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Computer Assisted, Mechanism Directed Design of a New Ligand for the Highly Enantioselective Catalytic Addition of Diethylzinc to Aldehydes.

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Abstract: A new ligand, (1*R*,2*R*)-1-(*cis*-2,6-dimethylpiperidino)-1-phenyl-3-trityloxypropan-2-ol **1c**, designed on the basis of molecular modelling (AM1) studies to increase the energy gap between the *re* and *si* attacks in the aminoalcohol promoted addition of diethylzinc to benzaldehyde, has been synthesised in 73% overall yield from enantiomerically pure epoxycinnamyl alcohol. Ligand **1c** induces the highly enantioselective addition of Et_2Zn to a broad range of aromatic and aliphatic aldehydes.
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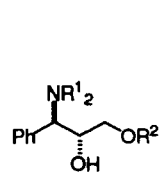
We have recently reported[1] the modular synthesis of a family of enantiomerically pure aminoalcohols **1**, designed as fine-tunable ligands for asymmetric synthesis, starting from readily accessible, enantiopure epoxyalcohol **2**.[2] Through an iterative process, we have been able to identify structural parameters key to high catalytic activity and enantioselectivity in the addition of Et_2Zn to aldehydes: compounds **1a** and **1b**, depicting optimal catalytic characteristics, present in their structures the nitrogen atom embedded in a six-membered ring and bear a very bulky trityl protecting group.[1]



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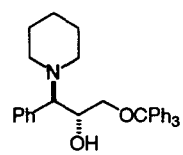
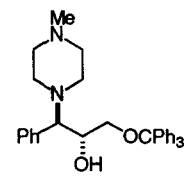


1a



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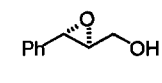


2

In an attempt to further improve the ligand design, we centered our attention on the analysis of the commonly accepted mechanism[3,4] of the aminoalcohol promoted addition of Et_2Zn to aldehydes. We wish to report here the mechanism-guided conception of a new ligand, which has been successfully designed for improved enantioselectivity through selective destabilisation of the diastereomeric transition states leading to the minor enantiomer in the addition process.

Noyori *et al.*[4] have recently reported the results of an *ab initio* MO study of the mechanism of the addition of dialkylzinc to aldehydes using a model system: the addition of Me_2Zn to formaldehyde promoted by 2-aminoethanol. If the results of this study are applied to the case of ligand **1** (Figure 1), the proposed catalytic species would be the tricoordinate Zn compound **3** which, acting as a bifunctional catalyst, would assemble the dialkylzinc and aldehyde (**4**) molecules to give the product-forming complex **5**. Alkyl delivery would then take place *via* a tricyclic transition state (TS) which can present *anti*- or *syn*- stereochemistry.[5]

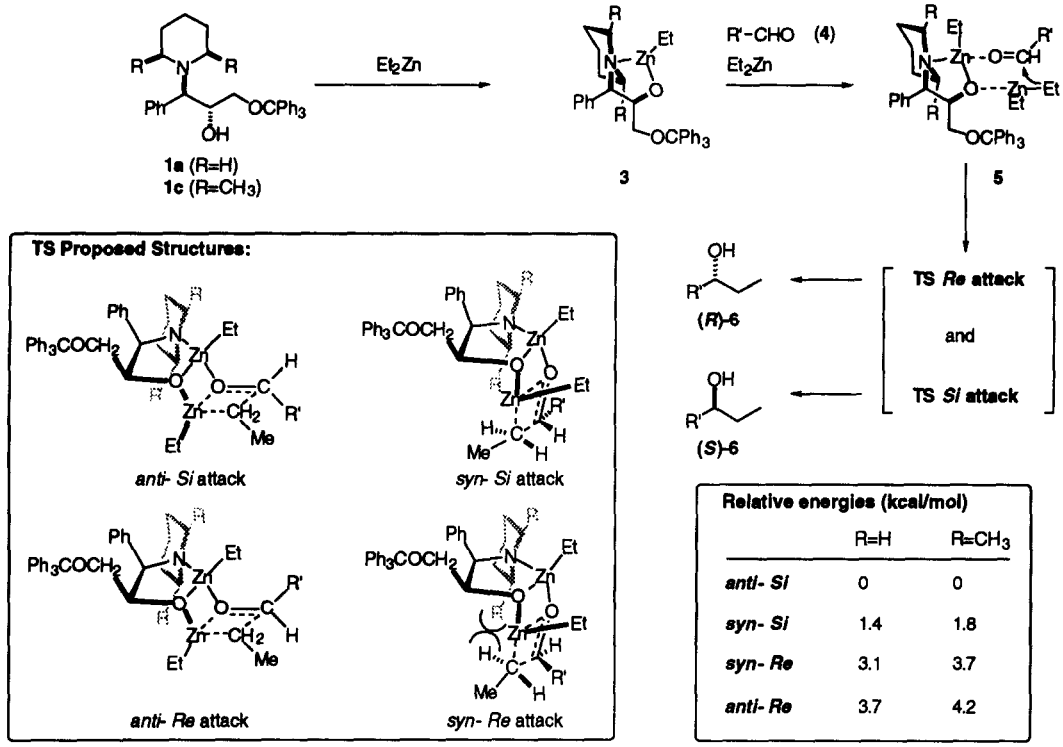


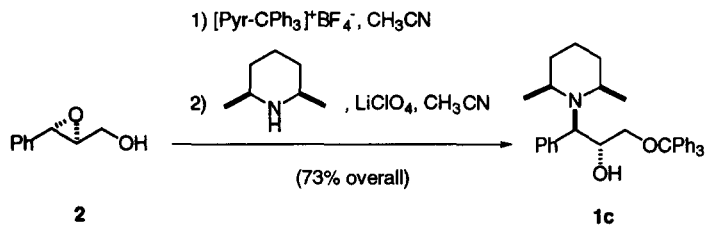
Figure 1

When a prochiral aldehyde and a chiral aminoalcohol are considered, as in the present case, the stereochemical outcome of the reaction will depend on the relative energies of the four possible diastereomeric transition states (*anti-Si*, *syn-Si*, *anti-Re*, *syn-Re*) as depicted in Figure 1. From the outcome of the reaction of Et_2Zn with benzaldehyde promoted by **1a**, where the *S* enantiomer of 1-phenyl-1-propanol (**6a**) is predominantly formed,[1] it is clear that at least one of the TS's in which the alkyl group is delivered to the *Si* face of the aldehyde must be the most favourable.

A theoretical scrutiny of the geometries and relative energies of these four species would greatly help in the understanding of the observed enantioselectivities; however, location of TS's at the *ab initio* level of theory for reactions involving more than hundred atoms is still beyond a reasonable limit. On the other hand, parametrization of the element Zn in semi-empirical procedures, such as AM1,[6] suffers from an imperfect description of tetracoordinate species.[7] According to that, in order to estimate the relative energies of the four possible transition states in the reactions promoted by **1a** we decided to follow a hybrid approach: The coordinates of the six atoms defining the dioxadizincabicyclo[2.2.0]hexane core were frozen to the values reported by Noyori for the parent system, and the resulting structures were then optimized subject to this restriction at the AM1 level.[8] In so doing, we were pleased to find (Figure 1) that not only the sense of the enantioselectivity induced by **1a** is correctly predicted (*anti-Si* and *syn-Si* attacks are the most favourable ones), but also that the predicted energy gaps between the TS's for *Si* and *Re* attacks are in reasonable agreement with the observed e.e. of the resulting (*S*)-1-phenyl-1-propanol (91% at room temperature). An inspection of the geometries of these transition state models suggested that steric repulsions between the equatorial hydrogen α to nitrogen in the piperidine ring and one of the α hydrogens in the ethyl group being transferred could be

responsible for the destabilisation of the transition structures corresponding to the *syn-Si* and the *syn-Re* attacks relative to the most favourable *anti-Si* one. We reasoned that, if this steric interaction could be strengthened, the relative energy of the transition state corresponding to the undesired *syn-Re* attack would be raised and, hence, the enantioselectivity of the reaction increased. The ready availability of *cis*-2,6-dimethylpiperidine, an inexpensive material, brought to our attention the possibility of substitution of the piperidino moiety in **1a** for a *cis*-2,6-dimethylpiperidino one; no further chirality would be introduced in the molecule and the considered α group (R in Figure 1) might be able to adopt in all instances a minimum energy conformation *via* nitrogen or ring inversions. The relative energies of the new transition state models (R= CH_3) were evaluated as in the case of **1a**.[9] In agreement with our expectations, the *anti-Si* attack was once again found to be the most favourable one and, interestingly, *both the* syn-Si *and the* syn-Re *attack TS's were predicted to be destabilized relative to the corresponding ones in the case of* ***1a*** *(R= H)*, as shown in Figure 1.

To test the validity of the results of the modelling study, the synthesis of **1c** was undertaken. Thus, enantiomerically pure **2** was sequentially submitted to tritylation (1.1 equiv. of tritylpyridinium tetrafluoroborate in acetonitrile at room temperature) and regioselective ring-opening[1] (10 eq. of *cis*-2,6-dimethylpiperidine in 6M $LiClO_4$/ CH_3CN at 55°C) to afford regio- and diastereomerically pure **1c** in 73% overall yield.



2 **1c**

Scheme 1

When **1c** (6% mol) was used as a ligand at room temperature to induce the addition of Et_2Zn to benzaldehyde, we were delighted to observe the formation of 95% e.e. (*S*)-1-phenylpropanol **6a** (91% e.e. **6a** was formed with ligand **1a** under identical conditions), in full agreement with the results of the modelling studies. A further improvement in the enantioselectivity (up to 97% e.e.) could be achieved by simply performing the reaction at 0 °C. This highly active new ligand was also studied in the addition of Et_2Zn to a family of aldehydes **6b-h**, with good overall enantioselectivity. The results of these reactions have been summarised in Table 1, where the corresponding results with ligand **1a**[1] have also been included for comparison. The best enantioselectivities were obtained with *p*-substituted benzaldehydes (**6b-d**) and, in contrast with many previously reported ligands which are catalytically active in this particular process,[3] the e.e.'s recorded with *ortho* substituted benzaldehydes (**6e-f**) or with aliphatic aldehydes (**6g-h**) were in all cases higher than 90%. *It is worth noting that* ***1c*** *behaves for all tested aldehydes more efficiently than* ***1a***.

For preparative purposes, the amount of ligand **1c** could be lowered to 2%. In this way, the addition of Et_2Zn to **4a** was complete (conversion >99%) in less than 5h at 0 °C, leading to 97% e.e. **6a** (*cfr.* entry a in Table 1). Interestingly, no decreases in enantioselectivity were detected at all in preparative runs, isolated yields and ligand recovery being almost quantitative.[10]

In conclusion, we have employed a rational, mechanism-guided approach to the design of a highly efficient and selective ligand for the enantioselective addition of Et_2Zn to aldehydes. On the basis of postulated transition state geometries, the first generation ligand **1a**[1] has been modified in order to increase the energy gap between the desired and undesired TS's and, hence, increase the enantioselectivity of the reaction. This newly designed ligand, being readily available in multigram amounts in both enantiomerically pure forms, has proved to be extremely efficient, both in terms of high catalytic activity and enantioselectivity, in the addition of Et_2Zn to a broad range of aldehydes. The current development of computational chemistry should allow the application of

similar approaches to other catalytic processes of known mechanism. Straightforward progress towards efficient versions of such reactions would doubtlessly benefit from it.

Table 1. Catalytic enantioselective addition of Et_2Zn to aldehydes[a] (**4a-h**) leading to alcohols **6a-h**[b] mediated by ligands **1c** and **1a**[c].

Starting Aldehyde	Resulting Alcohol	E.e.[d] (%) of resulting alcohol	
		with **1c**	with **1a**
Benzaldehyde (**4a**)	(*S*)-**6a**	**97**	92
4-Methylbenzaldehyde (**4b**)	(*S*)-**6b**	**97**	92
4-Methoxybenzaldehyde (**4c**)	(*S*)-**6c**	**98**	91
4-Fluorobenzaldehyde (**4d**)	(*S*)-**6d**	**97**	93
2-Chlorobenzaldehyde (**4e**)	(*S*)-**6e**	**93**	87
1-Naphthaldehyde (**4f**)	(*S*)-**6f**	**90**	82
3-Phenylpropanal (**4g**)	(*S*)-**6g**	**92**	86
Isovaleraldehyde (**4h**)	(*S*)-**6h**	**90**	85

[a]All reactions were performed using a 6% molar amount of **1c** or **1a** at 0 °C for 4 hours, conversions being 99% or higher. [b]The *S* enantiomer is preferentially obtained in all cases. The absolute configuration has been established by comparing the sign of the optical rotation except for **6e** in which the *S* configuration has been assumed. [c]Results for **1a** (ref. 1) are included for comparison. [d]By GC with α- or β-DEX 120 columns.

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References and Notes:

1 Vidal-Ferran, A.; Moyano, A.; Pericàs, M.A.; Riera, *J. Org. Chem.* **1997**, *62*, 4970-4982.

2 Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H.; Sharpless, K.B. *J. Am. Chem. Soc.* **1987**, *109*, 5765-5780.

3 (a) *Asymmetric Catalysis in Organic Synthesis*; Noyori, R.; John Wiley & Sons, Inc.: New York, 1994, ch. 5, p. 255-297. (b) Noyori, R.; Kitamura, M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49-69. (c) Soai, K. *Chem. Rev.* **1992**, *92*, 833-856.

4 Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327-6335.

5 These terms refer to the *anti-* or *syn-* relationship between the two terminal rings in the tricyclic system.

6 Dewar, M.J.S.; Zoebish, E.G.; Healy, E.F.; Stewart, J.J.P. *J. Am. Chem. Soc.* **1985**, *107*, 3902-3909.

7 Dewar, M.J.S.; Merz, K.M., Jr. *Organometallics* **1988**, *7*, 522-524.

8 The calculations were performed with the Restricted-Hartree-Fock (RHF) version of AM1 as implemented in the MOPAC module in the CERIUS2 package of programs (BIOSYM/Molecular Simulations, San Diego, California).

9 The N-Zn distance was kept constant at the value optimized for R=H.

10 In a typical experiment, benzaldehyde (2.12 g, 20 mmol) was slowly added to a solution of **1c** (202 mg, 0.40 mmol, 2 mol %) and Et_2Zn (30 mL of a 1M solution in hexanes) in toluene (40 mL) at 0°C over 3 hours under N_2. The mixture was stirred for 2 h. The reaction was then quenched by careful addition of a saturated NH_4Cl solution (200 mL) and the resulting mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*, and the residue was purified by bulb-to-bulb distillation to give 2.58 g of (*S*)-1-phenylpropanol (95% yield): e.e. 97%, selectivity 99%. The chiral ligand was recovered (99 %) by chromatography of the distillation residue.

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