ORGANIC LETTERS

2000
Vol. 2, No. 16
2511−2513

Kinetic Investigations of Product Inhibition in the Amino Alcohol-Catalyzed Asymmetric Alkylation of Benzaldehyde with Diethylzinc

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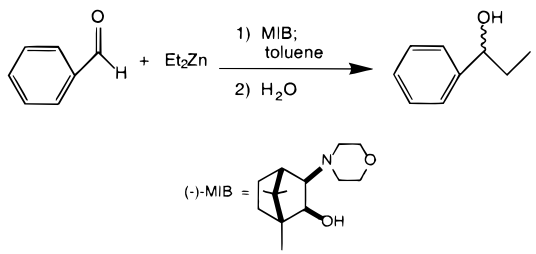
Received June 9, 2000

ABSTRACT



In situ reaction rate measurements help to define the role of product inhibition in the asymmetric alkylation of benzaldehyde with diethylzinc using (–)-MIB as a chiral reagent. Reaction calorimetry and kinetic modeling demonstrated that the rate behavior over consecutive reactions may only be rationalized when reversible binding of the product alkoxide is taken into consideration. These results may have implications for the conversion dependence of product enantioselctivity in reactions using enantioimpure catalysts.

The enantioselective addition of organozinc reagents to aldehydes using chiral amino alcohols has received wide attention as a model system for exploring asymmetric C−C bond formation.[1] Extensive mechanistic studies by Noyori and co-workers utilizing DAIB **1** as the amino alcohol ligand[2] have led to a good understanding of this complex reaction. They have shown that the reaction proceeds via in situ formation of a monomeric zinc aminoalkoxide catalyst species which exists in equilibrium with a noncatalytically active dimer (Scheme 1). Their mechanistic model also demonstrates how the active catalyst concentration may be affected by a subtle interplay of reaction parameters.

One of the most striking features of this reaction is the strong asymmetric amplification in product enantioselectivity that is observed when enantioimpure chiral amino alcohols are employed in the reaction.[3] Because of the complex reaction network and the dimer/monomer catalyst equilibrium, nonlinear effects in this system are more complicated than those predicted in the ML_2 model introduced by Kagan and co-workers[4] for systems in which the active catalyst is itself a dimeric species.

Noyori and co-workers showed that computer simulations of the overall profile of this nonlinear effect were in

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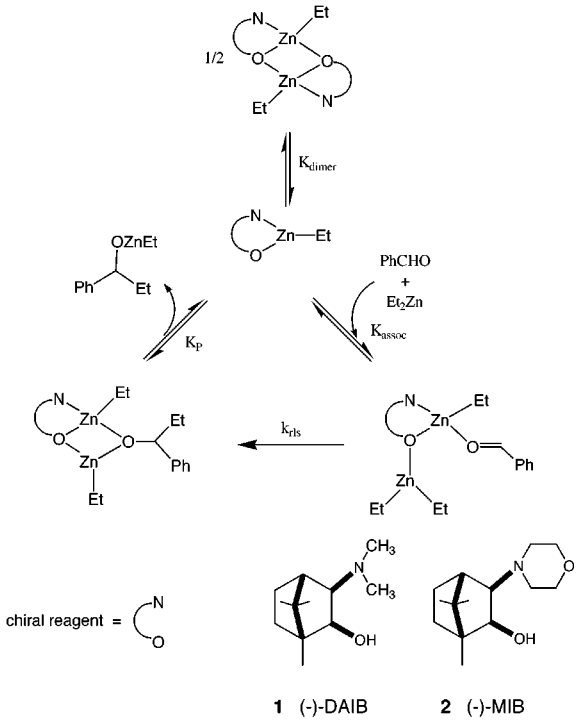
10.1021/ol006181r CCC: $19.00
Published on Web 07/06/2000

Scheme 1. Reaction Network



agreement with experimental trends.[2c] Quantitative validation of the kinetic model is hindered, however, by the difficulty in obtaining extensive and quantitative experimental kinetic data covering a wide range of substrate concentrations. For example, a discrepancy between the predicted and observed influence of conversion on product enantioselectivity was attributed to product inhibition, but this could not be confirmed experimentally.

We report here in situ experimental kinetic studies of the addition of diethylzinc to benzaldehyde using **2**, (2*S*)-(−)-3-*exo*-(*N*-morpholino)isoborneol, (−)-MIB, which was recently shown by Nugent[5] to be a practical and efficient chiral amino alcohol for the alkylation of aldehydes. We show that the combination of detailed and accurate experimental reaction rate measurement and kinetic modeling can successfully account for the effects of the presence of the product in reactions using enantiopure catalysts. In particular, a "one-pot" monitoring of consecutive reactions allows us to decouple product inhibition from the primary reaction kinetics. These results may lead to a quantification of the influence of the product alkoxide in the asymmetric amplification observed when the reaction is carried out using enantioimpure chiral reagents. The importance of reaction rate measurements in conjunction with enantioselectivity in the use of nonlinear effects as a mechanistic tool was recently highlighted by Blackmond.[6]

Reaction rate data for this study were obtained by monitoring of the heat flow resulting from formation of the alkoxide product as a function of time, which provides a sensitive and accurate measure of reaction progress. The reaction was carried out in an Omnical CRC90 reaction calorimeter by injecting an aliquot of neat benzaldehyde (yielding 0.05−0.07 M solution) into a 2 mL mixture of 1 M diethylzinc in toluene containing a catalytic amount of (−)-MIB at 25 °C. Catalyst amounts ranging from 15 to 30 μmol were employed. Heat flow data may be acquired at the rate of 1 datum point/6 s, providing the equivalent of 300 separate initial rate measurements at different substrate concentrations in a half-hour experiment. The reaction heat flow also allows determination of the molar heat of reaction, ΔH_{rxn}, from the area under the heat flow curve divided by the number of moles of substrate reacted. This was found to be 44 ± 4 kcal/mol. Conversion of substrate may be obtained from the partial heat flow at any point during the reaction. Comparison of conversion obtained in this way with that obtained from GC analysis of samples extracted from the mixture verified that the calorimetric measurement provided a valid measure of the rate of formation of the alkoxide product. Benzyl alcohol was the only side product and was observed in low concentrations (<1% of product). Enantioselectivity was found to be 96−98% for all reactions.[7]

The reaction heat flow rose rapidly to a maximum with injection of benzaldehyde and then decreased smoothly with time as the reaction proceeded to completion. The decreasing rate as a function of time is attributed to the positive order kinetics in both substrates but also to the presence of a catalyst-bound product which builds up over the course of the reaction and effectively removes active species from the catalytic cycle.

When diethylzinc is used in excess, further reactions may be monitored in the same reaction vial by injecting additional aliquots of benzaldehyde. Each subsequent reaction is thus carried out with increasing amounts of catalyst-bound product present in the mixture. A four-part reaction of this type is shown in Figure 1. By comparing the heat flow profiles from the reaction of the first and subsequent aliquots of benz-

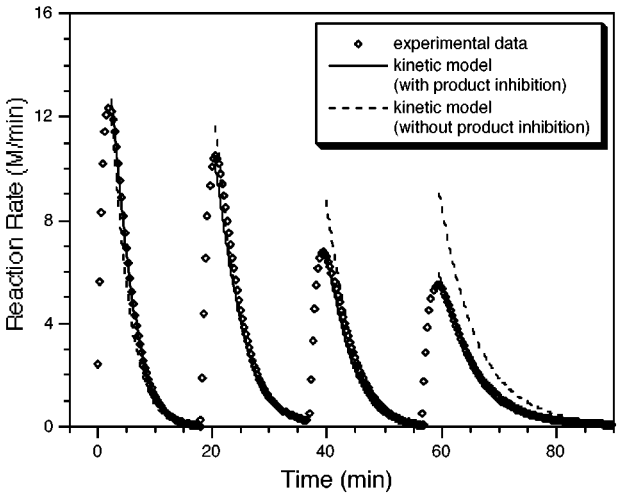


Figure 1. Reaction rate (from heat flow) as a function of time for a four-part reaction in which subsequent aliquots of benzaldehyde were injected into a reaction vial containing an excess of diethylzinc (0.05−0.07 M benzaldehyde injected into ca. 1 M diethylzinc in toluene, 0.014 M (−)-MIB).

aldehyde, we are able to observe the influence of a known amount of product in the reaction mixture.

To quantify the influence of the presence of product on the reaction rate, we employed a kinetic model derived from the mechanism shown in Scheme 1, based on that proposed by Noyori. We have modified this model to allow for the possibility that the product may not readily dissociate, thus inhibiting further reaction by occupying catalytic sites. The modified reaction rate expression is presented in eq 1. The

$$rate = \frac{2k_{rls}K_{assoc}[PhCHO][Et_2Zn][MIB]}{\left(1+K_{assoc}[PhCHO][Et_2Zn]+K_P[P]\right)+\sqrt{\left(1+K_{assoc}[PhCHO][Et_2Zn]+K_P[P]\right)^2+8K_{dimer}[MIB]}}$$

influence of product is accounted for in the term K_p[P] in the denominator, where K_p represents the product binding constant and [P] is the product concentration at any time during the reaction. This term approaches zero ($K_p = 0$) if product inhibition is considered to be negligible.

Table 1 presents the values of the kinetic and equilibrium constants determined by fitting the four-reaction sequence

Table 1. Kinetic and Thermodynamic Parameters Determined from Kinetic Modeling of the Data Shown in Figure 1 for the Reaction Network Shown in Scheme 1

constant	without product inhibition	with product inhibition
k_{rls} (min^{-1})	2820	1380
K_{assoc} (M^{-2})	45.4	116
K_P (M^{-1})		36.9
K_{dimer} (M^{-2})	978	344

to eq 1. The model fits are shown in Figure 1, with the solid line representing the model including product inhibition and the dashed line representing the best fit which could be obtained without including the influence of product in the model ($K_P = 0$). It is clear that the rate is indeed inhibited as product builds up in the system; after ca. 10 turnovers, the kinetic model can no longer provide an accurate description of the reaction rate unless binding of the product to the catalyst is taken into consideration.

The magnitudes of the equilibrium constants determined by the two models are also of interest. When the influence of product is not included (K_p set equal to zero), the model attempts to compensate by predicting a smaller value of K_{assoc}. Further, the dimer−monomer equilibrium is predicted to be driven further toward the dimer species (larger value for the dimerization constant K_{dimer}) in the absence of product inhibition. The dimer−monomer equilibrium position has important implications for the asymmetric amplification observed when enantioimpure catalysts are employed, and an inaccurate value of K_{dimer} could lead to an incorrect prediction of the equilibrium position for the heterochiral dimer which is formed under enantioimpure conditions. Thus, a failure to take the role of product into consideration may lead to erroneous conclusions about the relative concentrations of catalytic species in the reaction mixture.

In most cases one seeks to avoid complications due to the influence of product by carrying out experimental kinetic studies under initial reaction conditions. However, study of the initial reaction period neglects valuable fundamental information about the reaction which may be important in practical applications where the reaction cannot be limited to initial conditions. The monitoring of catalyst behavior over the entire course of the reaction helps to broaden our understanding of complex reaction networks. Coupled with kinetic modeling, the multiple reaction experimental protocol described in this paper provides a useful approach to complicating issues such as product inhibition. The ability to predict rate and selectivity as a function of reaction progress greatly expands the synthetic utility of complex reactions.

Acknowledgment. D.G.B. gratefully acknowledges a grant from Pfizer Central Research supporting this research and a grant from the EPSRC for purchase of the reaction calorimetry system.

OL006181R

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