

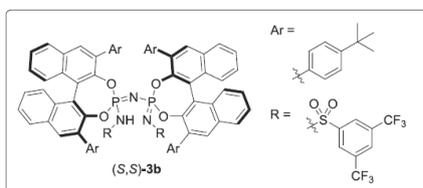
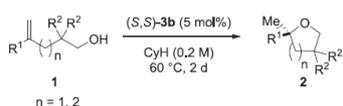
## Structure and Dynamics of a Stereoselective Brønsted Acid Catalyst using RDC, NOE Distances and Chemical Shifts as MD Constraints

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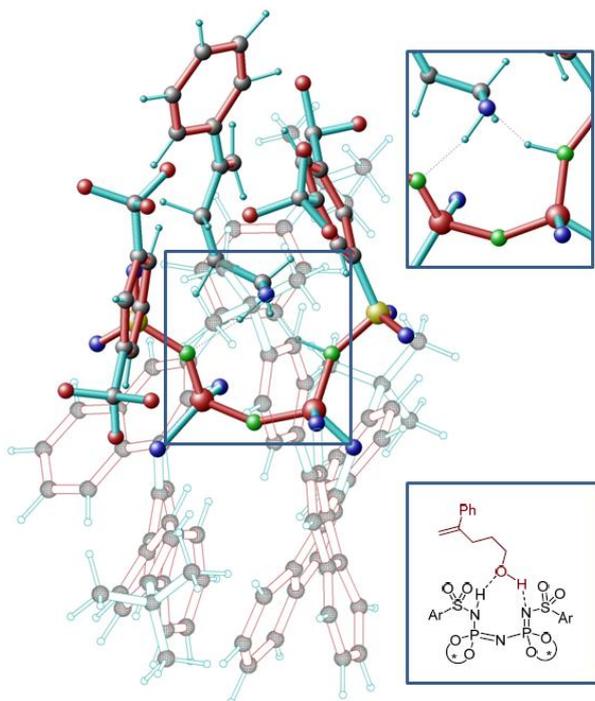
The catalyst consists of two S-BINOL groups that are connected by the IDPi motif formed by a  $-\text{SO}_2-\text{N}=\text{PO}_2-\text{N}=\text{PO}_2-\text{NH}-\text{SO}_2-$  group. This compound activates olefins in reactions to chiral products with high stereo selectivity<sup>1</sup>.



We performed MD simulations that were driven by 12 <sup>13</sup>C-<sup>19</sup>F and 88 <sup>13</sup>C-<sup>1</sup>H RDC (MDOC simulations<sup>2</sup>) and during which 235 NOE

distance constraints had to be fulfilled. Orientational pseudo-forces that are calculated from tensorial RDC constraints lead to a tumbling of the molecule and to reorientations of all side chains. Finally, the 20ns trajectory fulfilled all NMR constraints within the experimental error bounds.

It turned out that the rotations around central N-P-N-P bonds are possible with maxima at about 150° but these two dihedrals are closely correlated. The chiral character of the two S-BINOL groups leads to an asymmetry in the surrounding of the central P-N-P system. The dihedral distributions of the right and left part of the molecule become clearly different.



2000 MD snapshots were geometry-optimized using experimental <sup>13</sup>C chemical shifts as constraints. The chemical shifts and their gradients with respect to the Cartesian coordinates of the atoms were calculated at every step of the geometry optimization to define CS pseudo-forces. The <sup>13</sup>C CS values are calculated using the Bond Polarization Theory (BPT)<sup>3</sup>. The optimizations caused only minor changes of the dihedral angles of the molecular models so that the trajectory is nearly completely preserved. The conformer that fits best to the <sup>13</sup>C chemical shifts (RMSD of ~1ppm) was selected. This structure is optimal for docking the substrate in a model called intermediate I (left Figure). This structure could be considered as the starting point of the reaction and in contrast to former models<sup>1</sup>, this catalyst-substrate complex has a much lower symmetry.

<sup>1</sup> N. Tsuji, J. L. Kennemur, T. Buyck, S. Lee, S. Prévost, P. S. J. Kaib, D. Bykov, C. Farès, B. List, *Science* 2018, **359**, 1501–1505.

<sup>2</sup> U. Sternberg, R. Witter, A. S. Ulrich, *J. Biomol. NMR* 2007, **38**, 23.

<sup>3</sup> I. Jakovkin M. Klipfel, C. Muhle-Goll, A. S. Ulrich, B. Luy and U. Sternberg; Rapid calculation of protein chemical shifts using bond polarization theory and its application to protein structure refinement; *Phys. Chem. Chem. Phys.* 2012, **14**, 12263-12276.