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ENANTIOSELECTIVE SYNTHESIS OF *SEC*-ALLYLALCOHOLS BY CATALYTIC ASYMMETRIC ADDITION OF DIVINYLZINC TO ALDEHYDES.

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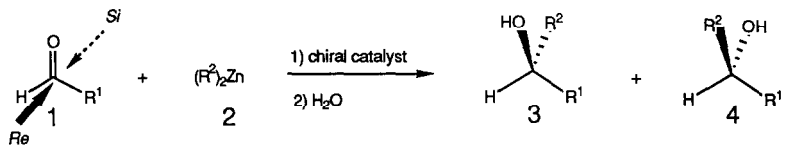
Readily available chiral tridentate ligand 8 catalyzes the highly *Si*-face selective addition of diethyl-, di-*n*-propylzinc and, more significantly, of divinylzinc to aromatic and aliphatic aldehydes whereas bidentate ligands 11 and 12 exert a topologically reversed catalytic bias.

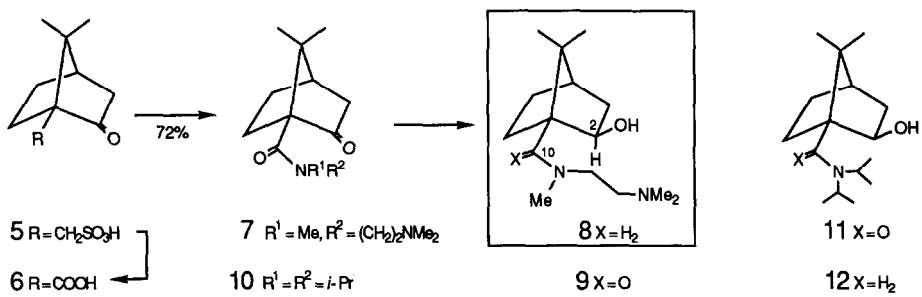
Asymmetric formation of C,C- bonds by means of chiral catalysts is a formidable challenge to the organic chemist [1]. Recent years have witnessed very encouraging progress on β-aminoalcohol catalyzed π-face selective 1,2-additions of diethylzinc to aldehydes (1 + 2 → 3 or 4, Scheme 1) [2,3].

Scheme 1



However, high induction (90 - 98% e.e.) has been described only on transfer of ethyl (methyl) groups, preferably to aryl- or α,β-unsaturated aldehydes. In view of the pivotal role of chiral allylalcohols in organic synthesis catalytic stereofacially biased delivery of alkenyl groups to a more general array of aldehydes would be desirable [4]. To this end a series of new bi- and tri-dentate ligands was prepared from camphor-10-sulfonic acid as exemplified by compounds 8, 11 and 12 (Scheme 2).

Scheme 2



Amidation of ketopinic acid 6 [5] gave ketoamide 7 [6] (72%) which on reduction with $LiAlH_4$ furnished directly 8 [6,7] (71.5%, m.p. of di-hydrogenmaleate 163 - 164° (MeOH)). *Exo*-diaminoalcohol 8 was also obtained by selective ketone reduction of 7 ($NaBH_4$, MeOH, 0°) to give recrystallized amidoalcohol 9 [6] (70%, m.p. 85 - 86°) which was further reduced ($LiAlH_4$) to 8 (91%). Analogous amidation 6 → 10 [6] (89%, m.p. 130 - 131°) and reductions 10 → 11 [6] (90%, m.p. 184 - 185°) → 12 [6] (84%, m.p. 70 - 73°) furnished bidentate ligands 11 and 12.

The stereochemical bias of ligands 8, 11 and 12 on the process 1 + 2 → 3 + 4 is summarized in the Table [8)]

Table: Enantioselective Catalyzed Additions of $(R^2)_2Zn$ to Aldehydes

Entry	Aldehyde R^1	$(R^2)_2Zn$ R^2 (equiv)	Catalyst (mol%)	Product	%Yield[1)]	%e.e.	Configuration
1	C_6H_5	C_2H_5 (1.2)	8 (5)	3a	85	87[2)]	*S*
2	C_6H_5	C_2H_5 (1.2)	8 (20)	3a	85	92[2)]	*S*
3	C_6H_5	C_2H_5 (1.2)	12 (20)	4a	35 (96)	82[2)]	*R*
4	C_6H_5	C_2H_5 (1.2)	11 (20)	4a	68 (98)	91[2)]	*R*
5	C_6H_5	n-C_3H_7 (1.2)	8 (20)	3b	85	92[2)]	*S*
6	C_6H_5	CH_2=CH (2.0)	8 (2)	3c	96	87[3)]	*S*
7	$CH_3(CH_2)_4$	CH_2=CH (2.0)	8 (2)	3d	88	88[4)]	*R*
8	$CH_3(CH_2)_4$	CH_2=CH (2.0)	8 (10)	3d	82	92[4)]	*R*
9	$CH_3(CH_2)_4$	CH_2=CH (2.0)	8 (20)	3d	90	>96[4)]	*R*
10	$CH_3(CH_2)_5$	CH_2=CH (2.0)	8 (2)	3e	86	87[4)]	*R*
11	*cycl*-C_6H_{11}	CH_2=CH (2.0)	8 (2)	3f	83	82[4)]	*S*

[1)] Yields in parentheses based on unchanged PhCHO; [2)] GC of *(1R,2S,5R)*- menthylcarbonate; [3)] GC of *(1S)*-camphanic acid ester; [4)] ^{1}H-NMR of *(1S)*-camphanic acid ester; *Entry 9*: no trace of 4d was detected in the product mixture.

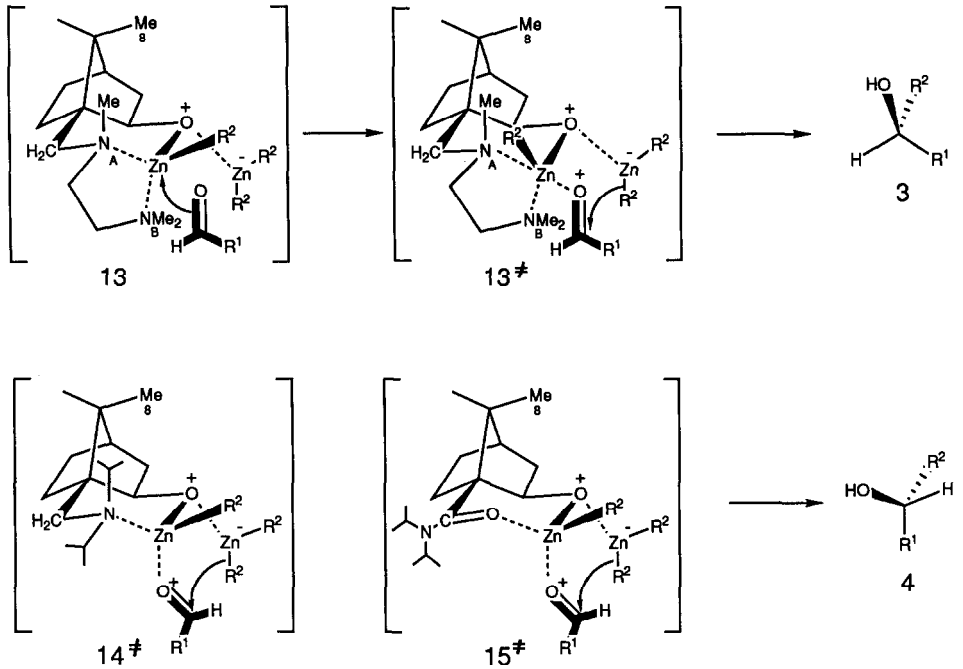
Entries *1* - *4* deal with the reference addition [2,3)] of diethylzinc to benzaldehyde. Treatment of Et_2Zn (1.2 molequiv, hexane, Aldrich) with the corresponding ligand (hexane, 0°) followed by addition of PhCHO (1 equiv), stirring at 0° for 1 - 3 h, quenching with sat aq. NH_4Cl, extraction (Et_2O) and FC gave 1-phenyl-1-propanols 3a and 4a. Thus, the *(S)*-enantiomer 3a was obtained smoothly in 87% or 92% e.e. when employing tridentate ligand 8 (5 mol% or 20 mol%, respectively) [9)]. It is interesting to note that the bidentate ligands 12 and 11 accelerate the addition process less efficiently but exert a reversed asymmetric induction [10)] leading to the *(R)*-antipode 4a in 82% and 91% e.e. (*Entries 3,4*).

Entry 5 illustrates the transfer (promoted by 8) of the *n*-propyl group to benzaldehyde giving the *(S)*-product 3b in 92% e.e..

We then focussed our attention on the asymmetric addition of divinylzinc to a variety of aldehydes. Following the above mentioned protocol, but using only 2 mol% of tridentate ligand 8 and adding a solution of divinylzinc [11)] (2.0 molequiv in Et_2O) to PhCHO gave *(S)*-allylic alcohol 3c in 87% e.e. (*Entry 6*). Divinylzinc adds to linear, (*Entries 7 - 10)* and α-branched (*Entry 11*) aliphatic aldehydes in the presence of 8 (2 mol%) to furnish allylic alcohols 3d, 3e and 3f in comparable yields and enantiomeric purities (82 - 88% e.e.). *Entries 7 - 9* show an increase of induction 88% → ~100% e.e. on raising the amount of 8 from 2 to 20 mol%.

To clarify the mechanism of this catalytic induction we first established the expected involvement of two zinc atoms in the addition process [2e)]. Sequential additions of ~ equally reactive [12)] $(C_2H_5)_2Zn$ and $(C_2D_5)_2Zn$ to 8 followed by PhCHO (1:1:1:1) gave $PhCH(OH)C_2D_5$ (95%, GC) whereas adding $(C_2D_5)Zn$ first, then $(C_2H_5)_2Zn$ and benzaldehyde yielded $PhCH(OH)C_2H_5$ (94% GC, 82% isol.). Accordingly, the observed stereochemical outcome is consistent with the rationalization depicted in the Scheme 3.

Scheme 3



Thus $(R^2)_2Zn$ reacts first with alcohol 8 to provide the chiral catalyst 13. In 13 the central Zn^{II}-alkoxide is chelated by the nitrogens N_A and N_B forming a 6-membered ring featuring an "sp^3-Zn^{II}" species [13]. Coordination of aldehyde-oxygen (*trans* to R^1) with 13 occurs distal to the C(8)Me group probably by forming a pentacoordinated Zn- intermediate [13]. Then R^2 is transferred *via* a six-centered bimetallic transition state 13# to give (after aq. workup) alcohols 3.

In contrast, the topicity of transition state 14# corresponds more closely to the models proposed for β-aminoalcohol-catalyzed diethylzinc-aldehyde additions [2e]. Accordingly, in the complex formed from γ-aminol 12 the central Zn^{II}-atom is trisubstituted so that its fourth valence orbital can be occupied by coordination with R^1CHO. Subsequent transfer of R^2 from the peripheral Zn leads to the antipodal product 4. The catalytic role of amide 11 may be explained by an analogous transition state 15# showing chelation of the central Zn^{II} to the amide oxygen. Apparently, 14# is sterically more congested than 15#, consistent with the lower rate enhancing efficiency of amine 12.

In summary, ligand 8 so far compares favorably with other catalytic systems described for the enantioselective addition of diethylzinc to aldehydes [2,3]. Chirophor 8 and its enantiomer are readily accessible in three simple steps from either (+)- or (-)-camphor-10-sulfonic acid (both relatively inexpensive bulk chemicals). It catalyzes (2 mol%), in particular, the asymmetric addition of divinylzinc to aromatic and aliphatic aldehydes at a convenient temperature (0°) thus providing a new access to chiral allylalcohols in synthetically useful enantiomeric purities. Further exploration of this and other bornane-10,2-bifunctionalized chiral ligands is presently under way in our laboratories [14].

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3) For a chiral dilithiated piperazine catalyzing additions of diethyl- and dimethylzinc to aromatic aldehydes: K. Soai, S.Niwa, Y.Yamada, H.Inoue, *Tetrahedron Lett.* 1987, *28*, 4841

4) For a skeptic comment on the suitability of asymmetrically catalyzed dialkenylzinc/aldehyde additions see: J.M.Hawkins, R.H.Grubbs, *Chemtracts* 1988, *1*, 21.

5) P.D.Bartlett, L.H.Knox, *Organic Syntheses* Coll Vol.V, p. 689.

6) All isolated new intermediates and products were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and MS.

7) A solution of 6(5.47 g) in $SOCl_2$ (25 ml) and pyridine (0.2 ml) was stirred at RT for 2 h, then co-evaporated with benzene. Dissolution of the residue in benzene (25 ml) addition of *N,N,N'*-trimethylethylenediamine (7.8 ml) at 0°, stirring at 0° for 10 min, warming to RT, aq. workup and FC (AcOEt/Et_3N 10:1) gave 7 (5.72g, 72%). Addition of 7 (1.28 g, in 5 ml THF) to $LiAlH_4$ (5 molequiv) in THF at -40°, stirring at -40° for 1.5 h, then at -20° for 1h, then at 0° for 1 h, then under reflux for 1h, quenching with 20% aq. NaOH at 0°, extraction with Et_2O, FC and bulb-to-bulb distillation (140°,bath/0.02 Torr) gave 8 (853 mg, 71.5%).

8) The absolute configurations of products 3 and 4 were determined by chiroptic comparison with published values. 3a, 4a, 3b, 3c, 3d: "Stereochemistry" Ed. H.B.Kagan, G.Thieme Publ. 1977, Vol 4; 3e: M.Bessodes, E.Abushanab, K.Antonakis, *Tetrahedron Lett.* 1984, *25*, 5899; 3f: P.A.Aristoff, P.D.Johnson, A.W.Harrison, *J. Am. Chem. Soc.* 1985, *107*, 7967.

9) A diaminolithiumalkoxide has been reported to efficiently catalyze asymmetric diethylzinc/benzaldehyde additions: ref 2f). Indeed, successive addition of *n*-BuLi (0.1 equiv), Et_2Zn (1.1 molequiv), and PhCHO (0.1 equiv) to γ-diaminol 8 (0.1 equiv) in toluene at -78°, stirring at -78° for 16 h, then → RT (over 16h) gave 3a (61%) in 82% e.e..

10) In general, 2-*exo*-hydroxy-10-amino (amido)- or 2-*exo*-hydroxy-1-dimethylamino- bornane bidentate ligands, derived from (+)-camphor catalyzed the *Re*-face selective attack of Et_2Zn to PhCHO to give 4a (31 - 91% e.e.).

11) Divinylzinc: B.Bartocha, H.D.Kaesz, F.G.A.Stone, *Z. Naturforsch.*,1959, *14b*, 352.

12) The following decreasing order of reactivity was found on $(R^2)_2Zn$/PhCHO- additions, catalyzed by 8: $Et_2Zn \approx (C_2D_5)_2Zn > n\text{-}Pr_2Zn > Me_2Zn$. Exclusive ethyl group transfer has been reported on successive addition of *n*-BuLi, Et_2Zn and PhCHO to a polymer-bound β-aminol: ref 2e).

13) Most coordinatively saturated organozinc compounds contain a tetrahedrally surrounded Zn: J.Boersma "Comprehensive Organometallic Chemistry" Eds G, Wilkinson, F.G.A.Stone, E.W.Abel, Pergamon Press 1982, Vol 2 p. 823. For X-ray structures featuring pentacoordinated (trigonal-bipyramidal) Zn^{II} complexes see: P.L.Orioli, M.Di Vaira, L.Sacconi, *J.Chem. Soc. Chem. Commun.* 1965, 103; N.F.Curtis, I.R.N.McCormick, T.N.Waters *J. Chem. Soc. Dalton Trans.* 1973, 1537: N.W.Alcock, K.P.Balakrishnan, A.Berry, P.Moore, C.J.Reader, *ibid.*, 1988, 1089; M.Nagase, Y.Yukawa, Y.Inomata, T.Takeuchi, *Bull. Chem. Soc. Jpn.*, 1988, *61*, 775. Replacement of the central Zn^{II} in 13 by Li^{I} provided also a *Si*-face-directing catalyst see note 9). An alternative attempt to explain a coordination of Zn^{II}-complex 13 with the aldehyde by displacing the ligand N_A seems to be less plausible.

14) Reviews on camphor-derived chiral auxiliaries: W.Oppolzer, *Tetrahedron*, 1987, *43*, 1969, Erratum: *ibid.*, 1987, *43*, issue 18; W.Oppolzer, *Pure & Appl. Chem.* 1988, *60*, 39.

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