Organozinc Additions: A DFT Study

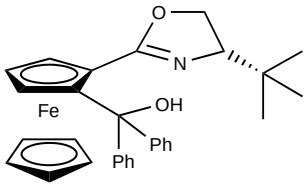
Phenyl versus Ethyl Transfer in the Addition of Organozinc Reagents to Aldehydes: A Theoretical Study**

*Jens Rudolph, Torben Rasmussen, Carsten Bolm, and Per-Ola Norrby**

The discovery of the amino-alcohol-catalyzed enantioselective alkyl transfer to aldehydes by Oguni and Omi in 1984 initiated the ever-growing interest in the development of new and highly selective chiral ligands for the asymmetric synthesis of secondary and tertiary alcohols.[1] In line with the initial use of (*S*)-leucinol, most new ligands are based on β-amino alcohols or their derivatives.[2] Significant developments in the addition of organozinc compounds to aldehydes have led to tremendous progress in terms of the variety of ligand structures and available transferable moieties. Among the latter, enantioselective aryl transfer to aromatic aldehydes is interesting in that it gives access to chiral diarylmethanols, important precursors for pharmacologically and biologically active compounds.[3] In the organozinc route to diarylmethanols, enantioselectivity is achieved by differentiation between an aryl group and a hydrogen atom, whereas alternative routes, such as asymmetric reduction of diarylketones, rely on differentiation between two similar aryl groups, a task which can be successful in isolated instances[4] but cannot easily be generalized. Initially, the organozinc route relied on the use of pure diphenylzinc or mixed phenylzinc reagents prepared in situ,[2,5–7] but has recently been extended to a general method for asymmetric aryl transfer utilizing aryl boronic acids.[8]

Several features distinguish the reactivity of diarylzinc reagents from the related dialkylzinc compounds. First, the background reaction rate is substantially higher: Ph_2Zn adds to aldehydes at room temperature even in the absence of ligand. However, the reaction is still ligand-accelerated,[9] and a substantially faster reaction and moderate-to-good enantioselectivity are obtained in the presence of a chiral ligand.[6]

A remarkable result is obtained by using a mixture of Et_2Zn and Ph_2Zn as phenyl source. The reaction is slightly slower than with Ph_2Zn alone,[10] but shows substantially higher enantioselectivity (up to 98% *ee* with ligand **1**) for a wide variety of aldehydes, and is completely selective for Ph transfer.[6] Under optimized conditions[6b–e,10] (1.3 equiv Et_2Zn and 0.65 equiv Ph_2Zn), the Et/Ph ratio at full conversion is approximately eight, and still no ethyl transfer is observed; that is, phenyl transfer is orders of magnitude faster. This interesting result promted us to undertake a theoretical study to probe the underlying causes for the difference in reactivity.



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The mechanism for the addition of Et_2Zn to aldehydes has been the subject of intense research.[11] Noyori et al. proposed a convincing mechanism based on a combination of experimental and theoretical investigations.[12,13] Several groups have extended and validated the computational model for a large range of systems.[14,15] A concensus on the source of selectivity is depicted in Figure 1. Generally, the major

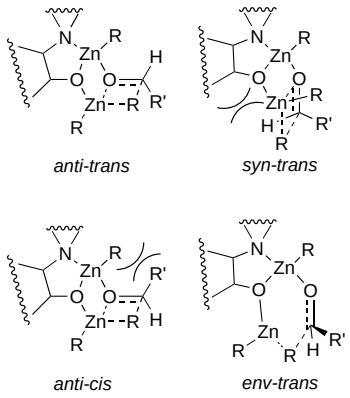

Figure 1. Proposed transition states for the addition of R_2Zn to aldehydes.

enantiomer is produced from the *anti-trans* path, in which the aldehyde coordinates to the catalytic Zn center through the *trans* lone pair, and the R group *anti* to the ligand is transferring. The minor enantiomer can arise from several sources: The *inv* path (not shown), in which imperfect blocking by the ligand allows coordination to the opposite face of the catalytic Zn center; the *anti-cis* path, in which the aldehyde has inverted and coordinates with the *cis* lone pair; the *syn-trans* path, in which the *syn* R group is transferring; and the *env-trans* path, in which the *syn-trans* transition state

[*] Prof. Dr. P.-O. Norrby
Department of Chemistry
Technical University of Denmark
Building 201, Kemitorvet, 2800 Kgs. Lyngby (Denmark)
Fax: (+45) 45933968
E-mail: pon@kemi.dtu.dk

Dipl.-Chem. J. Rudolph, Prof. Dr. C. Bolm
Institut für Organische Chemie der RWTH Aachen
Professor Pirlet Str. 1, 52074 Aachen (Germany)

Dr. T. Rasmussen
Department of Theoretical Chemistry, Lund University
Chemical Center, P.O. Box 124, 22100 Lund (Sweden)

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(TS) opens to give a six-membered cyclic TS in an envelope conformation.[15] For unhindered aliphatic aldehydes, the *anti-cis* path is generally only slightly disfavored, and it leads to low selectivity, whereas aromatic aldehydes experience a severe steric clash due to the strong conjugation in the TS.[13b,15b] When a ligand capable of blocking one face of the catalytic Zn center is used in combination with a conjugated aldehyde, the minor enantiomer usually arises from the *syn-trans* path, which is inherently disfavored by about 10–15 kJ mol^{-1} for alkyl transfer.[13,15]

Here we present a DFT investigation of reaction paths for Ph_2Zn in the presence and absence of Et_2Zn, and addressing the reactivity pattern and plausible causes for selectivity in phenyl transfer.

All calculations were performed at the B3LYP/LACVP* level (Hay–Wadt double-ζ valence + ECP for Zn,[16] 6-31G* for other atoms) in Jaguar 4.2 from Schrödinger Inc.[17] Stationary points were verified by analytical normal-mode analysis. The model system employed here is based on our previous study:[15a] a β-dimethylaminoethanol ligand, acetaldehyde (R′ = Me), and alkyl substituents R (Figure 2). For

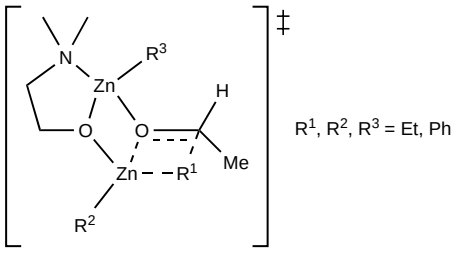
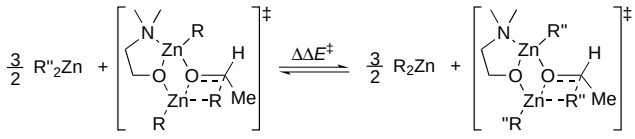


Figure 2. Computational model system, exemplified by an *anti-trans* transition state.

the last-named, we tested all eight combinations of Et and Ph in the *anti-trans* TS. For the all-Ph combination we also located the *syn-trans*, *anti-cis*, and *env-trans* TSs depicted in Figure 1. All calculated structures are available as Supporting Information. Relative activation energies calculated from the isodesmic comparison depicted in Scheme 1 are given in Table 1.



Scheme 1. Example of an isodesmic equilibrium for calculating relative activation energies.

The data in Table 1 clearly show the higher reactivity for Ph compared to Et transfer. The best TS for Et transfer (entry 4) is 40 kJ mol^{-1} higher in energy than the best TS for Ph transfer (entry 8). The difference can be understood from a detailed analysis of the TS structures. For both moieties, the TS geometry is reminiscent of the free anion, with the filled lobe pointing between the Zn atom and the carbonyl C atom (Figure 3); the TS is the point of minimum overlap of the

Table 1: Calculated relative activation energies $\Delta\Delta E^{\neq}$ [kJ mol^{-1}] (Scheme 1), with R^1–R^3 as defined in Figure 2.

Entry	$R^1R^2R^3$	TS type	$\Delta\Delta E^{\neq}$ [kJ mol^{-1}]
1	EtEtEt	*anti-trans*	50
2	EtEtPh	*anti-trans*	41
3	EtPhEt	*anti-trans*	47
4	EtPhPh	*anti-trans*	40
5	PhEtEt	*anti-trans*	18
6	PhEtPh	*anti-trans*	10
7	PhPhEt	*anti-trans*	9
8	PhPhPh	*anti-trans*	0
9	PhPhPh	*syn-trans*	27
10	PhPhPh	*env-trans*	19
11	PhPhPh	*anti-cis*	2

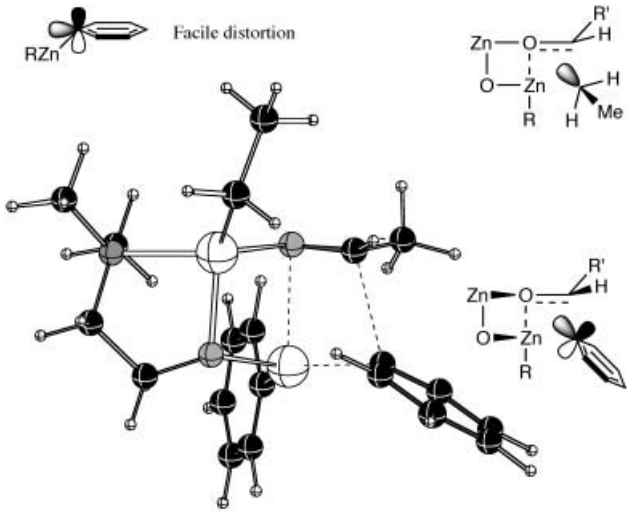


Figure 3. Comparison of Et and Ph transfer, and the transition state for entry 7, Table 1.

anion with an electron acceptor. However, for the Ph moiety the filled aromatic π orbital (illustrated by a p orbital in Figure 3) is overlapping with the electron-poor Zn and C atoms, and this provides additional stabilization. Calculations on simple organozinc reagents show that the overlap with the π system of the phenyl group is also possible in the reagent itself, as seen in the crystal structure of the Ph_2Zn dimer.[18] The phenyl group easily bends to expose the anionic lobe (Figure 3), whereas the corresponding distortion for the ethyl moiety is a high-energy process. Thus, even in the presence of a 10- or even 100-fold excess of ethyl reagent, clean phenyl transfer would be expected. This is in good agreement with the observations of Bolm et al.[6b–e,10]

The transition states are formed from combination of R_2Zn with the aldehyde and the actual catalyst, an RZn–ligand complex.[13] The availability of the combinations of R groups required for the paths in Table 1 was investigated by calculating the equilibrium $Ph_2Zn + Et_2Zn \rightleftarrows 2\,PhEtZn$, which was found to be virtually thermoneutral ($\Delta E = 0.2$ kJ mol^{-1}). Thus, all three R_2Zn complexes will be present in the reaction mixture, in agreement with the observation by NMR spectroscopy of formation of an additional Ph–Zn moiety on addition

of Et_2Zn to Ph_2Zn.[10] Fast exchange of R groups is expected from the crystal structure of the Ph_2Zn dimer,[18] so that R_2Zn can be assumed to be present as a statistical mixture (Curtin–Hammett conditions).[19]

Looking more closely at the possible paths for the reagent mixture reveals that the highest reactivity is obtained with the pure phenyl system, in perfect agreement with the observation of higher reactivity in the absence of Et_2Zn.[6b–e,10] Replacing one spectator phenyl with an ethyl group increases the activation energy by 9–10 kJ mol^{-1} (Table 1, entries 6 and 7). The effect is additive; replacing both spectator groups causes an increase in activation energy of 18 kJ mol^{-1} (Table 1, entry 5). The more electronegative phenyl group increases the Lewis acidity of Zn, and thus increases the reactivity of the coordinated aldehyde. As a consistent trend, replacing an ethyl with a phenyl group causes a slight increase in the Mulliken charge at the directly bonded Zn atom. Furthermore, the bystander phenyl group can also stabilize the hypovalent, three-coordinate Zn atom in the product by π bonding. By coincidence, the magnitudes of these effects add to give similar numerical values for both bystander groups.

From earlier studies on ethyl transfer at the same level of theory as the current study,[15a] we know that the *anti-cis* TS is only slightly higher in energy than the *anti-trans* TS, and hence low selectivities result for unencumbered aliphatic aldehydes unless the ligand has a geometry that specifically disfavors the *anti-cis* pathway.[15b] For conjugated aldehydes, the *anti-cis* path is selectively disfavored by a steric clash with the bystander alkyl group on the catalytic Zn center, and can generally be ignored.[15b] Thus, for aromatic aldehydes, the minor enantiomer is mostly produced by the *syn-trans* and possibly the *env-trans* pathway. Interestingly, these two paths (especially *syn-trans*) are highly disfavored for Ph transfer (Table 1, entries 9 and 10). The *syn-trans* path is 27 kJ mol^{-1} higher in energy than the *anti-trans* path in the all-Ph case, as opposed to a difference of about 15 kJ mol^{-1} for alkyl transfer.[15a] On the other hand, it is not a priori certain that the *anti-cis* path is also prohibited for aryl transfer to aromatic aldehydes; phenyl–phenyl interactions can stabilize transition states if the geometry is suitable.[20] A full computational analysis of the selectivity should include both the aromatic aldehyde and ligand **1** in the calculation. However, such an analysis at the DFT level is still beyond our computational resources. We plan to address the selectivity issue further by Q2MM[20,21] or QM/MM[14c–e] calculations.

With regard to the selectivity, we know from experimental studies that for most aldehydes, the *ee* values obtained with only Ph_2Zn and ligand **1** is lower than when the Ph_2Zn/Et_2Zn mixture is employed. There can be two reasons for such a difference: either addition of Et_2Zn opens up a new, faster, and more selective path, or it suppresses the nonselective path by depleting the concentration of the required components. Both experiment and theory indicate that the latter explanation is operative here. The activation barriers are not lowered by the introduction of ethyl groups (Table 1), and the observed reaction rate does not increase.[10] Furthermore, the computational results for the reagent pre-equilibrium, as well as tentative NMR spectroscopic assignment of the same equilibrium in THF,[10] indicates that Ph_2Zn (required for the all-Ph path, Table 1, entry 8, and also for the background reaction) is still present in the reaction mixture after addition of a twofold excess of Et_2Zn. This leaves us with the last component of the reaction, the catalyst formed from deprotonated ligand **1** and RZn. The size of the ligand has so far precluded a DFT investigation, but it is reasonable to assume that the bulk of the system would disfavor the phenyl group. If most of the catalyst is present as EtZn·**1**, only paths with R^3 = Et would contribute to product formation. This could also rationalize the higher selectivity in the presence of Et_2Zn. For phenyl transfer, we expect most of the minor enantiomer to arise from the *anti-cis* path (Table 1, entries 9–11), and we know from previous studies that R^3 = Et selectively disfavors this path for aromatic aldehydes,[15b] whereas preliminary calculations indicate that the phenyl–phenyl interaction in systems with R^3 = Ph is less repulsive. Thus, a depletion of the concentration of PhZn·**1** in favor of EtZn·**1** upon addition of Et_2Zn rationalizes the experimental observations, and also clarifies why ligand **1** in combination with the Ph_2Zn/Et_2Zn mixture generally gives high *ee* values, whereas other ligand systems for phenyl transfer seem to be very dependent on the exact reaction conditions.

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