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Chiral Zinc Amidate Catalyzed Additions of Diethylzinc to Aldehydes

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ABSTRACT

A series of bifunctional spiro ligands bearing "carboxamide–phosphine oxide" groups and ethylzinc carboxamidates from these ligands as catalysts for Et_2Zn additions to aldehydes were reported. Excellent yields were obtained with moderate ee's in Et_2Zn additions to benzaldehyde derivatives, implying effectiveness of our newly designed catalytic structures as well as mediocre stereocontrol by these chiral ligands. Possible transition states were suggested based on the crystal structures of two ligands.

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Introduction

Asymmetric additions of organozinc reagents to aldehydes or ketones may produce chiral secondary or tertiary alcohols, which are structural motifs in many natural products or bioactive compounds.[1] Since Noyori's pioneering and prominent research on dialkylzinc additions to aldehydes catalyzed by (2*S*)-DAIB (Figure 1a),[2] various amino alcohols and other *N*,*O*-ligands have been used in similar reactions.[2c, 3] The hydroxy group in an amino alcohol reacts with dialkylzinc to generate an alkoxy zinc species, which coordinates to the adjacent tertiary amino group to form a chiral zinc complex *in situ*. The coordinatively unsaturated zinc center in the complex works as a Lewis acid to activate the aldehyde or ketone substrate. On the other hand, a Lewis basic O atom of the ligand would coordinate with a molecule of dialkylzinc, enhancing its nucleophilicity. Such a finely elaborated Lewis acid–Lewis base assembly[4] involving one catalytic and one reacting zinc species can not only accelerate the reaction but also realize high enantioselectivities. Two decades after Noyori's report, combinations of "phosphinamide–tertiary amino" and "phenoxy–phosphonamide/phosphonate/phosphine oxide" (Figure 1b), in substitution for the bifunctional "hydroxy–tertiary amino" structure, were developed by Ishihara to catalyze asymmetric additions of organozinc reagents.[5] High enantioselectivities were realized in alkyl zinc additions to ketones.[5d] Due to the importance of chiral alcohols for multipurpose applications, development of a highly effective ligand is still in demand. In the course of our investigations of a new class of compounds bearing spiro[indane-1,2′-pyrrolidine] backbone as chiral catalysts or ligands, we envisioned 7-diarylphosphinoyl-spiro[indane-1,2′-pyrrolidin]-5′-ones (Figure 1c), which have an amide group capable of deprotonation by dialkylzinc and a Lewis basic P=O group,[4f–j, 5–8] could act as potential ligands for alkyl zinc additions. Here, we report our results of asymmetric additions of diethylzinc to aldehydes catalyzed by Zn amidates from these spiro compounds. To the best of our knowledge, this is the first example using a carboxamide group to introduce a Lewis acidic zinc center to a chiral catalyst for alkyl zinc additions. To date, there has been no research on Zn carboxamidate catalyzed reactions.

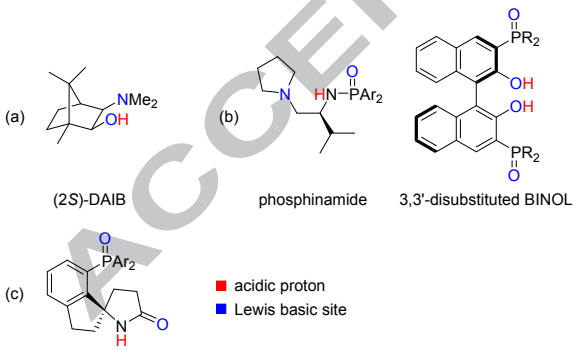
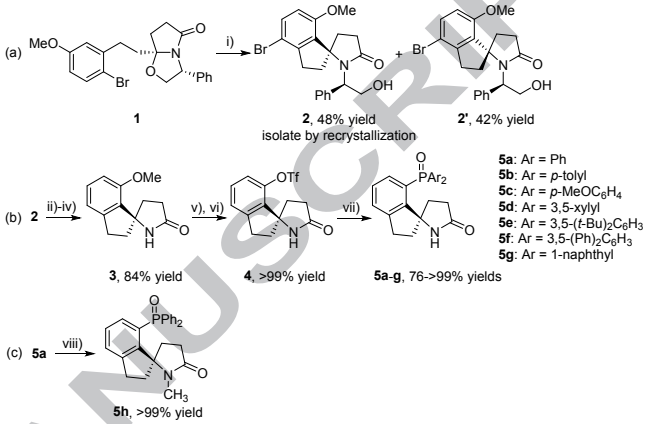


Figure 1. (a) (2*S*)-3-*exo*-(Dimethylamino)isoborneol (DAIB). (b) Ishihara's chiral ligands for alkyl or aryl zinc additions. (c) Our new ligands bearing spiro[indane-1,2′-pyrrolidin]-5′-one backbone.

Results and Discussion

(1*R*)-7-Diarylphosphinoyl-spiro[indane-1,2′-pyrrolidin]-5′-ones (**5a**–**h**) were easily prepared in a cost-effective way from (3*R*,4*S*,7a*S*)-7a-[2-(2-bromo-5-methoxyphenyl)ethyl]-3-phenyltetrahydropyrrolo[2,1-*b*]oxazol-5-one (**1**) (Scheme 1), which was obtained in a quantitative yield from *D*-phenylglycinol and 6-(2-bromo-5-methoxyphenyl)-4-oxo-hexanoic acid.[9] $AlCl_3$ mediated intramolecular Friedel–Crafts type reaction of **1** produced two diastereomers **2** and **2′**,[10] which were conveniently separated by recrystallizations (Scheme 1a). The chiral auxiliary from *D*-phenylglycinol was removed in excellent yields by dehydration followed by acidic hydrolysis.[11] The blocking Br group was removed by hydrogenolysis. Demethylation of **3** and subsequent esterification[12] with $PhNTf_2$ gave **4** in a quantitative yield, which was a key starting material for the preparation of ligands **5a**–**h**. Introduction of a diarylphosphinoyl group to **4** was accomplished under Pd catalyzed C–P coupling conditions established by Morgans and Hayashi (Scheme 1b).[13] A methyl group was installed to generate **5h** from **5a**.



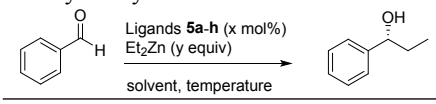
Reagents and conditions: i) $AlCl_3$ (3.0 equiv), DCE, −10 °C, 90% total yield; ii) $LiOH{\cdot}H_2O$ (10 equiv), DMSO, 170 °C, 90% total yield; iii) 4 N HCl, THF, 70 °C, 93% yield; iv) H_2, Pd/C, MeOH, >99% yield; v) BBr_3 (5.0 equiv), CH_2Cl_2, −20 °C, >99% yield; vi) $PhNTf_2$ (1.5 equiv), Cs_2CO_3, DMF, >99% yield; vii) $Ar_2P(O)H$ (2.0 equiv), $Pd(OAc)_2$, dppb, *i*-Pr_2NEt, DMSO, 76–>99% yields; viii) NaH (3.0 equiv), CH_3I (3.0 equiv), DMF, rt, >99% yield.

Scheme 1. Preparation of chiral ligands **5a**–**h** bearing spiro[indane-1,2′-pyrrolidin]-5′-one backbone.

With the ligands **5a**–**h** in hands, the reactivities and enantioselectivities of their Zn complexes in asymmetric additions of Et_2Zn to benzaldehyde were evaluated in toluene (Table 1). At 0 °C and rt, **5a** gave the product in high yields and similarly low ee′s (entries 1, 2). Decreasing the temperature to −10 °C, the yield decreased to 60% and the ee was at the same level (entry 3). In Et_2O, 36% ee and 68% yield were obtained (entry 4). Then **5b**–**g** were tested in toluene at 0 °C (entries 5–10). A *para*-methyl or methoxy group on the phenyl ring of the phosphinoyl group did not improve the result. 3,5-Methyl groups on the phenyl ring slightly improved the ee and the yield (entry 7), indicating a bulkier shielding group was good for *enantio* differentiation. When **5e** bearing two *t*-Bu groups on the phenyl ring was used, 96% yield and 79% ee were obtained (entry 8). Changing the *t*-Bu group to phenyl group, lower yield (80%) was obtained while the ee was almost the same (entry 9). When **5g** bearing di(1-naphthyl)phosphinoyl group was used, only 31% yield was obtained while the ee was in the same range as when **5a**–**c** were used. These results indicated the aryl groups on the P atom influenced the reactivity and the enantioselectivity mainly through steric effects. Ligand **5e** worked as the most promising one. Using **5e** as the ligand, solvents other than toluene, the catalyst loading and the amount of Et_2Zn were examined in the hope of improving the ee (entries 11–18). In hexanes **5e** gave comparable results as in toluene. In PhCl 24% yield was obtained while in CH_2Cl_2, THF, or MTBE no product was obtained at all (Table 1, entries 12–15). In toluene, 20 mol% **5e** gave a quantitative yield and 86% ee in 12 h (entry 16). Further increasing the amount of **5e** did not improve the result (entry 17). When 1.5 equiv Et_2Zn was used, the yield was only 10% though 20 mol% **5e** was used (entry 18). Finally, significance of the

active proton of the amide group was demonstrated. When the acidic proton of the amide group in **5e** was replaced by a Me group, the resulting **5h** completely lost the function as a ligand (entry 19), indicating deprotonation of the amide group in **5a–g** by Et_2Zn was involved in the generation of the chiral catalyst. Thus, **5e** was determined as the optimal "carboxamide–phosphine oxide" type bifunctional ligand, and 0 °C and toluene were the optimal conditions.

Table 1. Asymmetric additions of Et_2Zn to benzaldehyde catalyzed by **5a–h**.



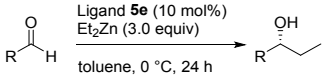
Entry	Ligand	x	y	Solvent	T (°C)	Time (h)	Yield (%)	Ee (%)[a]
1	**5a**	10	3.0	toluene	0	12	95	30
2	**5a**	10	3.0	toluene	rt	12	93	38
3	**5a**	10	3.0	toluene	−10	36	60	31
4	**5a**	10	3.0	Et_2O	0	36	68	36
5	**5b**	10	3.0	toluene	0	24	61	30
6	**5c**	10	3.0	toluene	0	24	71	25
7	**5d**	10	3.0	toluene	0	24	83	52
8	**5e**	10	3.0	toluene	0	24	96	79
9	**5f**	10	3.0	toluene	0	24	80	78
10	**5g**	10	3.0	toluene	0	24	31	32
11	**5e**	10	3.0	hexanes	0	24	75	83
12	**5e**	10	3.0	C_6H_5Cl	0	24	24	80
13	**5e**	10	3.0	CH_2Cl_2	0	24	n.r.	n.d.
14	**5e**	10	3.0	THF	0	24	n.r.	n.d.
15	**5e**	10	3.0	MTBE	0	24	n.r.	n.d.
16	**5e**	20	3.0	toluene	0	12	>99	86
17	**5e**	30	3.0	toluene	0	12	>99	83
18	**5e**	20	1.5	toluene	0	36	10	n.d.
19	**5h**	10	3.0	toluene	0	36	n.r.	n.d.

[a] Ee was determined by chiral HPLC using a Daicel OB-H column. (*R*)-Enantiomer was the major one.

Then **5e** was used to catalyze the additions of Et_2Zn to several aldehydes. The results were collected in Table 2. For benzaldehydes bearing various substituent except nitro group, 64–89% ee′s were obtained with generally high yields (>92%) (entries 1–12). For other tested aromatic aldehydes except ferrocenecarboxaldehyde, moderate yields (80–87%) were obtained with low ee′s (45–72%) (entries 13–16). With 3.0 equiv Et_2Zn, cinnamaldehyde gave nearly racemic product while 3-phenylpropanal gave the addition product in 34% ee (entries 17, 19). When 1.5 equiv Et_2Zn was used, cinnamaldehyde gave the addition product in 25% ee and 43% yield (entry 18). $(n\text{-Bu})_2Zn$, prepared *n*-BuLi and $ZnCl_2$, was reacted with PhCHO. But poor yield (45%) and ee (28%) were obtained (entry 21).

Additions of Ph_2Zn or EtZnC≡CPh to aromatic aldehydes as well as Et_2Zn addition to acetophenone were also tested. Ph_2Zn, prepared from PhMgBr and $ZnCl_2$, was reacted with *p*-$CH_3OC_6H_4CHO$ or *p*-ClC_6H_4CHO. Nearly racemic products (8% ee and 2% ee) were obtained in quantitative yields. In the presence of Et_2Zn, reactions of phenylacetylene with PhCHO or *o*-$CH_3C_6H_4CHO$ also gave nearly racemic (6% ee and 3% ee) products in 98% and 91% yields, respectively, most of which were possibly generated with no participation of ligand **5e**. When acetophenone was reacted with Et_2Zn in the presence of **5e**, no addition product was observed.

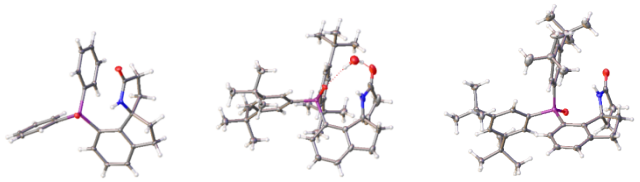
Table 2. Asymmetric additions of Et_2Zn to aldehydes catalyzed by **5e**.



Entry	R	Time (h)	Yield (%)	Ee (%)[a]
1	Ph	24	96	79
2	*o*-$CH_3C_6H_4$	12	>99	89
3[b]	*o*-$CH_3C_6H_4$	24	85	65
4[c]	*o*-$CH_3C_6H_4$	12	>99	85
5	*o*-$CH_3OC_6H_4$	24	>99	78
6	*o*-ClC_6H_4	24	>99	86
7	*m*-$CH_3C_6H_4$	24	>99	64
8	*p*-$CH_3C_6H_4$	24	92	82
9	*p*-$CH_3OC_6H_4$	24	>99	82
10[d]	*p*-$CH_3OC_6H_4$	12	>99	83
11	*p*-ClC_6H_4	24	>99	84
12	*p*-BrC_6H_4	24	96	82
13	*p*-$CF_3C_6H_4$	12	>99	84
14	*m*-$O_2NC_6H_4$	24	n.r.	n.d.
15	*p*-$O_2NC_6H_4$	24	n.r.	n.d.
16	1-Naphthyl	24	85	52
17	2-Naphthyl	24	87	72
18	2-Furyl	24	80	45
19	Ferrocenyl	24	n.r.	n.d.
20	(*E*)-2-Phenylethenyl	24	85	2
21[e]	(*E*)-2-Phenylethenyl	24	43	25
22	2-Phenylethyl	24	70	34
23	Cyclohexyl	24	n.r.	n.d.
24[f]	Ph	24	45	28
25[g]	*p*-$CH_3OC_6H_4$	5	>99	8
26[g]	*p*-ClC_6H_4	5	>99	2
27[h]	Ph	12	98	6
28[h]	*o*-$CH_3C_6H_4$	12	91	3

[a] Ee was determined by chiral HPLC on a Daicel OB-H, OD-H, AD-H or OJ-H column. (*R*)-Enantiomer was the major one. The abs. configuration was determined by comparison of the HPLC data with literature one[3h,5a–c,7b,14]. [b] 5 mol% **5e** was used. [c] The reaction temperature was rt. [d] 20 mol% **5e** was used. [e] 1.5 equiv Et_2Zn was used. [f] $(n\text{-Bu})_2Zn$ was used instead of Et_2Zn. [g] Ph_2Zn was used instead of Et_2Zn. [h] EtZnC≡CPh was used instead of Et_2Zn.

To gain some insight into the structures of the chiral zinc amidates obtained from **5a–g**, we tried to get a crystal of the zinc amidate from **5a** and Me_2Zn but failed. Alternatively, we got the crystal structures of **5a** and **5e** (Figure 2).[15] For **5a**, a single conformer with the P=O and N–H groups orienting in the same direction was present in the crystal (Figure 2a). For **5e**, two conformers with the P=O and N–H groups orienting in the same (Figure 2b) or the opposite direction (Figure 2c) were present in the crystal. In both compounds, we believe rotation about the C7–P bond (Figure 2d) was restricted to a small range due to the highly constrained spiral structure and the sterically demanding geminate aryl groups on the P atom. The two observed conformers in the crystal of **5e** represented the extreme ones with maximum rotation around the C7–P bond. It was due to the restricted rotation about the C7–P bond that the N atom of the amide group and the O atom of the P=O group are closely located and well positioned to await Et_2Zn, which should facilitate the formation of a stable but unusual "Zn–ligand" complex of a seven-membered ring structure. It was reasonable to suppose that **5a** or **5e** possess a conformation shown in Figure 2a and 2b, respectively, in the zinc complex.

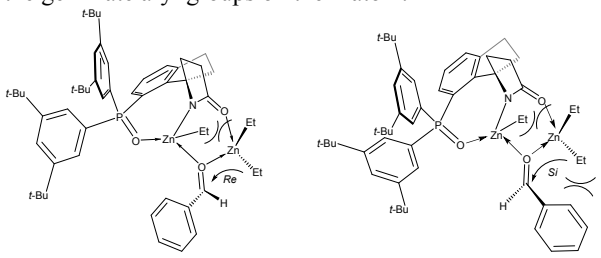


(a) (b) (c)

Figure 2. (a) Single conformer of **5a** in the crystal. (b) One conformer of **5e** in the crystal. (c) The other conformer of **5e** in the same crystal. The ellipsoids were drawn at 50% probability.

Based on the crystal structures of **5a** and **5e**, and the absolute configurations of the major enantiomers of the addition products, we proposed the following transition state assemblies for **5e** catalyzed additions of Et_2Zn to benzaldehyde. Et_2Zn

deprotonated the amide group of **5e** to generate the ethylzinc amidate. The zinc amidate was then coordinated with the O atom of the proximal P=O group, forming the Lewis acid catalyst precursors, in which several complicated species might be included. When benzaldehyde was added to the reaction mixture, the ethylzinc amidate, benzaldehyde and the reacting Et_2Zn might form an assembly via coordination, among which the amidate group, the O atom of benzaldehyde and two zinc ions constructed a six-membered ring adopting a half-chair conformation (Figure 3). For both transition states in Figure 3, the pseudo *axial* Et group from Et_2Zn was hindered by the Et group from ethylzinc amidate moiety. According to the transition state in Figure 3a, the pseudo *equatorial* Et group would preferably attack the C=O group of benzaldehyde from *Re* face to give the major (*R*)-enantiomer of 1-phenyl-1-propanol. The minor (*S*)-enantiomer of 1-phenyl-1-propanol could be produced through the transition state in Figure 3b, which was less favored due to possible repulsion between the attacking Et group and the Ph group of benzaldehyde. The generally moderate ee could be ascribed to the moderately selective control of the configuration of benzaldehyde in the transition state assembly by the chiral zinc catalyst, which seems hard to be further improved by modifying the geminate aryl groups on the P atom.



(a)

(b)

Figure 3. Proposed transition state assembly of the addition reaction: (a) Major one; (b) Minor one.

Conclusion

In conclusion, we disclosed chiral zinc amidate catalyzed additions of Et_2Zn to aldehydes. The *in situ* formed Zn complexes of a new type of chiral spiro ligands bearing "carboxamide–phosphine oxide" functional groups worked as effective catalysts. Excellent yields and moderate ee′s were obtained for benzaldehyde derivatives. Possible transition states were proposed according to the crystal structures of two chiral ligands. Though the ee′s were only moderate, carboxamide acting as an acidic group to introduce a Lewis acidic Zn center was demonstrated for the first time, which is conceptually new and might be of referential value for ligand design.

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15. (*R*)-**5a**: CCDC 1881374; (*R*)-**5e**: CCDC 1881376.

Supplementary Material

Supplementary data to this article can be found online at https://doi.org/10.1016.

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Graphical Abstract

Chiral Zinc Amidate Catalyzed Additions of Diethylzinc to Aldehydes

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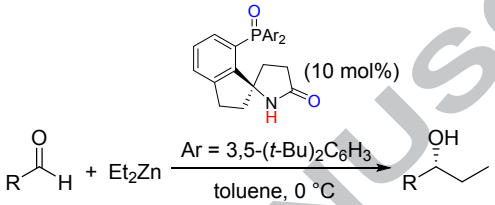
Jinxia Zhang, Shasha Li, Xinxin Zheng, Hongjie Li, and Peng Jiao*



- Chiral zinc amidate catalyzes additions of Et_2Zn to aldehydes in high yields and mediocre ee.
- Carboxamides bearing a phosphine oxide group work as bifunctional ligands.
- Spiro[indane-1,2′-pyrrolidin]-5′-one constitutes a rigid backbone for effective chiral ligands.