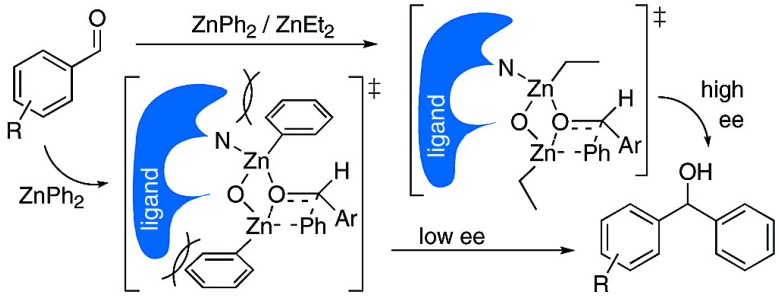
Article

New Insights into the Stereoselectivity of the Aryl Zinc Addition to Aldehydes

Jens Rudolph, Carsten Bolm, and Per-Ola Norrby

J. Am. Chem. Soc., **2005**, 127 (5), 1548-1552• DOI: 10.1021/ja046254s • Publication Date (Web): 14 January 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 10 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES
Published on Web 01/14/2005

New Insights into the Stereoselectivity of the Aryl Zinc Addition to Aldehydes

Jens Rudolph,[‡] Carsten Bolm,[‡] and Per-Ola Norrby*,[†]

Contribution from the Department of Chemistry, Technical University of Denmark, Building 201, Kemitorvet, DK-2800 Kgs. Lyngby, Denmark, and Institut für Organische Chemie der RWTH Aachen, Professor-Pirlet-Strasse 1, 52074 Aachen, Germany

Received June 24, 2004; E-mail: pon@kemi.dtu.dk

Abstract: The addition of Ph_2Zn to aldehydes has been investigated by DFT calculations. The experimentally observed increase in enantioselectivity upon addition of Et_2Zn to the reaction mixture is rationalized from calculations of all isomeric transition states. Spectator ethyl groups in the transition state do not lower the intrinsic activation barrier, but instead increase it. In the presence of a bulky ligand, the inherently preferred all-phenyl transition state is selectively disfavored. The paths with less sterically demanding spectator ethyl groups will experience a more drastic ligand acceleration, and thus the influence of the ligand would be expected to be stronger in the presence of Et_2Zn, in agreement with experimental observations.

Introduction

Asymmetric catalysis is one of the most important areas in modern organic chemistry.[1,2] Within this field, the construction of carbon−carbon bonds in an asymmetric fashion is of major relevance. A well-known example is the dialkyl zinc addition to aldehydes, catalyzed by β-amino alcohols or similar compounds.[3] The reaction takes advantage of the fact that pure dialkyl zincs do not react with aldehydes in the absence of a promoter. A plethora of compounds has been found to be catalytically active, and on this basis the selective addition of diethyl zinc to benzaldehyde became a common test reaction for newly developed chiral catalysts. Nevertheless, certain substrates and reagents such as nonbranched aliphatic aldehydes and dimethyl zinc, respectively, are still considered to be difficult, and their use mostly leads to unsatisfying reactivities and/or enantioselectivities.[4]

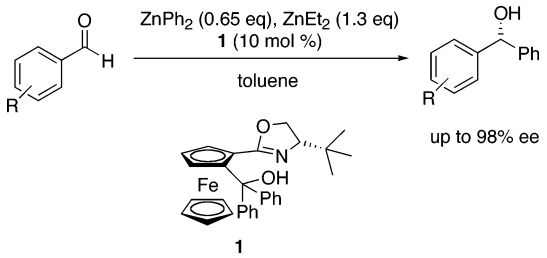
Due to the importance of enantiomerically pure diaryl methanols as precursors for biologically active compounds,[5,6] much effort has been made to develop highly selective, catalytic methods for their synthesis. This goal has partially been achieved by asymmetric reduction of prochiral ketones.[7] However, due to the required substitution pattern of the substrate, which is essential for a sufficient differentiation between the enantiotopic sides of the carbonyl group, this approach is severely limited. An alternative enantioselective route toward diaryl methanols involves the asymmetric aryl transfer to benzaldehydes. Reactions of this type are more facile, because there the face-selectivity of the nucleophilic attack is determined by the significant difference between the hydrogen and the aryl group of the aldehyde. Major breakthroughs in catalyzed diaryl methanol syntheses by such C−C-bond formations have been achieved by Fu,[8] and later by Bolm,[9] Pu,[10] and others[11] using $ZnPh_2$ as aryl transfer reagent. Their catalysts are highly face selective, and, furthermore, they lead to relatively fast phenyl transfer reactions, which over-ride the racemate-forming background reaction. With mixtures of $ZnPh_2$ and $ZnEt_2$ as the

[†] Technical University of Denmark.
[‡] Institut für Organische Chemie der RWTH Aachen University.

(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) *Transition Metals for Organic Synthesis*, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley−VCH: Weinheim, 2004. (c) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfalz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999. (d) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley−VCH: New York, 2000. (e) For a recent presentation of various aspects of enantioselective catalysis, see: *Chem. Rev.* **2003**, *103*, 2761−3400 (Bolm, C., Gladysz, J., Eds.).
(2) "Asymmetric Catalysis" was also highlighted by the 2001 Nobel prizes in chemistry. (a) Knowles, W. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1998−2007. (b) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008−2022. (c) Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2024−2032.
(3) For reviews, see: (a) Evans, D. A. *Science* **1988**, *240*, 420−426. (b) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49−69. (c) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856. (d) Pu, L.; Yu, H. B. *Chem. Rev.* **2001**, *101*, 757−824.
(4) For recent examples, see: (a) Paleo, M. R.; Cabeza, I.; Sardina, F. J. *J. Org. Chem.* **2000**, *65*, 2108−2113. (b) Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Synthesis* **2000**, *1*, 165−176. (c) Kawanami, Y.; Mitsuie, T.; Miki, M.; Sakamoto, T.; Nishitani, K. *Tetrahedron* **2000**, *56*, 175−178. (d) Dai, W.-M.; Zhu, H.-J.; Hao, X.-J. *Tetrahedron: Asymmetry* **2000**, *11*, 2315−2337. (e) Ooi, T.; Saito, A.; Maruoka, K. *Chem. Lett.* **2001**, 1108−1109. (f) Hu, Q.-S.; Sun, C.; Monaghan, C. E. *Tetrahedron Lett.* **2001**, *42*, 7725−7728. (g) Ohga, T.; Umeda, S.; Kawanami, Y. *Tetrahedron* **2001**, *57*, 4825−4829. (h) Steiner, D.; Sethofer, S. G.; Goralski, C. T.; Singaram, B. *Tetrahedron: Asymmetry* **2002**, *13*, 1477−1483. (i) Xu, Q.; Zhu, G.; Pan, X.; Chan, A. S. C. *Chirality* **2002**, *14*, 716−723. (j) Sato, I.; Kodaka, R.; Hosoi, K.; Soai, K. *Tetrahedron: Asymmetry* **2002**, *13*, 805−808.
(5) Class, S. Pharma Overview in *Chem. Eng. News* **2002**, *Dec. 2*, 44−46.
(6) (a) Meguro, K.; Aizawa, M.; Sohda, T.; Kawamatsu, Y.; Nagaoka, A. *Chem. Pharm. Bull.* **1985**, *33*, 3787−3797. (b) Toda, F.; Tanaka, K.; Koshiro, K. *Tetrahedron: Asymmetry* **1991**, *2*, 873−874. (c) Stanchev, S.; Rakovska, R.; Berova, N.; Snatzke, G. *Tetrahedron: Asymmetry* **1995**, *6*, 183−198. (d) Botta, M.; Summa, V.; Corelli, F.; Di Pietro, G.; Lombardi, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1263−1266. (e) Bolshan, Y.; Chen, C.-Y.; Chilenski, J. R.; Gosselin, F.; Mathre, D. J.; O'Shea, P. D.; Roy, A.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 111−114 and references therein.
(7) (a) Ohkuma, T.; Koizumi, M.; Ikehira, H.; Yokozawa, T.; Noyori, R. *Org. Lett.* **2000**, *2*, 659−662. (b) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1995**, *36*, 9153−9156. (c) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996**, *37*, 4837−4840. (d) Corey, E. J.; Helal, C. J. *Tetrahedron Lett.* **1996**, *37*, 5675−5678. General reviews: (e) Noyori, R.; Ohkuma, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 40−73. (f) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986−2012.
(8) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444−445.

10.1021/ja046254s CCC: $30.25

Scheme 1. Enantioselective Phenyl Transfer to Aldehydes According to Bolm's Protocol



phenyl source, excellent enantioselectivities (of up to 98% ee) could be achieved as demonstrated by Bolm (Scheme 1).[9b−g]

The transformation shown in Scheme 1 is remarkable for a number of reasons. First, as compared to the phenyl transfer from pure $ZnPh_2$, the presence of the 2-fold excess of $ZnEt_2$ relative to $ZnPh_2$ significantly increases the enantioselectivity for a wide variety of aldehydes. Furthermore, the reaction is slightly slower than with $ZnPh_2$ alone, and moreover only phenyl (and no ethyl) transfer is observed. We recently communicated a rationalization for the higher reactivity of the phenyl group based on DFT calculations.[12] In short, the phenyl π-system allows a simultaneous overlap with both zinc and the reacting carbonyl, which substantially lowers the energy of the transition state as compared to the simple alkyl group transfer. In recent work by Pericàs and co-workers,[11d] the reagent preequilibrium was studied by DFT methods, and the selectivity was addressed by PM3 calculations. Of high importance to the current work are the findings that the mixed reagent EtZnPh is formed in a virtually isoenergetic equilibrium and that the presence of reagent dimers can be neglected in the reaction.

The mechanism of the asymmetric addition of dialkyl zinc to aldehydes has fully been elucidated by a combination of kinetic and computational studies.[13] In the selectivity-determining step, first proposed by Itsuno and Fréchet,[14] and later supported and elaborated by Noyori and co-workers,[13,15] the reactants are gathered together by a bifunctional alkyl zinc−ligand complex, yielding a transition state of the type depicted in Figure 1.

Earlier quantum chemical studies of the alkyl transfer reaction have employed simple β-amino ethanol models of the ligand,[16,17] with steric effects of the ligand added at a molecular

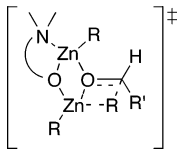


Figure 1. Selectivity-determining transition state in the catalyzed dialkyl zinc addition to aldehydes.

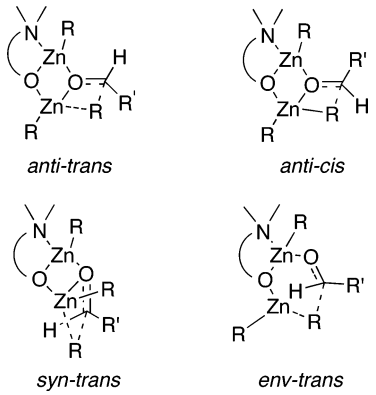


Figure 2. Plausible paths in the additions of dialkyl zincs to aldehydes.

mechanics[17c,d,i,18] or semiempirical level.[11d,17b,j] In the consensus mechanism, the primary role of the ligand is to block aldehyde coordination to one face of the catalytic zinc atom. The major enantiomer arises from the so-called *anti-trans* transition state, where the aldehyde coordinates to the catalytic zinc with the lone pair trans to the alkyl group, and the zinc alkyl anti to the ligand nitrogen is transferring. The minor enantiomer arises from one of several other possible ways of attacking the opposite face of the aldehyde (Figure 2).

In the current case, inclusion of the steric effects in the computational study poses a severe problem, because computational treatment of the ferrocene **1** is nontrivial by any of the previously employed methods. However, we have recently shown[9f] that the remarkable selectivity shifts obtained with **1** are closely mirrored (albeit with a lower overall selectivity in our test systems) by Soai's *N*,*N*-dibutyl norephedrine (DBNE).[19] For example, with 4-methylbenzaldehyde as test substrate, the phenyl transfer from pure $ZnPh_2$ in the presence of DBNE gave the corresponding diaryl methanol with 62% ee, whereas the mixture of $ZnPh_2$ and $ZnEt_2$ led to a product with 90% ee. In comparison, ferrocene **1** gave 77% with pure $ZnPh_2$ and 98% ee with the $ZnPh_2/ZnEt_2$ mixture.[9f] An ongoing computational study, evaluating DBNE in a DFT model in the ethyl transfer to aldehydes, shows close similarity of DBNE and simple amino ethanol in a selectivity prediction.[20] We thus expect the use of *N*,*N*-dimethyl amino ethanol as a simple model ligand for a

(9) (a) Bolm, C.; Muñiz, K. *Chem. Commun.* **1999**, 1295−1296. (b) Bolm, C.; Hermanns, N.; Hildebrand, J. P.; Muñiz, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3465−3467. (c) Bolm, C.; Kesselgruber, M.; Hermanns, N.; Hildebrand, J. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1488−1490. (d) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850−14851. (e) Bolm, C.; Hermanns, N.; Classen, A.; Muñiz, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1795−1798. (f) Rudolph, J.; Herrmanns, N.; Bolm, C. *J. Org. Chem.* **2004**, *69*, 3997−4000. (g) For a review on catalyzed asymmetric arylation reactions, see: Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284−3308.
(10) (a) Huang, W.-S.; Hu, Q.-S.; Pu, L. *J. Org. Chem.* **1999**, *64*, 7940−7956. (b) Huang, W.-S.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 145−149.
(11) (a) Zhang, H.; Wue, F.; Mac, T. C.; Chan, K. S. *J. Org. Chem.* **1996**, *61*, 8002−8003. (b) Zhao, G.; Li, X.-G.; Wang, X.-R. *Tetrahedron: Asymmetry* **2001**, *12*, 399−403. (c) Ko, D.-H.; Kim, K. H.; Ha, D.-C. *Org. Lett.* **2002**, *4*, 3759−3762. (d) Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532−2543.
(12) Rudolph, J.; Rasmussen, T.; Bolm, C.; Norrby, P.-O. *Angew. Chem., Int. Ed.* **2003**, *40*, 3002−3005.
(13) (a) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327−6335. (b) Yamakawa, M.; Noyori, R. *Organometallics* **1999**, *18*, 128−133.
(14) Itsuno, S.; Fréchet, J. M. J. *J. Org. Chem.* **1987**, *52*, 4142−4143.
(15) (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028−4036. (b) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 9800−9809. (c) Kitamura, M.; Oka, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 3605−3614.
(16) Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* **2001**, *123*, 2464−2465.
(17) (a) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1997**, *38*, 8773−8776. (b) Goldfuss, B.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 8998−9006. (c) Goldfuss, B.; Steigelmann, M.; Khan, S. I.; Houk, K. N. *J. Org. Chem.* **2000**, *65*, 77−82. (d) Vázquez, J.; Pericàs, M. A.; Maseras, F.; Lledós, A. *J. Org. Chem.* **2000**, *65*, 7303−7309. (e) Goldfuss, B.; Steigelmann, M.; Rominger, F. *Eur. J. Org. Chem.* **2000**, 1785−1792. (f) Davis, T. J.; Balsells, J.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2001**, *3*, 699−702. (g) Panda, M.; Phuan, P.-W.; Kozlowski, M. C. *J. Org. Chem.* **2003**, *68*, 564−571. (h) Gung, B. W.; Xue, X. W.; Knatz, N.; Marshall, J. A. *Organometallics* **2003**, *22*, 3158−3163. (i) Kozlowski, M. C.; Dixon, S. L.; Panda, M.; Lauri, G. *J. Am. Chem. Soc.* **2003**, *125*, 6614−6615. (j) Munoz-Muniz, O.; Juaristi, E. *J. Org. Chem.* **2003**, *68*, 3781−3785. (k) For lithium salt effects, see: Sosa-Rivadeneyra, M.; Munoz-Muniz, O.; de Parrodi, C. A.; Quintero, L.; Juaristi, E. *J. Org. Chem.* **2003**, *68*, 2369−2375.
(18) Rasmussen, T.; Norrby, P.-O. *J. Am. Chem. Soc.* **2003**, *125*, 5130−5138.
(19) Soai, K.; Yokoyama, S.; Ebihara, K.; Haysaka, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1690−1691.

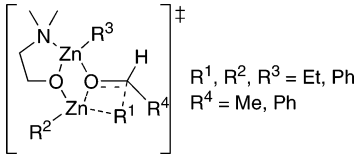
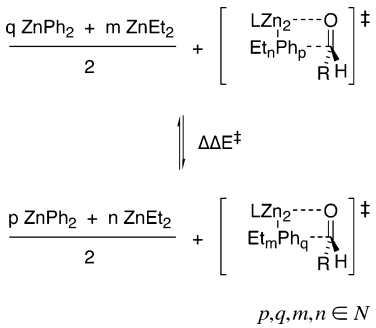


Figure 3. Model systems employed in the current study.

Scheme 2. Pseudoequilibrium for Comparison of Similar Transition States[a]



[a] The ligand L is modeled by dimethylaminoethanolate, and the labels *m*, *n*, *p*, and *q* denote the number of ethyl and phenyl moieties in the two TS being compared: $n + p = m + q = 3$.

computational investigation to reproduce the selectivity shift observed for DBNE, and by similarity of experimental results, also for **1**. A qualitatively correct picture of the main factors influencing the enantioselectivity can then be obtained by only allowing one of the two mirror image coordination geometries around the catalytic zinc.[18]

Methods

The presented study is an extended theoretical investigation of the phenyl transfer to aldehydes, which was communicated by us earlier in preliminary form.[12] The model system employed in the current study is depicted in Figure 3. For acetaldehyde (R^4 = Me), all eight combinations of Et and Ph alkyl groups were tested, whereas for benzaldehyde (R^4 = Ph), only the phenyl transfer was investigated (R^1 = Ph, four combinations). For every combination, all transition states were located at the B3LYP[21]/LACVP* level (Hay-Wadt double-ζ valence + ECP for Zn and Fe,[22] 6-31G* for other atoms) in Jaguar 4.2 from Schrödinger Inc.[23] Stationary points were verified by analytic normal-mode analysis.

To compare the relative activation barriers of all transition states, we need to account for the fact that different transition states are formed from different reagents in the reaction mixture, as depicted in Scheme 2. Assuming that the different forms of the catalysts and reagents are in rapid equilibrium (Curtin−Hammett conditions[24]), we can obtain the relative activation barriers by summation of the energies of the unused reagents on each side of the pseudoequilibrium to the energies of the transition states. We note that when comparing two phenyl transfer processes which only differ in spectator alkyl groups, the comparison is formally isodesmic, which simply means that systematic errors in the calculations can be expected to be similar on both sides of the pseudoequilibrium, and therefore to a large extent to cancel. Any possible influence of dimers of the zinc reagents was excluded on the basis of the results by Pericàs[11d] and therefore neglected in the comparison. We also verified computationally that the reaction energy of forming the mixed zinc reagent PhZnEt from $ZnPh_2$ and $ZnEt_2$ was insignificant also with our current computational methods. The reaction energy is only 0.3 kJ/mol at the B3LYP/LACVP* level, in close accordance with the findings by Pericàs at a similar level of theory.[11d]

Table 1. Relative Energies of the Different Transition States with Acetaldehyde, R^4 = Me

entry	$R^1R^2R^3$	*anti-trans* **P**[a] $\Delta\Delta E^‡$/kJ mol^{-1}	*syn-trans* *ent*-**P**[a] $\Delta\Delta E^‡$/kJ mol^{-1}	*env-trans* *ent*-**P**[a] $\Delta\Delta E^‡$/kJ mol^{-1}	*anti-cis* *ent*-**P**[a] $\Delta\Delta E^‡$/kJ mol^{-1}
1	EtEtEt	50	63	63	55
2	EtEtPh	41	56	55	46
3	EtPhEt	47	57	64	44
4	EtPhPh	40	51	52	43
5	PhEtEt	18	35	32	15
6	PhEtPh	10	28	22	10
7	PhPhEt	9	31	28	11
8	PhPhPh	0	27	19	2

[a] **P** and *ent*-**P** stand for the product and its mirror image, respectively, which are produced from the described TS.

Table 2. Relative Energies of Transition States for Phenyl Transfer to Benzaldehyde, $R^1 = R^4$ = Ph

entry	$R^1R^2R^3$	*anti-trans* **P**[a] $\Delta\Delta E^‡$/kJ mol^{-1}	*syn-trans* *ent*-**P**[a] $\Delta\Delta E^‡$/kJ mol^{-1}	*env-trans* *ent*-**P**[a] $\Delta\Delta E^‡$/kJ mol^{-1}	*anti-cis* *ent*-**P**[a] $\Delta\Delta E^‡$/kJ mol^{-1}
1	PhEtEt	15	31	31	23
2	PhPhEt	10	28	27	15
3	PhEtPh	7	25	22	18
4	PhPhPh	0	28	18	9

[a] **P** and *ent*-**P** stand for the product and its mirror image, respectively, which are produced from the described TS.

Results and Discussion

All relative activation energies obtained with acetaldehyde are shown in Table 1. As we have shown earlier,[12] ethyl transfer is significantly disfavored as compared to phenyl transfer, by 30−40 kJ/mol. This is due to an overlap with the π-system of the transferring phenyl, which significantly lowers the barrier to bending of the C−Zn bond out of the plane of the phenyl group. The effect can clearly be seen in the published crystal structure of $ZnPh_2$.[25]

As expected, the most favored transition state has an *anti-trans* configuration, and, in line with previous studies,[18] we see that for the small, unhindered model aldehyde employed here, the *anti-cis* transition state is very close in energy (within computational uncertainty) for all combinations of alkyl groups. We know that for the ethyl transfer, the *anti-cis* transition state is selectively disfavored for aromatic aldehydes.[18] Thus, for a quantitative selectivity analysis of the phenyl transfer, we need to include reactions with benzaldehyde (R^4=Ph). Note that this is still only a model system. The experimental studies are always performed with substituted benzaldehydes, because phenyl transfer to benzaldehyde leads to an achiral product. The results for the larger model system, limited to phenyl transfer only, are shown in Table 2.

When comparing the results in Table 2 with those of Table 1, we can immediately see that the calculated selectivity has increased, as expected. In the all-phenyl case (entry 4), the *anti-cis* transition state is still the most favorable route to the minor enantiomer. This contrasts the results with ethyl transfer to

(20) Rasmussen, T.; Doelker, N.; Maseras, F.; Norrby, P.-O., manuscript in preparation.
(21) (a) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(22) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 270−283.
(23) See http://www.schrodinger.com.
(24) Maskill, H. *The Physical Basis of Organic Chemistry*; Oxford University Press: Oxford, 1985; pp 293−295.
(25) Markies, P. R.; Schat, G.; Akkerman, O. S.; Bickelhaupt, F. *Organometallics* **1990**, *9*, 2243−2247.

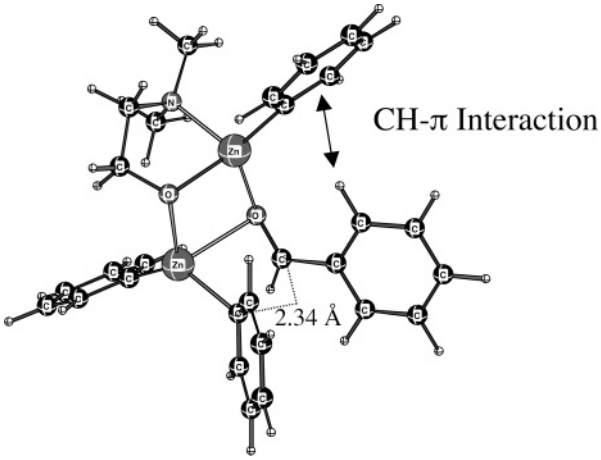


Figure 4. *Anti-cis* transition state with spectator phenyl groups and benzaldehyde as substrate (Table 2, entry 4).

benzaldehyde.[18] Looking in detail at the transition state geometry, we can see that coordination of the *cis* lone pair of benzaldehyde brings the ortho protons in close proximity to the spectator phenyl group on the catalytic zinc atom, leading to a stabilizing CH$-\pi$ interaction (Figure 4; the closest C$-$H$\cdot\cdot$C distance is 2.59 Å). The *anti-cis* transition state is still crowded relative to the *anti-trans* transition state, but not as severely as in the case of ethyl transfer to benzaldehyde.[18] Interestingly, the *syn-trans* path, which is frequently the most significant source of minor enantiomer in ethyl transfer,[18] is always the least important path for any reagent combination in Table 2.

The results in Table 2 do not directly rationalize the effect of added $ZnEt_2$. We can see that any ethyl group in the transition state increases the activation barrier, and we would therefore expect the reaction to proceed via the all-phenyl path (entry 4) as long as there is a reasonable concentration of $ZnPh_2$ in solution. As a rule of thumb, a 10-fold excess of one reagent is needed to compensate an activation energy difference of 6 kJ/mol. The experimental results clearly show a change in the selectivity-determining step upon addition of $ZnEt_2$. The computed preequilibrium (vide supra) indicates that $ZnPh_2$ is always present in a statistical mixture. If the numbers in Table 2 were a true representation of the actual reaction instead of a model system, we would expect the all-phenyl path to dominate even with a 2-fold excess of $ZnEt_2$, and thus the selectivity to be relatively unaffected, in disagreement with experimental results. This could be rationalized by a larger preference for the mixed complex than our calculations would indicate,[11d] so that the ratio EtZnPh/$ZnPh_2$ is substantially larger than 10 in the reaction mixture, but we also wanted to consider the direct influence of the ligand. The higher selectivity obtained with ferrocene **1** as compared to, for example, DBNE indicates that the ligand has an effect beyond blocking one face of the catalytic zinc. A full determination of the transition states in the title reaction employing **1** is currently beyond our computational resources. However, we have been able to calculate the structure of the postulated active catalyst (Figure 5). It is immediately obvious that the catalyst is very crowded, in particular around the alkoxy oxygen, which will coordinate the stoichiometric zinc reagent in the transition state. Thus, it is reasonable to assume that transition states with multiple phenyl groups, which are more sterically demanding than ethyl groups, are selectively disfavored by the ligand.

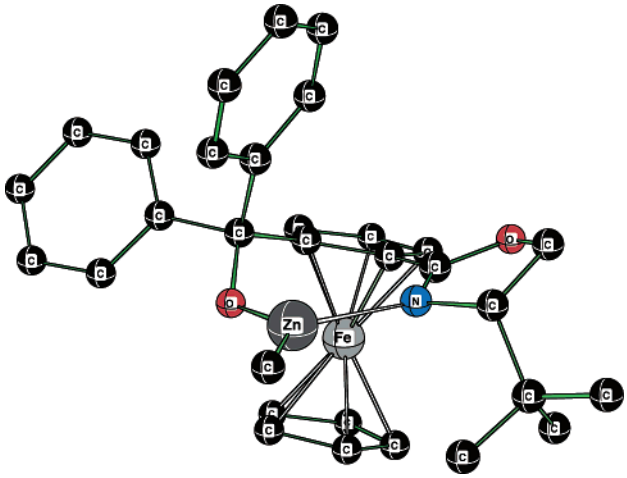
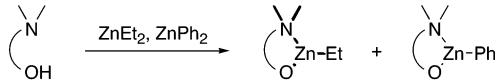


Figure 5. Catalyst obtained from ferrocene **1** + $ZnMe_2$, converged at the B3LYP/LACVP* level.

Scheme 3. Formation of the Active Catalyst



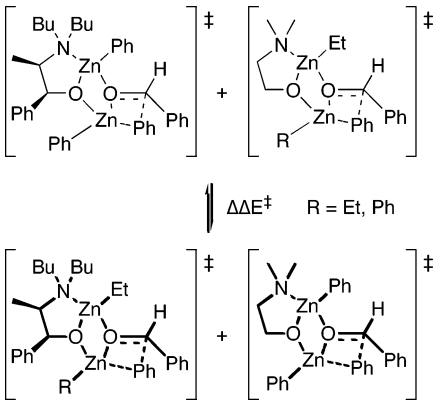
Another way to state this is that the ligand acceleration[26] is limited in the all-phenyl case for steric reasons and becomes more efficient when the steric repulsion between ligand and reagent is reduced by replacement of the bulky phenyl by ethyl groups. In the combined experimental and computational study of a similar system by Pericàs and co-workers, it was shown that the preferentially formed catalyst had an ethyl substituent (Scheme 3),[11d] demonstrating the steric preference of the catalytic system. Thus, the major role of the added $ZnEt_2$ is to enable formation of smaller reagents and catalysts, thus increasing the ability of the catalyst to compete with the background reaction.

As stated, a computational testing of the combined effect of ligand and transition state bulk employing ligand **1** is beyond our computational resources. However, the same type of selectivity increase upon $ZnEt_2$ addition is seen also with the DBNE ligand, which can just barely be included in a computational treatment. Assuming that the selectivities obtained with DBNE (vide supra) in the most extreme case result from a competition between a ligand-free process giving the racemate and a ligand-accelerated, completely selective reaction, we see that with pure $ZnPh_2$ the ratio between the two processes is 38:62, whereas with the mixture the ratio is 10:90, corresponding to an increase in the ligand acceleration ability of about 4 kJ/mol when $ZnEt_2$ is added. This shift could in principle be rationalized by the assumption that both PhZnEt and $ZnPh_2$ are efficient reagents for the ligand-accelerated process, whereas only $ZnPh_2$ can give ligand-free reaction. As indicated by Pericàs, the addition of $ZnEt_2$ significantly reduces the concentration of free $ZnPh_2$ in solution.[11d] However, we desired to test the steric demand of the DBNE ligand as compared to our computational model in two test cases, depicted in Scheme 4 (cf., Scheme 2).

Calculation of the pseudoequilibrium energies depicted in Scheme 4 should in principle show if the bulk of the DBNE

(26) Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059−1070.

Scheme 4. Ligand Exchange Pseudoequilibrium, *Anti-trans* Geometries



ligand has an influence on the rate beyond that captured by our model ligands. Due to the size of the system, it has not been possible to calculate vibrational contributions, which could have an influence if the butyl groups suffer from hindered rotation in the proximity of a phenyl moiety on zinc. Thus, only the potential energies can be compared. We see a very minor effect, 0.5−1 kJ/mol depending on whether one or two phenyl groups is exchanged for ethyl. The effect follows our prediction, but is within the computational uncertainty of our methods. Thus, we cannot say for certain whether DBNE is bulky enough to selectively disfavor the all-phenyl TS. However, the close correspondence with the DBNE-containing structures at least validates the choice of our small computational model.

An additional factor, which cannot be tested with our currently available computational methods, is how much ferrocene **1** is able to directly influence the relative energies of the various paths to the minor enantiomer. For no entry in Table 2 is the major enantiomer (from the *anti-trans* path) favored by more than 9 kJ/mol, corresponding closely to the ca. 90% ee obtained with the DBNE ligand. The higher selectivity obtained with **1** (up to 98% ee) indicates that this ligand is able to block the path to the minor enantiomer selectively. However, computational testing of this proposal will require either QM/MM methods able to handle two separated QM regions, an extended Q2MM force field incorporating parameters for both phenyl transfer and ferrocene moieties,[16] or other equally efficient methods.

Summary

Additions of diaryl zincs to aldehydes show some differences from the related, more thoroughly investigated additions of dialkyl zincs. The reactivity of the aryl reagent is higher, and the inherent selectivity is slightly lower. The latter effect is attributed to a more favorable *anti-cis* process with the aryl reagent, due to a weakly stabilizing CH−π interaction. The increased selectivity upon addition of diethyl zinc is discussed in detail. Spectator ethyl groups in the transition state do not lower the activation barrier of the core transition structure assembly, but instead increase it. Thus, with sterically undemanding substrates and ligands, such as aminoethanol, the pathway with bulkier spectator phenyl groups is dominant. The picture is expected to changed, however, when sterically demanding ligands such as ferrocene **1** are employed. The pathway with less bulkier ethyl groups then may become dominant because pendant group effects control the reaction pathway for steric reasons in this case. With less bulky ligands such as DBNE, it is likely that most of the increased selectivity results from transforming the $ZnPh_2$ reagent into EtZnPh, with less propensity for unassisted addition.

Acknowledgment. Support from the Danish Natural Sciences Research Council and the Carlsberg Foundation is gratefully acknowledged. C.B. and J.R. are grateful to the Fonds der Chemischen Industrie and to the Deutsche Forschungsgemeinschaft (DFG) within the Collaborative Research Center (SFB) 380 and the Graduiertenkolleg 440 for financial support. We also want to thank Torben Rasmussen for many helpful discussions.

Supporting Information Available: All calculated structures (*xyz* coordinates) and all calculated energies. This material is available free of charge via the Internet at http://pubs.acs.org.

JA046254S