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ASYMMETRIC SYNTHESIS XVII. NEW CHIRAL CATALYSTS FOR THE STEREOCONTROLLED ADDITION OF BENZALDEHYDE BY DIETHYLZINC

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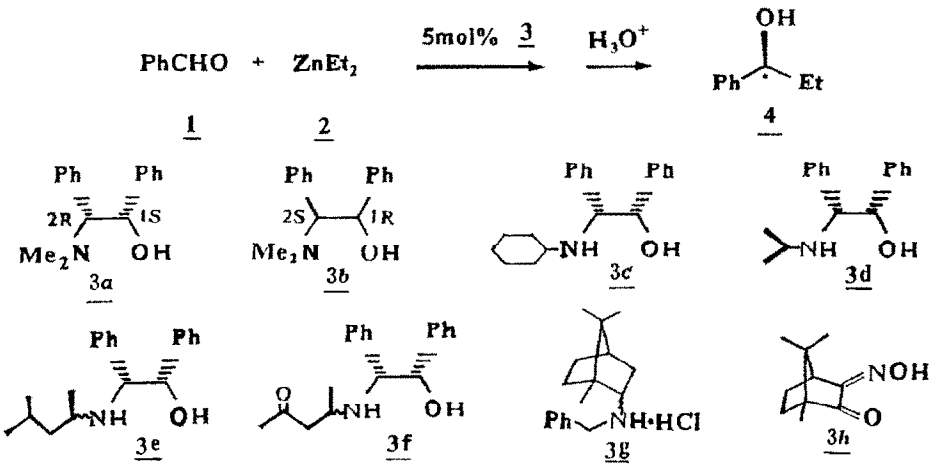
Summary: Enantioselective addition of benzaldehyde with diethylzinc catalyzed by a few classes of new chiral ligands (3a–3h) and their structural relations are disclosed herein. The stereocontrolled syntheses of both (S)– and (R)–1–phenyl–1–propanol are achieved in high chemical yield (up to 99.3%) with high enantiomeric excess (up to 96.8% e. e.) utilizing (1S, 2R)–(3a) and (1R, 2S)–2–N, N–dimethylamino–1,2–diphenyl ethanol (3b), respectively.

Asymmetric syntheses of optically active organic compounds via the intermolecular asymmetry / chirality transformations between a chiral catalyst and reactant are an important, fascinating current topic in chemistry. Most of these are stereoselective organotransition–metal–mediated reactions[1]. Therefore, the structures and reactivities of both the organometallic species and the chiral moieties (ligands / catalysts) are dominant factors. With regard to the structure of the organometallic species, the geometry, hybridized state, polarity of the metal–ligand bond and vacant orbitals of the central metal[1b, 2] all contribute to the complexing process of the organometallic fragment with chiral ligands. On the other hand, the chiral ligands take a more important role in the course of the asymmetric induction. So, they must contain appropriate electronegative donors so as to exhibit appropriate complexing capacities to accomplish the induction. Some well studied chiral ligands which have appeared in the literature[1] can be categorified as follows according to their donor atoms: 1. O–O class (dialcohols, diethers and crown ethers); 2. N–N class (diamines, diamides, disulfonamides); 3. P–P class (diphosphines); 4. N–O class (β–amino alcohols and β–amino ethers); 5. Mixed class (class 1–4); and 6. Others (such as, chiral complex where the stereogenic center is the metal itself).

In recent years, a great many investigations[2–3] have focused on the asymmetric additions of aromatic and aliphatic carbonyl compounds with diorganozinc reagents, which is catalyzed

by some sterically constrained β–tert–amino alcohols(such as DAIB, PDB) affording optically active alchohol compounds in high yields with high e. e.s (up to 100% e. e) and accomplishing asymmetric amplifications[2, 3j]. Other substrates, such as, chalones[4a], imines[4b], etc., afford the corresponding alkylated products in high yields and e. e.s. All of these results have proven that the stereoselective additions involving diorganozinc reagents are typical ones for the investigation of intermolecular asymmetry transformations. However, with regard to the structure of the chiral catalysts, only a few reports appeared in the literature[3c–3e].

In the course of our asymmetric catalysis investigations, we have prepared a series of catalysts(3a–3h) and selected the enantioselective addition of benzaldehyde with diethylzinc (DEZ) to examine their asymmetric catalytic capabilities. Being prompted by the above results, we would like to disclose the results herein.



Scheme I

As regards the present series of catalysts the following generations apply: 1. 2–N,N–dialkylamino alcohols (3a & 3b, i.e. β–tert–amino alcohols, N–O class); 2. 2–N–monoalkylamino alcohols (3c–3f, i.e. β–sec–amino alcohols, N–O class); 3. N–benzyl bornylamine (3g, mono N class); and for the sake of comparison, 4. (+)–3–hydroxyiminocamphor (3h, with hydroxyimino and carbonyl functions) was also applied. Catalysts 3a—3f were synthesized starting from (1S,2R)– and (1R,2S)–2–amino–1,2–diphenyl ethanols[5] via either the simple but efficient and convenient bis–methylation[6] or the facile monoalkylation (3c–3f)[7] procedures. Catalyst 3g was prepared

from (+)–camphor via asymmetric reduction[7] and 3hwas obtained employing a procedure in the literature[8].

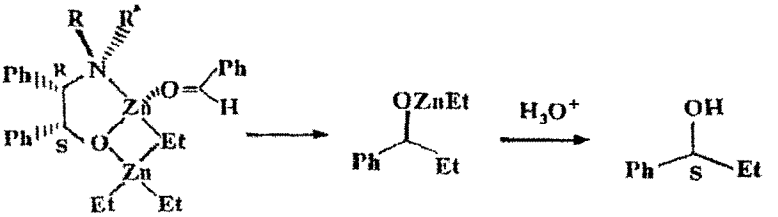
The catalytic enantioselective addition of benzaldehyde with DEZ was run at −78℃ initially[9] then r. t. employing 2 equiv of DEZ and 0.05 equiv of 3 per equiv of 1. In the results (Scheme I, table) we find that the β–tert–amino alcohols (3a & 3b) are the most efficient catalysts, thus affording optically active 1–phenyl–1–propanol in high chemical yield (C. Y., up to 99.3%) and high e. e.(up to 96.8% e. e.). Moreover, both (S)– and (R)– 1–phenyl–1–propanol can be obtained via the appropriate configurational catalyst(entry 1,2). Nevertheless, the β–sec–amino alcohols (3c–3f) led to optically active 1–phenyl–1–propanol in poor to high C. Y.(29.4–97.4%) but with low to moderate e. e. s(7.7–75.7% e. e., entries 3–6), however, they are more efficient than the mono N class catalyst (3g) and the hydroxyimino catalyst (3h), which resulted in 1–phenyl–1–propanol in only 88.2% C. Y.(entry 7, 11.6%e. e.) and 44.1% C. Y.(entry 8, 11.7%e. e.), respectively. Furthermore, catalyst possessing a carbonyl function (3f, 3h) spoils the addition in both chemical and enantioselective aspects (entry 6, 8). The asymmetric amplifications (nonlinear effect, NLE) were also accomplished by partially resolved catalysts 3a and 3b[10].

Table. Results of 3 Catalyze the Enantioselective Addition of Benzaldehyde with DEZ

Entry[a]	3	4			
		Yield[b](%)	$[\alpha]_D^t$ (t, c, solv.)	E. e[c](%)	Congfig[d]
1	a	99.3	−44.01(20,0.68,$CHCl_3$)	96.8	S
2	b	84.6	+44.15(20,0.95,$CHCl_3$)	96.8	R
3	c	97.4	−34.40(15,0.45,$CHCl_3$)	75.7	S
4	d	95.6	−23.30(12,1.66,$CHCl_3$)	51.3	S
5	e	91.9	−3.50(12,1.50,$CHCl_3$)	7.7	S
6	f	29.4	+8.60(12,0.28,$CHCl_3$)	18.9	R
7	g	88.2	+5.30(20,0.74,$CHCl_3$)	11.6	R
8	h	44.1	−5.30(20,0.40,$CHCl_3$)	11.7	S

note: a. the reaction(1:2:3 = 1:2:0.05, molar ratio) was run at −78℃ initially then r. t.[11]; b. isolated yield; c. based on the reported rotations (S form: $[\alpha]_D$ −45.45($CHCl_3$); R form: $[\alpha]_D$ +45.60($CHCl_3$)) [3f] and checked by GC analysis (CD column) of the corresponding trifluroacetic esters; d. based on the specific optical rotations.

Results obtained in this asymmetric addition can be rationalized by consideration of the mechanism of asymmetric induction proposed by Noyori[2]. The ethylation proceeds via dinuclear zinc complexes and the configuration of the alcoholic product is controlled by that of 5 / 4–fused bicyclic intermediates. Thus, a dinuclear intermediate possesing S–configurational Zn and O atoms resulted in the S–product (Scheme Ⅱ).



Scheme Ⅱ

As indicated by Noyori, the migration of ethyl groups takes place only at the bridging ones[2], so in the case of β–tert–amino alcohol catalysts (entry 1, 2), the methyl group ($R' = CH_3$) is more sterically hindered than the hydrogen ($R' = H$) in the case of β–sec–amino alcohol catalysts (entries 3–6), therefore, alcoholic products having high e. e.s were generated. However, in the case of the catalyst possessing a carbonyl function (3f,3h), a competing transfer of ethyl groups is probably existing between the catalyst and substrate (as efforts to recover the catalyst were in vain[13]), thus, affording the alcoholic products in poor chemical and optical yields (low e. e.s). The carbonyl function may also overturn the stereoselective outcome, as entry 6 indicated that the alcoholic product with R form enantiomer in excess was obtained, which was not consistent with those obtained from the other catalysts(3a–3e). Catalyst only possessing an amino function (3g) results in, though a good yield, but a minor asymmetric induction (entry 7). This revealed that the lack of an alcoholic hydroxyl function in a catalyst may reduce the stereoselectivity of the reaction.

Moreover, the stereoselective outcomes(entries 5–6) are also inffluenced by the stereogenic centers in the groups attached to the amino function of the catalyst.This may be one of the factors attributing to the reduced stereoselectivity (entry 5, 6), as the chiral catalyst (3e,3f) containing the racemic stereogenic center in the side groups attached to the amino function was employed.

Furthermore, alkylation or reduction of chiral ligand 3f or 3h would also probably yield new catalyst with some interesting properties[14].

In conclusion, optically astive(up to 96.8% e.e.) (S)– and (R)–1–phenyl–1–propanol were synthesized by the stereocontrolled addition of benzaldehyde with DEZ utilizing a catalytic amount of the easily prepared, either 3a or 3b, respectively. In addition, the outcome (both C. Y. and e. e.) of the asymmetric addition of benzaldehyde with DEZ is intimately related to the structure of catalyst employed.

EXPERIMENTAL

Bis–methylation of (1S,2R)–and (1R,2S)–2–amino–1,2–diphenyl ethanol for the preparation of 3a and 3b.

A modified procedure of the literature[6] is as follows. To 0.6ml(0.58g, 12.5mmol) of 85% aq HCOOH cooled by an ice bath was added 0.53g(2.5mmol) of the corresponding 2–amino–1,2–diphenyl ethanol and 0.5ml(0.17g, 6mmol) of 36% aq HCHO, the slurry was stirred until all solid disappeared. Then the ice bath was removed, and the mixture was refluxed (oil bath 110–120℃) for 4h. The excess amount of HCHO was distilled, and the mixture was cooled to room temperature, treated with H_2O (10ml) and 2N NaOH (PH≈10), the suspension was extracted with CH_2Cl_2(20ml × 3), washed by H_2O (10ml × 3), dried under $MgSO_4$ overnight. $CH_2Cl_2$was distilled from the filtrated solution. The pure white solid 2–N,N–dimethylamino–1,2–diphenyl ethanol was obtained from the wax residue by bulb to bulb distillation (colorless oil, 150–155℃ / 0.1–0.3mmHg, solified after cooling).

(1S,2R)–2–N,N–dimethylamino–1,2–diphenyl ethanol (3a): Yield 0.52g (86.2%); mp: 75.5–77.5℃; $[\alpha]_D^{22}$ +122.43(C 0.272, EtOH (a.)), E.e. = 99.5%;

(1R,2S)–2–N,N–dimethylamino–1,2–diphenyl ethanol (3b): Yield 0.59g(97.8%); mp: 74.5–76.0℃; $[\alpha]_D^{22}$ –102.22(C 0.270, EtOH (a.), E.e. = 83.1%;

IR (KBr, $\gamma_{chara.}$,cm^{-1}): 3480(OH), 775, 750, 700(C_6H_5). ^{1}HNMR($CDCl_3$, δ_H, ppm): 2.35(S, 6H), 3.05–3.25(m, 2H, D_2O 1H exch., J4Hz), 5.25(d, 1H, J4Hz), 6.75–7.20(m, 10H). Anal. Calcd. for $C_{16}H_{19}NO$: C, 79.67; H, 7.88; N, 5.81. Found: C, 79.53; H, 7.99; N, 5.71.

Monoalkylation of (1S,2R)–2–amino–1,2–diphenyl ethanol for the preparation of 3c–3f.

General. (1S,2R)–2–amino–1,2–diphenyl ethanol(1mmol,> 99%e.e.) and the corresponding ketone (1.5mmol) were dissolved in absolute EtOH(1ml) under N_2 (or Ar) atmosphere. After the formation of oxazolidine was over (monitoring by TLC: Silica GF_{254}, eluent, $CHCl_3$ / CH_3COCH_3, 3 / 1, v / v), $NaBH_4$(1.5–2.0mmol) was added into the solution with cool-

ing by an ice bath. The mixture was acidified with 10% HCl(aq). Then the solvent was removed and the residue was taken up in H_2O (5ml). The suspension was made basic with 2N NaOH(aq), extracted with CH_2Cl_2, and washed with brine, followed by H_2O. The solution was dried over $MgSO_4$ and solvent was distilled. A white solid was obtained and recrystallized from CH_2Cl_2–petroleum ether (bp 60–90℃).

2–N–cyclohexylamino–1,2–diphenyl ethanol(3c). Cyclohexanone was used; Yield 98%; mp: 161℃; $[\alpha]_D^{18}$ –41.55(C 0.55, $CHCl_3$); IR(KBr, $\gamma_{chara.}$,cm^{-1}): 3290(NH); ^{1}HNMR($CDCl_3$, δ_H, ppm): 1.00–2.00(m, 10H), 2.5(m, 1H), 4.17(d, 1H, J4Hz), 5.15(d, 1H, J4Hz), 5.30(m, 2H, D_2O 2H exch.), 7.00–7.20(m, 10H); MS(m / e): 188(100%), 106, 83; Anal. Calcd. for $C_{20}H_{25}NO$: C, 81.36; H, 8.48; N, 4.75. Found: C, 81.76; H, 8.61; N, 4.71.

2–N–isopropylamino–1,2–diphenyl ethanol (3d). Acetone was used; Yield 82%; mp: 138–140℃; $[\alpha]_D^{18}$ –29.59 (C 0.49, $CHCl_3$);IR(KBr, $\gamma_{chara.}$,cm^{-1}): 3298(NH); ^{1}HNMR ($CDCl_3$,δ_H, ppm): 0.80–1.20(m, 6H), 2.50–3.00(m, 1H), 4.14(d, 1H, J4Hz), 5.15(m, 3H, D_2O 2H exch.), 7.00–7.20(m, 10H); MS(m / e):148(100%), 106, 43; Anal. Calcd.for $C_{17}H_{21}NO$: C, 80.00; H, 8.24; N, 5.49. Found: C, 79.83; H, 7.98; N, 5.43.

2–N–(4–methylpentan–2–yl)amino–1,2–diphenyl ethanol (3e). 4–Methyl–2–pentanone was used; Yield 81%; mp: 96–98℃ ; $[\alpha]_D^{24}$ –16.07(C 0.056, $CHCl_3$); IR(KBr, $\gamma_{chara.}$,cm^{-1}): 3274(NH); ^{1}HNMR($CDCl_3$, δ_H, ppm): 0.65–1.25(m, 13H), 2.00–2.60(m, 2H, D_2O exch.), 4.00(m, 1H), 4.80(d, 1H, J4Hz), 6.90–7.50(m, 10H); MS (m / e): 298(M^++1), 190(100%), 106, 86; Anal. Calcd. for $C_{20}H_{27}NO$: C, 80.81; H, 9.09; N, 4.71. Found: C, 80.49; H, 9.28; N, 4.45.

2–N–(4–pentanone–2–yl)amino–1,2–diphenyl ethanol (3f). 2,4–Pentanedione was used; Yield 61%; mp: 157–159℃ ;$[\alpha]_D^{24}$ +347(C 0.10, $CHCl_3$); IR (KBr, $\gamma_{chara.}$,cm^{-1}): 3380 (NH); ^{1}HNMR ($CDCl_3$, δ_H, ppm): 1.60(S, 3H), 1.85(S, 3H), 1,92(d, 1H), 2.50(S, 1H), 4.47–4.66(m, 2H), 4.80(m, 2H, D_2O exch.), 4.95(d, 1H, J4Hz), 6.90–7.25(m, 10H); MS (m / e): 296 (M^+–1), 188(100%), 106, 146, 43; Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.77; H, 7.74; N, 4.75. Found: C, 76. 73; H, 7.43; N, 4.76.

Reduction of 1–N–benzyliminocamphor for the preparation of 3g.

1–N–benzyl bornylamine was prepared through the reduction of 1–N–benzyliminocamphor by a modified method[12] in which $NiCl_2H_2O$ was replaced by $NiCl_2$(anhy.), and a MeOH solution of $NaBH_4$ was utilized. The product was isolated by bulb to bulb distillation. 1–N–benzyl bornylamine: colorless oil,120–130℃ / 0.3–0.5mmHg, overall yield 74%; IR (neat,$\gamma_{chara.}$,cm^{-1}): 3340 (NH).

1–N–benzyl bornylamine hydrochloride (3g). White needles; mp: 200℃ (sublimaion);$[\alpha]_D^{24}$

–46.6(C 0.42, $CHCl_3$), 92.4% e.e., determined by ^{1}HNMR; IR(KBr,$\gamma_{chara.}$, cm^{-1}): 3240 (NH); ^{1}HNMR ($CDCl_3$,δ_H, ppm): 0.799(S,3H), 1.110(S, 3H), 1.202(S, 3H), 1.460–1.780(m, 6H), 2.437(m, 1H), 2.800(br, 1H, CHexo), 4.264(q, 2H), 7.569(m, 5H), 9.065 & 9.346 (br, S, NH_2Cl); Anal. Calcd. for $C_{17}H_{26}NCl$: C, 72.99;H, 9.30;N, 5.01. Found: C, 72.59; H,9.18;N,4.93.

The asymmetric addition of benzaldehyde with diethylzinc catalyzed by chiral ligand.

A typical experimental procedure is as follows (entry 1): In a flame–dried 20ml round–bottom flask were placed (1S,2R)–2–N,N–dimethylamino–1,2–diphenyl ethanol (3a, 24.1mg, 0.1mmol), dry toluene (12ml). Into this solution at –78℃ (dry ice–acetone bath) was syringed DEZ (4.4ml, Aldrich, 1.0M hexane solution) and the mixture was stirred for a few minutes. Then freshly distilled benzaldehyde was added. After being stirred for about 48 hrs (monitoring by TLC: Silica GF_{254}, eluent, $CHCl_3$ / Et_2O = 8 / 1, V / V, Rf(4°) = 0.56) at r. t., the solution was quenched by 2NHCl (10ml). The product was isolated by usual workup and further purified by bulb to bulb distillation or preparative TLC (Silica GF_{254}, 20cm × 20cm × 0.1cm, eluent $CHCl_3$ / CH_3OH, V / V).

Catalyst 3a, 3b, 3c, 3d, 3e,3g can be readily recovered from the acidic aqueous solution. The solution was treated with 2N NaOH(PH ≈ 10), and extracted with CH_2Cl_2, washed by H_2O, dried over $MgSO_4$. CH_2Cl_2 was removed from the filtrated solution and the pure ligand was obtained through bulb to bulb distillation or recrystalization.

Under the same conditions, catalyst 3f and 3h, connot be recovered. Only wax–state material was obtained.

The trifluroacetic ester of the alcohol product used for the determination of e.e. value was prepared as follows: 10μl of 1–phenyl–1–propanol was treated with 0.5ml of $(CF_3CO)_2O$ and 0.1ml of C_5H_5N at RT overnight. The excess amount of $(CF_3CO)_2O$ and CF_3COOH were removed under reduced pressure. Then 1ml of CH_2Cl_2 was added into the residue, stirred and condensed to about 0.5ml. This condensed solution was then taken to check the e.e. value on a SC–7 chromatograph (CD column, 14m × 0.23mm(id), column temperature 73℃, vaporizing temperature 270℃, carrier gas, N_2(99.99%), 13.8cm / sec.). Retention time (min.): t_S = 5.58, t_R = 5.95.

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9. note. We have a sense that in the course of the asymmetric addition, two of the thermodynamic processes (i. e. one is the complexing of the organometallic species with the chiral ligands, the other is the rupture of the chiral pro–product complex into optically active product) and one of the kinetic process (asymmetric induction) are involved. Therefore, it is important to run the experiment at −78℃ then r. t.
10. note: More detail investigations on the asymmetric amplifications via partially resolved 3a and 3b will be disclosed elsewhere.
11. Consult the experimental section.
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13. Only wax–state material was obtained.
14. Further studies have been undertaken.