ORGANIC LETTERS

2006
Vol. 8, No. 18
3895−3898

Ligand Anatomy: Probing Remote Substituent Effects in Asymmetric Catalysis through NMR and Kinetic Analysis

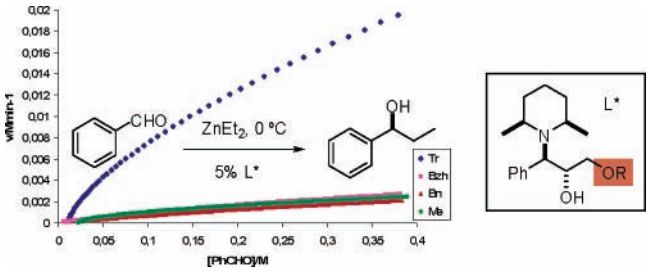
Ciril Jimeno,[†] Anton Vidal-Ferran,[‡] and Miquel A. Pericàs*[,§]

Institute of Chemical Research of Catalonia (ICIQ), Av. Països Catalans, 16, 43007 Tarragona, Spain, Departament de Química Orgànica, Universitat de Barcelona (UB), 08028 Barcelona, Spain, and ICREA

mapericas@iciq.es

Received May 18, 2006

ABSTRACT



A series of structurally related *β*-amino alcohols only differing in the steric bulk of a remote alkoxy group exhibit striking differences in kinetic behavior when used as ligands in the asymmetric diethylzinc addition to benzaldehyde (R = Trityl, much more active). A combination of NMR titration studies and kinetic analysis allows the quantitative decomposition of the remote substituent effect into a lower dimerization constant of the active species and a much faster ethyl addition step.

Modular ligands, when properly constructed, allow for the fine-tuning of catalytic properties through the independent optimization of molecular fragments. While peptides and peptide-like structures are paradigmatic examples in this approach,[1] we have shown that simple amino alcohols formed through nucleophilic ring-opening plus protection sequences from synthetic, yet enantiomerically pure epoxides, can be modularly optimized as ligands for a variety of catalytic enantioselective chemistries.[2]

The asymmetric addition of diorganylzincs to aldehydes is a well-established laboratory for the testing and optimization of new amino alcohol ligands.[3,4] The mechanism of the reaction has been studied in detail, both from the experimental and the theoretical points of view,[5] and, in addition

[†] ICIQ.
[‡] ICIQ and ICREA.
[§] ICIQ and UB.

(1) For recent examples, see: (a) Agarkov, A.; Greenfield, S.; Xie, D.; Pawlick, R.; Starkey, G.; Gilbertson, S. R. *Biopolymers* **2006**, *84*, 48. (b) Vaestilae, P.; Wettergren, J.; Adolfsson, H. *Chem. Commun.* **2005**, 4039. (c) Christensen, C. A.; Meldal, M. *Chem. Eur. J.* **2005**, *11*, 4121. (d) Murphy, K. E.; Hoveyda, A. H. *Org. Lett.* **2005**, *7*, 1255.

(2) (a) Imine alkylation: Jimeno, C.; Readdy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Org. Lett.* **2000**, 2, 3157. (b) Transfer hydrogenation: Pastó, M.; Riera, A.; Pericàs, M. A. *Eur. J. Org. Chem.* **2002**, 2337−2341. (c) Allylic alkylation: Pericàs, M. A.; Puigjaner, C.; Riera, A.; Vidal-Ferran, A.; Gómez, M.; Jiménez, F.; Muller, G.; Rocamora, M. *Chem. Eur. J.* **2002**, *8*, 4164. (d) Arylation of aldehydes: Fontes, M.; Verdaguer, X.; Solà, L.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **2004**, *69*, 2532.

(3) Soai, K.; Shibata, T. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. II.

(4) Fache, F.; Schulz, E.; Tommasino, M. L.; Lemaire, M. *Chem. Rev.* **2000**, *100*, 2159−2231.

(5) (a) Kitamura, M.; Okada, S.; Suga, S.; Noyori, R. *J. Am. Chem. Soc.* **1989**, *111*, 4028. (b) Kitamura, M.; Oka, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 3505. (c) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327. (d) Yamakawa, M.; Noyori, R. *Organometallics* **1999**, *18*, 128. (e) Vázquez, J.; Pericàs, M. A.; Maseras, F.; Lledós, A. *J. Org. Chem.* **2000**, *65*, 7303.

10.1021/ol0612197 CCC: $33.50
Published on Web 08/08/2006

to its synthetic value, interesting kinetic phenomena such as nonlinear effects[6] and autocatalysis[7] have been disclosed for this process.

Since the early mechanistic proposals,[5a,8] it was clear that catalyst dimerization played a fundamental role in the asymmetric amplification effects, but it was not until recently that product inhibition was established as an equally important equilibrium to be taken into account for an accurate description of the operation of the catalytic system throughout the whole reaction period.[9]

According to the accepted mechanism for these reactions, a modular amino alcohol like **1** would lead, in the presence of diethylzinc, to the catalytically active species **2**, from which the transition state **3** would be built through coordination of the reacting species onto the adjacent Lewis acid and Lewis base sites (Figure 1).

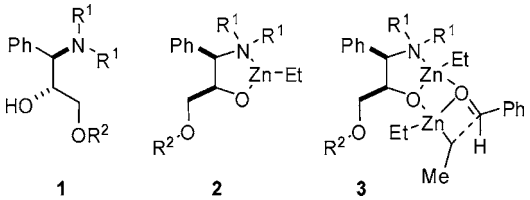
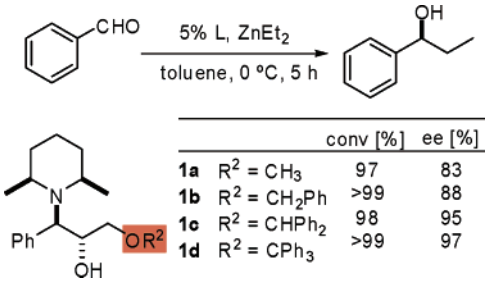


Figure 1. Ligand (**1**), active species (**2**), and transition state (**3**) in the addition of diethylzinc to benzaldehyde.

We have introduced amino alcohols **1** as highly efficient ligands for this chemistry. Extensive empirical and computational studies have led to the optimization of the NR^1_2 fragment as a *cis*-2,6-dimethylpiperidino substituent. On the other hand, it has been observed that bulky R^2 groups lead to ligands that are both more active and more enantioselective. [10]

While the mechanism by which the *cis*-2,6-dimethylpiperidino moiety controls enantioselectivity appears to be that of increasing the energy gap between *pro-S* and *pro-R* TS's,[10b] the origin of the effect by the remote R^2 group is less evident. Given the fundamental importance of TON in catalytic systems for practical application, we decided to undertake a systematic kinetic study of the effects of the remote substituent R^2 in a family of ligands **1a**−**d**, containing the optimal *cis*-2,6-dimethylpiperidino fragment (see the Supporting Information),[10] using the diethylzinc addition to benzaldehyde as a benchmark reaction (Scheme 1). Although

Scheme 1. Diethylzinc Addition to Benzaldehyde Using Ligands **1a**−**d**[a]



		conv [%]	ee [%]
1a	$R^2 = CH_3$	97	83
1b	$R^2 = CH_2Ph$	>99	88
1c	$R^2 = CHPh_2$	98	95
1d	$R^2 = CPh_3$	>99	97

[a] Conversion and ee were determined by GC using a chiral β-DEX capillary column.

remote steric effects in asymmetric catalysts have been known for years,[11] no systematic studies have been devoted to this topic.

When the final results of the reactions in Scheme 1 are analyzed, the only apparent difference between ligands **1a**−**d** lies on the increase in enantioselectivity throughout the series with the steric bulk of R^2. However, the situation is quite different with regard to reaction rate, since the process promoted by **1d** ($R^2 = CPh_3$) was completed in ca. 50 min, in sharp contrast with those promoted by **1a**−**c** that required the whole 5 h period.

To gain a quantitative insight on this behavior, the reactions promoted by **1a**−**d** were continuously monitored by FTIR, using an immersion ATR diamond probe to determine conversion vs time. The disappearance of the benzaldehyde carbonyl band (1710 cm^{-1}) was monitored for this purpose. It is to be noted that this sensitive technique affords large amounts of high quality data (a spectra every few seconds) that can be then submitted to mathematical analysis.

The results of this monitoring clearly confirmed that the decrease with time of benzaldehyde concentration is much faster for **1d** than for **1a**−**c** (see the Supporting Information). This effect is even more evident if the reaction progress kinetic analysis introduced by Blackmond is applied[12] and a rate vs [PhCHO] plot is constructed from the experimental data (Figure 2). Clearly, the reaction is much faster at every moment when $R^2 = CPh_3$. The other three catalysts, in turn, exhibit essentially identical kinetic behavior regardless of the bulk of the O-protecting group.

(6) (a) Oguni, N.; Matsuda, Y.; Kaneko, T. *J. Am. Chem. Soc.* **1988**, *110*, 7877. (b) Kitamura, M.; Suga, S.; Niwa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 4832. (c) Bolm, C.; Felder, M.; Müller, J. *Chem. Ber.* **1992**, *125*, 1205. (d) Reddy, K. S.; Solà, L.; Moyano, A.; Pericàs, M. A.; Riera, A. *Synthesis* **2000**, 165. (e) Chen, Y. K.; Costa, A. M.; Walsh, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 5378.

(7) (a) Shibata, T.; Yonekubo, S.; Soai, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 659. (b) Sato, I.; Urabe, H.; Ishiguro, S.; Shibata, T.; Soai, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 315. (c) Kawasaki, T.; Jo, K.; Iragashi, H.; Sato, I.; Nagano, M.; Koshima, H.; Soai, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 2774. (d) Kawasaki, T.; Sato, M.; Ishiguro, S.; Saito, T.; Morishita, Y.; Sato, I.; Nishimo, H.; Inoue, Y.; Soai, K. *J. Am. Chem. Soc.* **2005**, *127*, 3274. (e) Lutz, F.; Igarashi, T.; Kawasaki, T.; Soai, K. *J. Am. Chem. Soc.* **2005**, *127*, 12206.

(8) Kitamura, M.; Oka, H.; Noyori, R. *Tetrahedron* **1999**, *55*, 3605.

(9) Rosner, T.; Sears, P. J.; Nugent, W. A.; Blackmond, D. G. *Org. Lett.* **2000**, *2*, 2511.

(10) (a) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970. (b) Vidal-Ferran, A.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1997**, *38*, 8773.

(11) Representative examples: (a) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938. (b) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492. (c) Yang, D.; Yip, Y.-C.; Chen, J.; Cheung, K.-K. *J. Am. Chem. Soc.* **1998**, *120*, 7659. (d) Lau, S. Y. W.; Keay, B. A. *Synlett* **1999**, 605. (e) Moore, D.; Huang, W.-S.; Xu, M.-H.; Pu, L. *Tetrahedron Lett.* **2002**, *43*, 8831. (f) Zhang, Y.; O'Doherty, G. A. *Tetrahedron* **2005**, *61*, 6337.

(12) Blackmond, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4302.

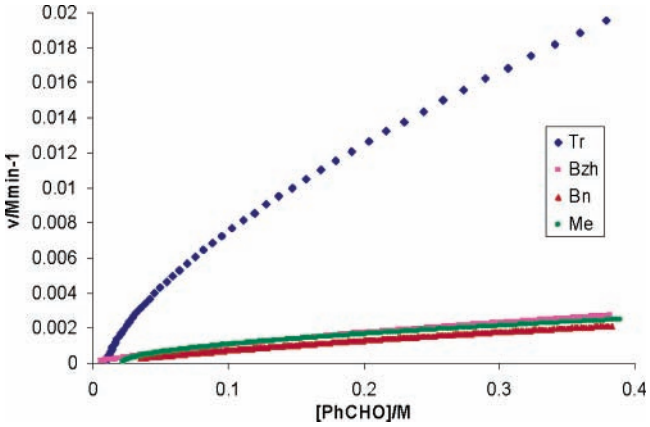
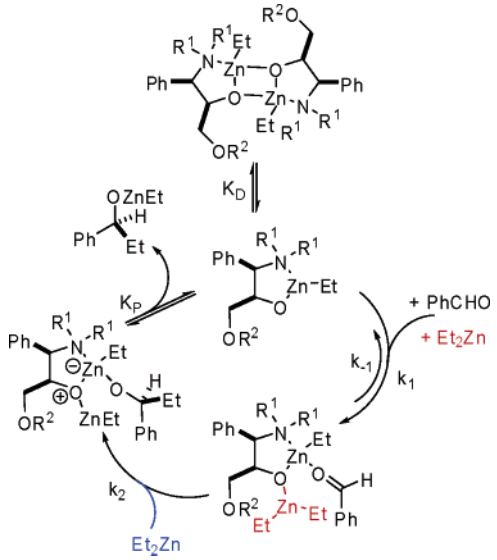


Figure 2. Rate vs [PhCHO] plots for the diethylzinc addition to benzaldehyde catalyzed by 5 mol % of **1a** (green), **1b** (red), **1c** (pink), and **1d** (blue). Reaction progress is from right to left.

To investigate the exact role played by the remote R^2 substituent, the kinetic model derived from the mechanism shown in Scheme 2 was considered. This mechanism takes into account all the important events associated to the catalytic cycle, such as dimerization of the active species (K_D) and product inhibition (K_P).[9] Within this scheme, the protecting group R^2 could act on the reaction rate at two different levels: (i) by affecting the value of K_D, since smaller values of the dimerization constant represent higher concentrations of active species and, hence, higher number of active catalytic cycles for a given amount of added ligand, and (ii) by affecting the rate constant of the addition step (k_2).

Scheme 2. Considered Mechanism for the Catalytic Addition of Et_2Zn to PhCHO (Et_2Zn in Red)[a]



[a] A modified version (Et_2Zn in blue) includes the indication from kinetic analysis that Et_2Zn is not involved in a preequilibrium (see below).

Fortunately, the value of the dimerization constant K_D can be determined independently by NMR, and this can provide a clue on the relative weight of the two considered factors. Therefore, the dimerization constants of the chelated ethylzinc aminoalkoxide intermediates **2a** and **2d**, which represent extreme situations in terms of steric bulk of R^2, were determined experimentally by ^1H NMR through the titration of ligands **1a** and **1d** with diethylzinc (Figure 3).

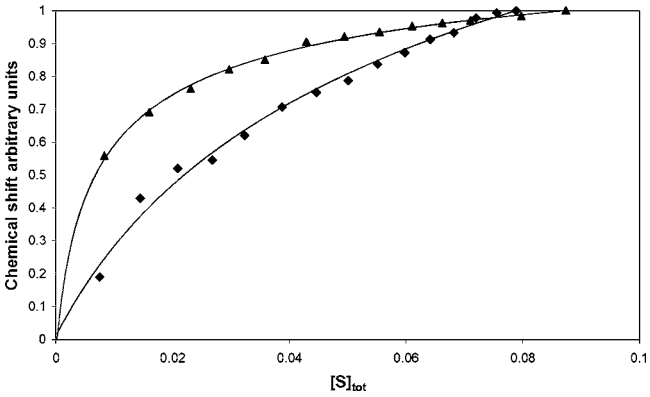


Figure 3. NMR titration curves of ligands **1d** (◆) and **1a** (▲) with $ZnEt_2$, and fitted curves (lines) for dimerization processes with constants, $K_D = 6\ M^{-1}$ for **1d**, and $66\ M^{-1}$ for ligand **1a**.

The recorded variations in chemical shift for key protons on the amino alcohol skeleton were fitted to a mathematical model for dimerization by the use of an iterative least-squares approach (see the Supporting Information). In this manner, dimerization constants (K_D) of $66\ M^{-1}$ for **2a** and $6\ M^{-1}$ for **2d** could be determined. Thus, the titration experiments clearly show that dimerization of the active species **2** is importantly controlled by the bulk of R^2.

Since saturation effects were observed in the kinetic experiments for PhCHO, but not for Et_2Zn, a simplified kinetic model was initially considered (see the Supporting Information).[12,13] In this model, described by eq 1, PhCHO (but not Et_2Zn) is involved in a preequilibrium with the active species:

$$\text{rate} = \frac{(k_1/k_{-1})k_2[\text{cat.}][\text{PhCHO}][\text{ZnEt}_2]}{1 + (k_1/k_{-1})[\text{PhCHO}]} \qquad (1)$$

Next, kinetic data for **1a**−**d** were fitted with Specfit[14] to the kinetic model describing the modified mechanism in Scheme 2 (Et_2Zn in blue). The concentration of Et_2Zn at every moment was calculated from its initial value and the instant concentration of PhCHO, and the evolution with time of the concentrations of both species was independently but simultaneously fitted. Moreover, at least two experiments with different initial concentrations were used for each ligand,

(13) Mathew, S. P.; Gunathilagan, S.; Roberts, S. M.; Blackmond, D. G. *Org. Lett.* **2005**, *7*, 4847.
(14) Specfit/32. Spectrum Software Associates, 1993−2004.

and the resulting constants averaged. It was assumed that catalyst dimerization and benzaldehyde binding to the catalyst were fast equilibria in comparison with that involved in product inhibition. Data for K_D arising from the NMR titration studies, and for k_1/k_{-1} and k_2 arising from the simplified kinetic model were used as starting values. The converged values for K_D, K_P, k_1/k_{-1}, and k_2 are summarized in Table 1 with their standard deviations.[15]

Table 1. Average Values of the Equilibrium and Kinetic Constants Fitted for the Modified Mechanism in Scheme 2

ligand	K_D (M^{-1})	k_1/k_{-1} (M^{-1})	K_P (M^{-1})	k_2 (M^{-1} min^{-1})
1a	60.0 ± 0.1	6.0 ± 0.6	8.0 ± 0.5	0.74 ± 0.08
1b	21.9 ± 1.9	6.0 ± 0.1	7.0 ± 0.9	0.30 ± 0.02
1c	19.5 ± 0.5	6.0 ± 0.1	6.0 ± 0.1	0.34 ± 0.09
1d	6.0 ± 0.1	6.0 ± 0.1	6.3 ± 0.3	2.8 ± 0.6

An initial analysis of these data shows that both the dimerization of the active species (K_D) and the addition step (k_2) are affected by the nature of R^2, while both the association/dissociation of benzaldehyde to/from the active species (k_1/k_{-1}) and inhibition by the reaction product (K_P) recorded in the reactions appear to be rather independent from the considered structural parameter in ligands **1a**−**d**.[16] Since both last processes mostly involve the participation of the Lewis acid site in the active species (the zinc atom) and occur in a very similar environment, far away from the R^2 group,[17] the results of the kinetic analysis fully agree with chemical intuition.

The equilibrium constants for the catalyst dimerization arising from kinetic analysis are in excellent agreement with the experimental values determined by NMR titration. Interestingly, K_D for ligands **1b** and **1c** is very similar, and has an intermediate value with respect to those for **1a** and **1d**. This is strongly indicative of a similar effective volume of the benzyl and benzhydryl groups, likely related to their ability to generate interaction-free conformers by simple rotation. This is no longer possible with the 3-fold symmetrical trityl group. Thus, the unavoidably congested, inactive dimer is destabilized for **1d** with respect to the active monomer.[18]

As for the rate-determining addition step, the converged values for k_2 indicate a similar trend: It is substantially faster with **1d**, and shows very similar values for **1b** and **1c**. Earlier observations and theoretical studies from our laboratories suggest again that this behavior is related to the ability of alkoxy groups bearing at least a hydrogen atom α to oxygen to avoid unfavorable steric interactions by simple rotation around the $O-C_\alpha$ bond.[15]

In summary, a combination of NMR and kinetic analysis of the effect on reaction rate exerted by a remote substituent has allowed the in depth interpretation of the strikingly different behavior of almost identical ligands. If the two limits of the studied series, **1a** and **1d**, are compared, the corresponding values for the dimerization constant (K_D) indicate that, for a similar amount of ligand added to a reaction mixture, the effective concentration of active species is 2.85 times higher for **1d** than for **1a**. In parallel to that, the differences between the rate constants for the addition step (k_2) provoke that with **1d** the catalytic cycles work ca. 3.8 times faster than with **1a**.

The combined effect of these two factors is that reactions mediated by **1d** are 1 order of magnitude faster than those mediated by **1a**−**c**.

For ligand design, the important lesson is that attention should not be exclusively paid to rate enhancement arising from energy barrier lowering, since the increase in the concentration of active species can be an equally important mechanism for ligand accelerated catalysis.[19] Apparently innocent, remote substituents can play an important role in controlling both factors.

Acknowledgment. We thank DGI-MCYT (Grant No. CTQ2005-02193/BQU), DURSI (Grant No. 2005SGR225), Consolider Ingenio 2010 (CSD2006-0003), and ICIQ Foundation for financial support. C.J. is a Torres Quevedo researcher. We thank Prof. P. Ballester (ICIQ) for help with the Specfit analysis.

Supporting Information Available: Experimental procedures and characterization of **1a**−**c**. Plots of concentration vs time and product inhibition. Measurement of dimerization constants by NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0612197

(15) Standard deviation in the fitting of k_2 and K_P with Specfit for **1a**−**d** is given in the Supporting Information.

(16) It is important to recall, however, that k_1/k_{-1} and K_P are highly dependent on one another and difficult to separate unless a wide range of concentration is considered. We thank an anonymous reviewer for bringing this point to our attention.

(17) K_P and (k_1/k_{-1}) are likely related to the thermodinamics of Zn−O bond formation/cleavage. For the dependence of NLE in the same reaction with electron-donating or -withdrawing groups at the aldehyde that modify the involved equilibria, see ref 6e and: Buono, F.; Walsh, P. J.; Blackmond, D. G. *J. Am. Chem. Soc.* **2002**, *124*, 13652.

(18) Jimeno, C.; Pastó, M.; Riera, A.; Pericàs, M. A. *J. Org. Chem.* **2003**, *68*, 3130.

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