry and the same stereogenic center (matched pair). On the basis of our experience with the 1,2-addition of diethylzinc to aromatic and aliphatic aldehydes,[24] the BHPC-based ketimines **2** are known to be a mismatched pair of ligands.

For our experiments we chose a relatively low loading of ligands of 2 mol % and a reaction temperature of −30 °C. Preliminary screenings had shown that these are reasonable conditions to observe high enantiomeric excesses and good yields.[11] The detailed results of the substrate screening are summarized in Table 1.

The ligands (S_P,S)-**1** and (R_P,S)-**1** catalyzed the addition of alkenylzinc to various aliphatic aldehydes ranging from moderate to good yields and good to excellent enantiomeric excesses (up to 95 % *ee*, Table 1). Functionalized aldehydes, such as α,β-unsaturated aldehydes[26] (entries 18–20) or benzyloxyacetaldehyde (entries 21, 22), were also tolerated.

The α-branched aldehydes **4a** and **d** gave enantiomeric excesses from 94 % to 95 % *ee*. The diastereomeric pair (S_P,S)-**1** and (R_P,S)-**1** showed the same selectivity for each substrate (matched pair).

We also studied the difference in selectivity of the BHPC ligands **2** compared with AHPC ligands **1** to illustrate the importance of a ligand screening. In some cases, the selectivity with (R_P,S)-**1** differed by up to 20 % *ee* in comparison with (R_P,S)-**2** (entries 1, 3 and 11, 13), which was quite remarkable. However, the (S_P,S)-**2** ligand showed nearly the same selectivity as (S_P,S)-**1**, since the difference was only 2–4 % *ee*.

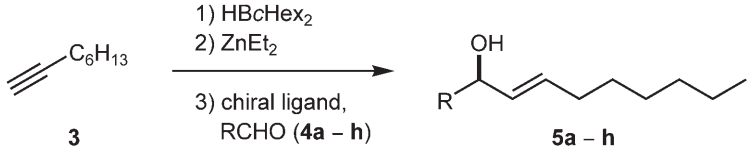
Linear aliphatic aldehydes have been difficult substrates in this kind of reaction. Here, even the linear hexanal (**4c**) showed a reasonable enantiomeric excess with 72 % *ee*. However, it was not possible to determine the selectivity in the case of undecanal (**4b**), either by GC on chiral stationary phase, or by ^{13}C NMR spectroscopy of the (*S*)-(−)-camphanic acid ester for *de* determination. Overall, we saw a general trend that the AHPC-based ligands **1** gave better results than ligands **2** derived from BHPC, and in the latter case the (S_P,S)-configurated ligand showed better selectivity than the (R_P,S)-diastereomer.

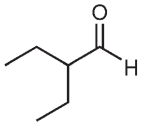
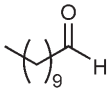
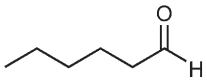
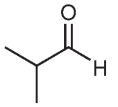
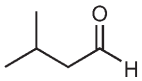
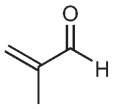
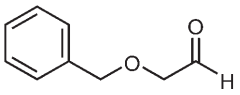
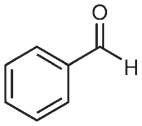
Additionally, three further aldehydes were tested. β-Branched 3-methylbutyraldehyde (**4e**) affirmed the previous results. Methacrolein (**4f**) as an α,β-unsaturated aldehyde was chosen to examine whether 1,2- or 1,4-addition was favored under the given conditions. We found that exclusively the 1,2-addition product **5f** was formed. This is an important difference to the alkyl transfer with [2.2]paracyclophane ligands examined earlier.[26] The yields were quite moderate for this special substrate, which correlated with the increased formation of condensation side products. Moreover, benzyloxyacetaldehyde (**4g**) could be applied in this reaction, but the enantiomeric excesses were not determinable although induction took place. This was shown by measurement of the optical rotation (see Experimental Section).

To draw a comparison between the first[11] and the second generation of our ligands, we chose benzaldehyde (**4h**, entries 23 and 24) as an aromatic substrate and we could achieve better yields and higher enantioselectivities (91 % *ee* compared to 86 % *ee*) under the given conditions.

After the successful application of the asymmetric addition of octenylzinc onto aliphatic aldehydes, the next step was the extension to heteroatom functionalized alkenylzinc species. These are interesting targets

Table 1. Scope of substrates for the alkenyltransfer to several functionalized aliphatic aldehydes.



Entry	Aldehyde		Ligand	Product[a]	Yield [%][b]	*ee* [%][c]
1	**4a**		(R_BS)-**1**	(+)-**5a**	59	94
2	**4a**		(S_BS)-**1**	(−)-**5a**	35	95
3	**4a**		(R_BS)-**2**	(+)-**5a**	51	74
4	**4a**		(S_BS)-**2**	(−)-**5a**	38	91
5	**4b**		(R_BS)-**2**	(+)-**5b**	53	nd[d]
6	**4b**		(S_BS)-**2**	(−)-**5b**	48	nd
7	**4c**		(R_BS)-**1**	(+)-**5c**	55	72[e]
8	**4c**		(S_BS)-**1**	(−)-**5c**	56	72[e]
9	**4c**		(R_BS)-**2**	(+)-**5c**	58	60[e]
10	**4c**		(S_BS)-**2**	(−)-**5c**	78	69[e]
11	**4d**		(R_BS)-**1**	(+)-**5d**	70	94
12	**4d**		(S_BS)-**1**	(−)-**5d**	49	94
13	**4d**		(R_BS)-**2**	(+)-**5d**	63	74
14	**4d**		(S_BS)-**2**	(−)-**5d**	56	92
15	**4e**		(R_BS)-**1**	(+)-**5e**	65	58
16	**4e**		(R_BS)-**2**	(+)-**5e**	70	50
17	**4e**		(S_BS)-**2**	(−)-**5e**	42	68
18	**4f**		(R_BS)-**1**	(+)-**5f**	23	63
19	**4f**		(R_BS)-**2**	(+)-**5f**	23	48
20	**4f**		(S_BS)-**2**	(−)-**5f**	20	74
21	**4g**		(R_BS)-**2**	(+)-**5g**	55	nd
22	**4g**		(S_BS)-**2**	(−)-**5g**	38	nd
23	**4h**		(R_BS)-**1**	(+)-**5h**	77	91[f]
24	**4h**		(S_BS)-**1**	(−)-**5h**	82	90[f]

[a] Configuration determined either by measurement of optical rotation or by GC (see Experimental Section); in the latter case indicators (+/−) were assigned in analogy to other experiments.
[b] Isolated yields.
[c] Determined by GC (CP-chirasil-dex).
[d] nd: not determinable by GC or NMR spectroscopy of the camphanic acid ester.
[e] The *ee* was determined after esterification with Ac_2O, room temperature, 24 h.
[f] Determined by HPLC (Chiracel OD)

regarding a future implementation of the method in natural product synthesis. As a test system, benzaldehyde (**4h**) was chosen and the experiments were performed according to the protocol described above using ω-functionalized alkynes **12**. Despite extensive experimentation, we were not able to conduct a clean 1,2-addition reaction. Instead, dimerization of the alkenyl species to dienes **11** was observed.[27] This was earlier rationalized by Walsh,[28] who found that a borane formed as a by-product was responsible (Figure 2). The reactive alkyl-alkenylzinc species **6** was converted into the dialkenyl species **8**, which un-

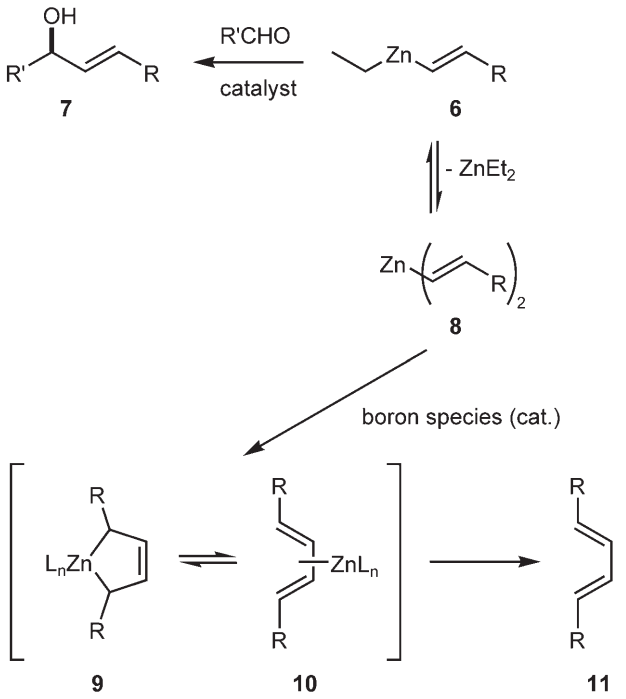


Figure 2.

derwent reductive coupling catalyzed by an unknown boron species. This proposed mechanism follows the investigations published by Walsh et al.[28]

Therefore, we switched to a method elaborated by Wipf et al.[9] involving a hydrozirconation step instead of hydroboration.

The alkyne **12** was treated first with the Schwartz reagent. After transmetalation with diethylzinc, the mixed alkenylzinc species was utilized in the reaction with benzaldehyde (**4h**). With this protocol the 1,2-addition proceeded well with reasonable to good yields (Table 2). As a minor side product from the 1,2-addition of diethylzinc to the aldehyde, 1-phenyl-propan-1-ol could be identified. This was quite surprising, since alkenylzinc species are usually more reactive than alkylzinc species, even though in our case there were examples for the ethyl group being competitively transferred with the vinyl group.[29,30]

Our first experiments with 1.1 equivalents of alkenylzinc reagent gave only moderate yields (Table 2, entry 4) with a poor ratio of by-product to desired product. This effect could be repressed by using 1.5 equivalents of the alkyne **12** as well as diethylzinc. It should be emphasized that the yields and product ratio were consistently higher in the experiments performed with the [2.2]paracyclophane ligands **1** than in the racemic control experiments performed with *N*,*N*-dimethylethanolamine. For linear alkynes of varying length and terminal group, good yields were also obtained, regardless of the size of the protective group used.

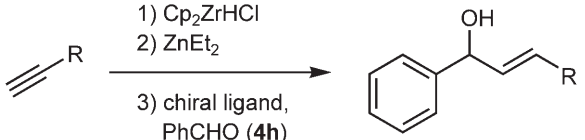
Unfortunately with these substrates and this method, the enantioselectivity remains on a low level (3–13% *ee* with 5 mol% ligand). One reason could be that the heteroatom in the alkenylzinc reagent impedes stereocontrol by the N,O ligand, irrespective of whether a halogen, an ether, or a silyl ether substituent was used. Alternatively, the Wipf method with zirconium was unsuitable for this special catalyst system. Even with higher catalyst loading (10 and 20 mol%) we could not observe better induction; on the contrary the yields decreased and the amount of side product resulting from the ethyl addition grew. Therefore two further sets of experiments were carried out.

We conducted the reaction following the usual protocol but in absence of a ligand and found that the allylic alcohols were formed nevertheless. Obviously, the uncatalyzed addition reaction proceeds at least as fast as the reaction with participation of a ligand. This finding corresponds to the observation of the previous experiments that only the 1,2-addition of diethylzinc is accelerated by the application of more ligand and provided an explanation for the weak stereocontrol.

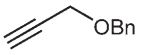
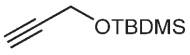
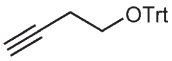
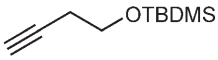
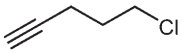
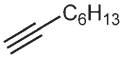
The direct cause was found by using 1-ocytne (**3**) as precursor for the alkenylzinc species. Following the hydroboration protocol, we had achieved excellent results with about 90% *ee*, however, with zirconium as co-metal the isolated allylic alcohols were virtually racemic, even though the reagent did not bear any heteroatom. Thus the low enantioselectivity must be attributed to the reaction conditions of the Wipf method, possibly due to the presence of zirconium compounds.

Within this article we have presented a highly selective access to aliphatic allylic alcohols producing reasonable to good yields and high enantiomeric excesses. Using the method developed by Oppolzer, various aliphatic aldehydes – including challenging linear, branched, α,β-unsaturated and α-substituted – were tested and proved to be suitable substrates with distinguished stereocontrol. As a powerful ligand set we used the second generation of N,O-[2.2]paracyclophanes. In the catalyzed asymmetric alkenylzinc addition, both enantiomers of the resulting allylic alcohols could be obtained depending on which diastereomer of the ligand was used. With the AHPC-based ligand **1** we observed a matched pair with 58–95% *ee*, whereas with BHPC-based ligands **2** different stereoselectivities (mismatched pair) were achieved. As we switched to heteroatom-substituted alkenylzinc reagents, the desired 1,2-addition product could not be obtained with the Oppolzer hydroboration method. We were obliged to use the Wipf protocol with the Schwartz reagent. However, under the given reaction conditions stereocontrol was suppressed and the uncatalyzed background reaction took place, even though the yields were satisfying.

Table 2. Substrates tested with the hydrozirconation protocol.



12a – f **13a – f**

Entry	Alkyne		Ligand	[mol%]	Product	Yield [%][a]
1	**12a**		($R_p S$)-**1**	5	**13a**	88
2	**12b**		($R_p S$)-**1**	5	(+)-**13b**	78
3	**12b**		($S_p S$)-**1**	5	(−)-**13b**	88
4	**12c**		($R_p S$)-**1**	5	**13c**	54[b]
5	**12d**		($R_p S$)-**1**	5	(+)-**13d**	69
6	**12d**		($S_p S$)-**1**	5	(−)-**13d**	68
7	**12d**		($R_p S$)-**1**	10	(+)-**13d**	46
8	**12d**		($S_p S$)-**1**	10	(−)-**13d**	47
9	**12d**		($R_p S$)-**1**	20	(+)-**13d**	39
10	**12d**		($S_p S$)-**1**	20	(−)-**13d**	38
11	**12e**		($R_p S$)-**1**	5	**13e**	77
12	**12f**		($R_p S$)-**1**	5	**13f**	64
13	**3**		($R_p S$)-**1**	5	(+)-**5h**	75
14	**3**		($S_p S$)-**1**	5	(−)-**5h**	71
15	**3**		($R_p S$)-**1**	10	(+)-**5h**	67
16	**3**		($S_p S$)-**1**	10	(−)-**5h**	66

[a] Isolated yields.
[b] 1.1 equivalents of alkyne.

Experimental Section

General Remarks

All catalyses were performed in 10-mL vials under an argon atmosphere. Aldehydes, 1-octyne (**3**), 5-chloro-pent-1-yne (**12e**), and TBDMS-protected alkynols (**12b** and **d**) were purchased from commercial sources and were used without further purification. *O*-Protected prop-2-yn-1-ols, but-3-yn-1-ols and pent-4-yn-1-ols were prepared using standard procedures[31,32] and purified by distillation (benzyl compounds **12a** and **f**) or recrystallization (trityl compounds **12c**), respectively. Diethylzinc was purchased as a 1 M solution in hexanes from Fluka. Ligands were synthesized according to literature procedures.[23] Enantiomeric excesses were determined by GC on chiral stationary phase (Varian with CP-Chirasil-Dex CB, 25 m × 0.25 mm, 0.25 μm), or by HPLC (Agilent with Diacel Chiracel OD, 250 × 4.00 mm, 10 μm).

^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 250 (250 MHz/62.5 MHz), Bruker AM 400 (400 MHz/100 MHz) and Bruker DRX 500 (500 MHz/125 MHz) spectrometers using $CDCl_3$ as the solvent and shift reference (7.26 ppm/77.00 ppm). Optical rotations were determined on a Perkin–Elmer 241 polarimeter (Na, 589 nm). All characterization data are available in the Supporting Information.

General Procedure A for Alkenylzinc Addition to Aldehydes (Hydroboration-Transmetalation Protocol)

In a 10-mL vial under an argon atmosphere 0.75 mL of borane-dimethyl sulfide complex solution (1.50 mmol, 2 M in toluene) were cooled to 0 °C, 304 μL (246 mg, 3.00 mmol) of cyclohexene were added, and the reaction mixture was stirred for 2 h at 0 °C. Then 223 μL (165 mg, 1.50 mmol) of 1-octyne (**3**) were added. After stirring at room temperature for 1 h, the reaction mixture was cooled to −78 °C and a solution of the ligand (2 mol%) in diethylzinc solution (2 mL, 2.00 mmol, 1 M in hexane) was added slowly. After warming from −78 to −30 °C over a period of 1 h, the aldehyde **4** (1.00 mmol) was added and the mixture was stirred for 14 h at −30 °C. The reaction mixture was quenched with water, diethyl ether was added and the organic layer was subsequently extracted with 5% acetic acid, 1 M HCl, and saturated $NaHCO_3$ solution. After washing with water the organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. Chromatography on silica gel (pentane/diethyl ether) yielded the allylic alcohol **5**.

The racemic control experiments were performed either with 3.70 mg (0.01 mmol, 1 mol%) of a mixture of diastereomers (*rac*)-(R_p,*S*)/(S_p,*R*)/(S_p,*S*)/(R_p,*R*)-4-hydroxy-5-[1-(1-phenylethylimino)-ethyl]-[2.2]paracyclophane or with 20 μL (18.0 mg, 0.20 mmol, 20 mol%) of *N*,*N*-dimethylethanolamine.

General Procedure B for Alkenylzinc Addition to Aldehydes (Hydrozirconation-Transmetalation Protocol)

To a suspension of 387 mg of zirconocene hydrochloride (Schwartz reagent, 1.50 mmol) in 3 mL of dry dichloromethane at room tempertaure under argon, the alkyne **12** (1.50 mmol) was added dropwise (crystalline compounds were dissolved in 1 mL of dichloromethane). The mixture was allowed to stir at room temperature for 15 min, giving a clear, light yellow solution, before all volatiles were removed under vacuum. The resulting yellow solid was dissolved in 3 mL of dry toluene, cooled to −65 °C, and then treated with 18.8 mg of chiral ligand **1** (0.05 mmol, 5 mol%) in 1.50 mL of diethyl zinc solution (1 M in hexanes, 1.50 mmol). The mixture was warmed to −20 °C during a period of 2 h, followed by the addition of 102 μL of benzaldehyde (**4h**, 106 mg, 1.00 mmol) in 1 mL of dry toluene. The reaction was allowed to proceed overnight before quenching with saturated $NaHCO_3$ solution. The mixture was extracted with diethyl ether; the organic layer was washed with saturated NH_4Cl solution, dried over $NaSO_4$, filtered, and solvents removed under vacuum. The crude product was chromatographed on silica gel.

The racemic control experiments were performed with 30 μL (26.7 mg, 0.30 mmol, 30 mol%) of *N*,*N*-dimethylethanolamine.

Acknowledgements

We would like to thank the DFG (SFB 380) and the Fonds der Chemischen Industrie (Fellowship for Julia Gall) for financial support. Cyclohexylethylamine (ChiPros®) used for the ligand synthesis was a generous gift from the BASF AG (Dr. Klaus Ditrich).

References

[1] a) P. Wipf, J. T. Reeves, *Chem. Commun.* **2002**, 2066–2067; b) R. Shen, C. T. Lin, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2002**, *124*, 5650–5651; c) R. Shen, C. T. Lin, E. J. Bowman, B. J. Bowman, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2003**, *125*, 7889–7901.

[2] a) M. G. Banwell, D. T. J. Loong, *Heterocycles* **2004**, *62*, 713–734; b) R. L. Soucy, D. Kozhinov, V. Behar, *J. Org. Chem.* **2002**, *67*, 1947–1952; c) M. Jorgensen, E. H. Iversen, A. L. Paulsen, R. Madsen, *J. Org. Chem.* **2001**, *66*, 4630–4634; d) K. Soai, K. Takahashi, *J. Chem. Soc., Perkin Trans. 1* **1994**, 1257–1258; e) H. Urabe, O. O. Evin, F. Sato, *J. Org. Chem.* **1995**, *60*, 2660–2661; f) S. V. Ley, M. Woods, A. Zanotti-Gerosa, *Synthesis* **1992**, 52–54; g) A. Boschetti, F. Nicotra, L. Panza, G. Russo, *J. Org. Chem.* **1988**, *53*, 4181–4185.

[3] P. Knochel, M. I. Calaza, E. Hupe, in: *Metal-Catalyzed Cross-Coupling Reactions*, (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**, pp. 619–670.

[4] For a recent review, see: a) L. Pu, *Tetrahedron* **2003**, *59*, 9873–9886; b) L. Pu; H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757–824.

[5] a) W. Oppolzer, R. N. Radinov, *Helv. Chim. Acta* **1992**, *75*, 170–173; b) W. Oppolzer, R. N. Radinov, E. El-Sayed, *J. Org. Chem.* **2001**, *66*, 4766–4770; c) W. Oppolzer, R. N. Radinov, *Tetrahedron Lett.* **1988**, *29*, 5645–5648.

[6] T. Shibata, K. Nakatsui, K. Soai, *Inorg. Chim. Acta* **1999**, *296*, 33–36.

[7] a) A. R. Kelly, A. E. Lurain, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 14668–14674; b) A. E. Lurain, P. J. Carroll, P. J. Walsh, *J. Org. Chem.* **2005**, *70*, 1262–1268; c) A. E. Lurain, A. Maestri, A. R. Kelly, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 13608–13609; d) H. Y. Kim, A. E. Lurain, P. García-García, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 13138–13139; e) C. A. de Parrodi, P. J. Walsh, *Synlett* **2004**, 2417–2420; f) S.-J. Jeon, H. Li, C. García, L. K. LaRochelle, P. J. Walsh, *J. Org. Chem.* **2005**, *70*, 448–455; g) S.-J. Jeon, Y. K. Chen, P. J. Walsh, *Org. Lett.* **2005**, *7*, 1729–1732; h) Y. K. Chen, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 3702–3703; i) H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 8355–8361.

[8] a) M. L. Richmond, C. M. Sprout, C. T. Seto, *J. Org. Chem.* **2005**, *70*, 8835–8840; b) C. M. Sprout, M. L. Richmond, C. T. Seto, *J. Org. Chem.* **2005**, *70*, 7408–7417; c) C. M. Sprout, M. L. Richmond, C. T. Seto, *J. Org. Chem.* **2004**, *69*, 6666–6673.

[9] a) P. Wipf, S. Ribe, *J. Org. Chem.* **1998**, *63*, 6454–6455; b) P. Wipf, C. Kendall, *Chem. Eur. J.* **2002**, *8*, 1779–1784; c) P. Wipf, N. Jayasuriya, S. Ribe, *Chirality* **2003**, *15*, 208–212; d) P. Wipf, R. L. Nunes, *Tetrahedron* **2004**, *60*, 1269–1279.

[10] S.-L. Tseng, T.-K. Yang, *Tetrahedron: Asymmetry* **2005**, *16*, 773–782.

[11] S. Dahmen, S. Bräse, *Org. Lett.* **2001**, *3*, 4119–4122.

[12] D.-H. Ko, S.-W. Kang, K.-H. Kim, Y. Chung, D.-C. Ha, *Bull. Korean Chem. Soc.,* **2004**, *25*, 35–36.

[13] S. E. Gibson, J. D. Knight, *Org. Biomol. Chem.* **2003**, *1*, 1256–1269.

[14] a) V. I. Rozenberg, T. I. Danilova, E. V. Sergeeva, I. A. Shouklov, Z. A. Starikova, H. Hopf, K. Kühlein, *Eur. J. Org. Chem.* **2003**, 432–440; b) V. I. Rozenberg, D. Y. Antonov, E. V. Sergeeva, E. V. Vorontsov, Z. A. Starikova, I. V. Fedyanin, C. Schulz, H. Hopf, *Eur. J. Org. Chem.* **2003**, 2056–2061; c) T. I. Danilova, V. I. Rozenberg, E. V. Vorontsov, Z. A. Starikova, H. Hopf, *Tetrahedron: Asymmetry* **2003**, *14*, 1375–1383.

[15] a) T. I. Danilova, V. I. Rozenberg, E. V. Sergeeva, Z. A. Starikova, S. Bräse, *Tetrahedron: Asymmetry* **2003**, *14*, 2013–2019; b) T. I. Danilova, V. I. Rozenberg, Z. A. Starikova, S. Bräse, *Tetrahedron: Asymmetry* **2004**, *15*, 223–229; c) N. Vorontsova, E. Vorontsov, D. Antonov, Z. Starikova, K. Butin, S. Bräse, S. Höfener, V. Rozenberg, *Adv. Synth. Catal.* **2005**, *347*, 129–134.

[16] A. H. Vetter, A. Berkessel, *Tetrahedron Lett.* **1998**, *39*, 1741–1744.

[17] a) H. Hopf, *Angew. Chem.* **1972**, *84*, 471–472; *Angew. Chem. Int. Ed.* **1972**, *11*, 419–420; b) D. Pamperin, H. Hopf, C. Syldatk, M. Pietzsch, *Tetrahedron: Asymmetry* **1997**, *8*, 319–325; c) H. Hopf, A. A. Aly, V. N. Swaminathan, L. Ernst, P. G. Jones, *Eur. J. Org. Chem.* **2005**, 68–71; d) K. El Shaieb, V. Narayanan, H. Hopf, I. Dix, A. Fischer, P. G. Jones, L. Ernst, K. Ibrom, *Eur. J. Org. Chem.* **2003**, 567–577; e) *Modern Cyclophane Chemistry*, (Eds.: R. Gleiter, H. Hopf), Wiley-VCH, Weinheim, **2004**.

[18] X.-W. Wu, T.-Z. Zhang, K. Yuen, X.-L. Hou, *Tetrahedron: Asymmetry* **2004**, *15*, 2357–2365.

[19] a) C. Bolm, T. Kühn, *Synlett* **2000**, 899–901; b) C. Bolm, T. Focken, G. Raabe, *Tetrahedron: Asymmetry* **2003**, *14*, 1733–1746; c) K. P. Bryliakov, E. P. Talsi, T. Kühn, C. Bolm, *New J. Chem.* **2003**, *27*, 609–614; d) T. Focken, G. Raabe, C. Bolm, *Tetrahedron: Asymmetry* **2004**, *15*, 1693–1706.

[20] For an account: S. Bräse, S. Dahmen, S. Höfener, F. Lauterwasser, M. Kreis, R. E. Ziegert, *Synlett* **2004**, 2647–2669.

[21] S. Dahmen, S. Bräse, *J. Am. Chem. Soc.* **2002**, *124*, 5940–5941.

[22] S. Dahmen, *Org. Lett.* **2004**, *6*, 2113–2116.

[23] F. Lauterwasser, M. Nieger, H. Mansikkamäki, K. Nättinen, S. Bräse, *Chem. Eur. J.* **2005**, *11,* 4509–4525.

[24] S. Höfener, F. Lauterwasser, S. Bräse, *Adv. Synth. Catal.* **2004**, *346*, 755–759.

[25] F. Lauterwasser, S. Vanderheiden, S. Bräse, *Adv. Synth. Catal.* **2006**, *348*, 443–448.

[26] In the reaction with diethylzinc and the ketimine ligands, α,β-unsaturated aldehydes show 1,4-addition. For further information see: S. Bräse, S. Höfener, *Angew. Chem.* **2005**, *117*, 8091–8093; *Angew. Chem. Int. Ed.* **2005**, *44*, 7879–7881.

[27] As a representative example for these undesired products 1,8-ditrityloxyocta-3,5-diene was characterized (for data see Supporting Information).

[28] a) C. García, E. R. Libra, P. J. Carroll, P. J. Walsh, *J. Am. Chem. Soc.* **2003**, *125*, 3210–3211; b) H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 6538–6539.

[29] S. D. Rychnovsky, N. A. Powell, *J. Org. Chem.* **1997**, *62*, 6460–6461.

[30] J. Rudolph, T. Rasmussen, C. Bolm, P.-O. Norrby, *Angew. Chem.* **2003**, *115*, 3110–3113; *Angew. Chem. Int. Ed.* **2003**, *42*, 3002–3005.

[31] S. Czernecki, C. Georgoulis, C. Provelenghiou, *Tetrahedron Lett.* **1976**, *39*, 3535–3536.

[32] S. K. Chaudhary, O. Hernandez, *Tetrahedron Lett.* **1979**, *2*, 95–98.

