

How Catalysts Control Substrate Structure

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The stereochemistry of substrate-catalyst-complexes in reaction mixtures is resolved by polarization-dependent 2D-IR spectroscopy and DFT computations, shedding light on the controversial reaction mechanism of an important textbook example of enantioselective synthesis. The influence of thermal fluctuations on 2D-IR structure determination is assessed by temperature-dependent measurements and *ab initio* MD simulations.

In enantioselective synthesis the spatial arrangement of reaction partners is crucial for obtaining a desired product. Typically catalysts and auxiliaries are used to control molecular conformation and accessibility of the reactive moiety and in this way steer the stereochemistry of a reaction. Frequently, various species of substrate and substrate-catalyst complexes coexist and interconvert rapidly. Polarized 2D-IR spectroscopy can identify the structures of transient species formed in such reaction mixtures, providing important information for the development and optimization of new catalytic reactions.

The enantioselective Diels-Alder reaction employing the chiral Evans auxiliary and a diethylaluminum catalyst (DEA) is an important textbook example of enantioselective synthesis. Various widely used reactions are thought to follow the same mechanism of stereocontrol. The mechanism, however, remained controversial. Already in Evans' seminal paper introducing the reaction, he proposed a mechanism involving a charged metal chelate that locks the conformation of the substrate (Fig. 1, left).[1] More recently, an open complex has been proposed instead (Fig. 1, right) as the relevant species for stereocontrol.[2] Spectroscopic evidence for either of the two, however, has been lacking. Polarization dependent 2D-IR spectroscopy unequivocally identifies the coordination and conformation in the catalyst-substrate complexes with DEA and other, related catalysts, even in the presence of rapid chemical exchange. Temperature dependent measurements in the range from $-70\text{ }^{\circ}\text{C}$ to $20\text{ }^{\circ}\text{C}$ in combination with *ab initio* molecular dynamics simulations assess the influence of thermal fluctuations on 2D-IR structure determination.

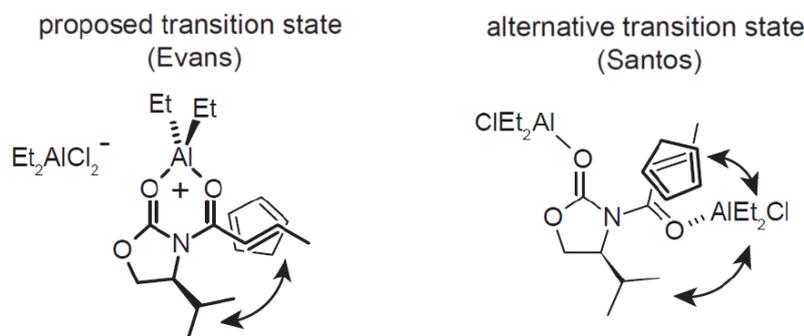


Fig. 1 Left: Charged chelate transition state as proposed by Evans and coworkers.[1] Right: Transition structure involving an open, neutral complex as proposed by Santos and coworkers.[2]

[1] D. A. Evans, K. T. Chapman, J. Bisaha, *J. Am. Chem. Soc.* **110**, 1238 (1988)

[2] S. M. Bakalova, F. J. S. Duarte, M. K. Georgieva, E. J. Cabrita, A. G. Santos, *Chem. Eur. J.* **15**, 7665 (2009)