Chiral Ion-Pairs: Dissociation, Dynamics and Asymmetric Catalysis

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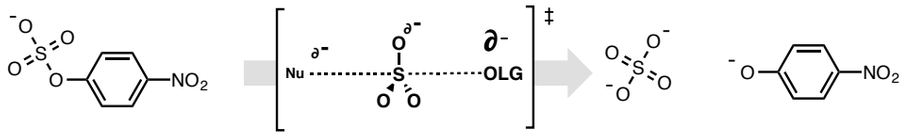
School of Chemistry, University of Edinburgh

11th ScotCHEM, 16th June 2017

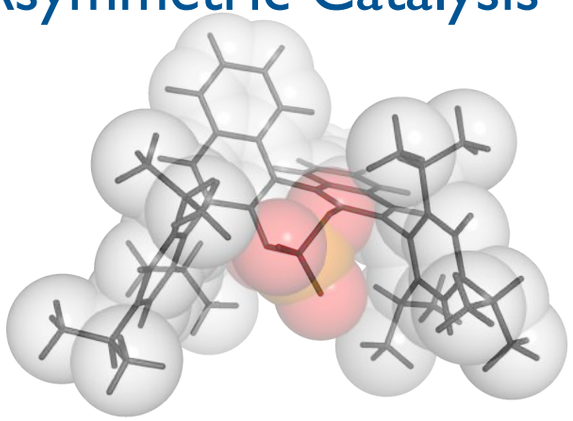
Theory and Chemistry: Learning from Nature

Reaction Mechanism



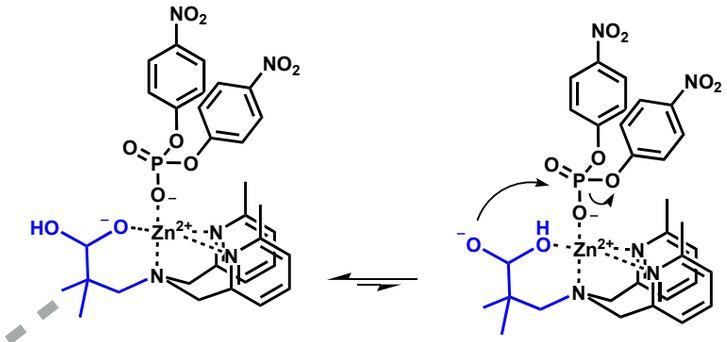
Angew. Chem. Int. Ed. **2017**, *127*, 4981
J. Am. Chem. Soc. **2015**, 137, 1081

Asymmetric Catalysis



J. Am Chem. Soc. **2017,** ASAP

Biomimetic Catalysis



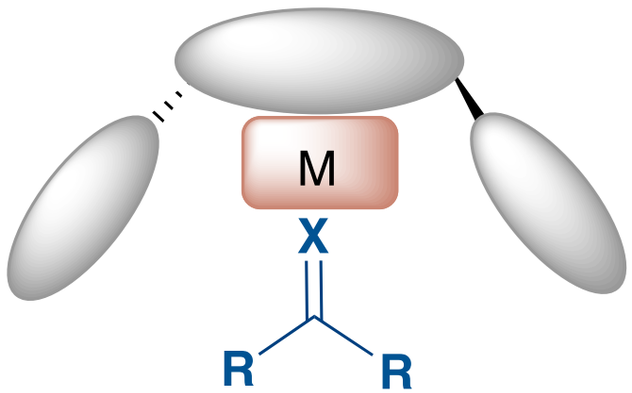
Angew. Chem. Int. Ed. **2014**, *53*, 8246

Enzyme Catalysis

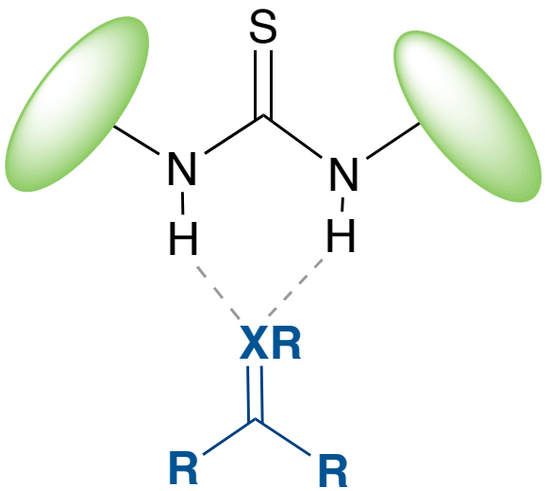
J. Am. Chem. Soc. **2015**, 137, 9061

Asymmetric Catalysis

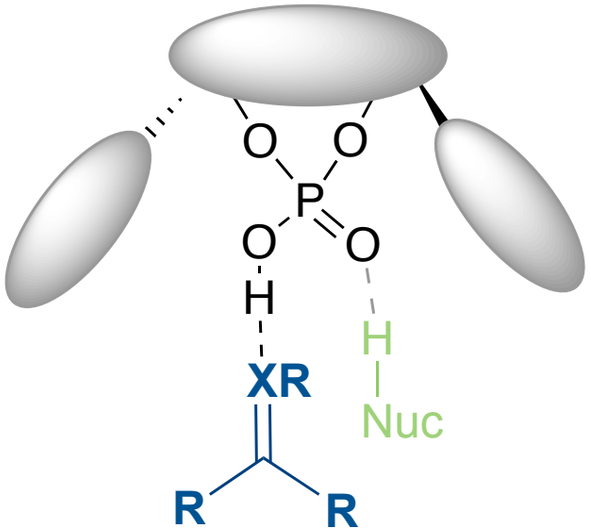
Metal Catalysis



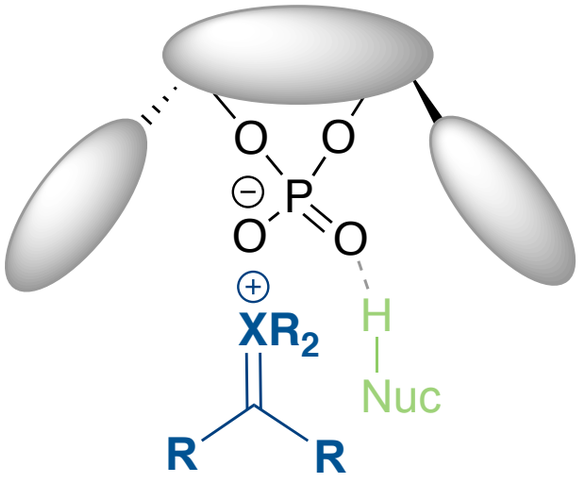
H-Bond Catalysis



Brønsted Catalysis



Ion-Pair Catalysis

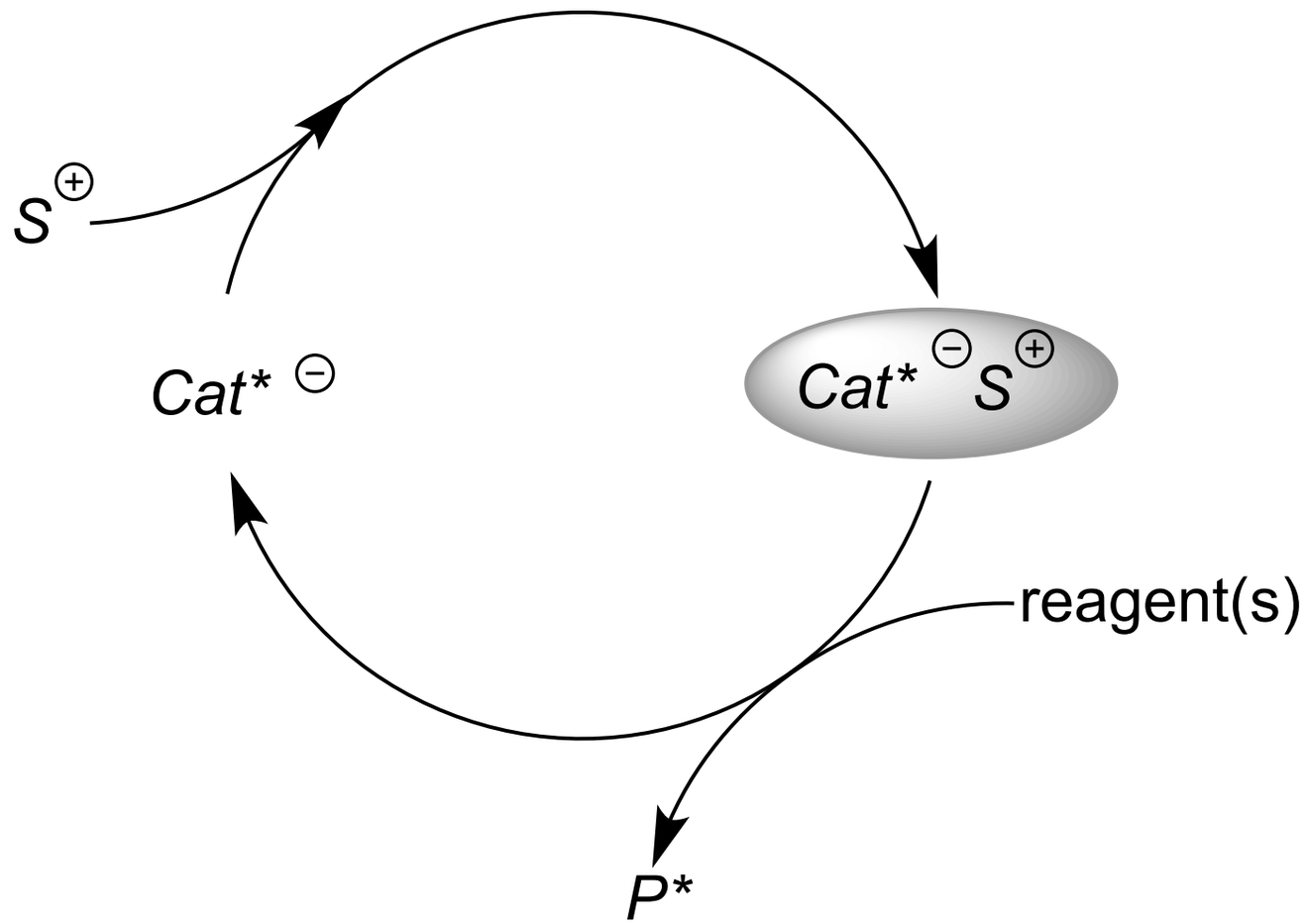


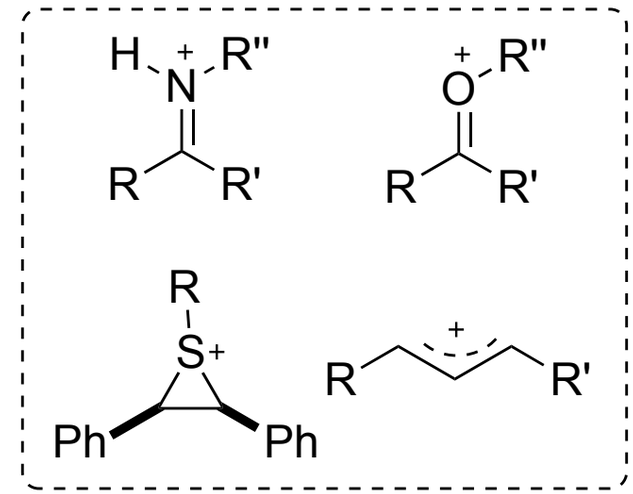
Toste *et. al. Nature Chem.* **2012,** 4, 603

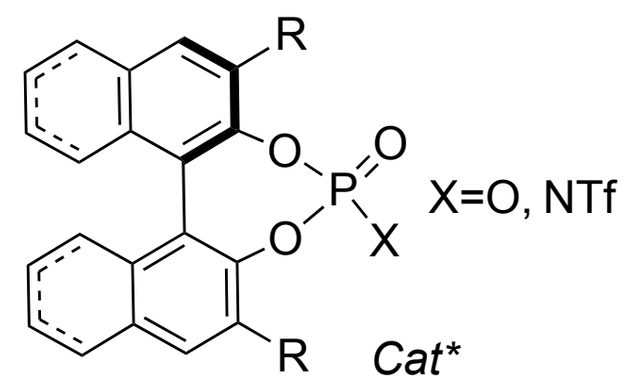
Gschwind, *et al. JACS* **2016**, 138, 15965; Gschwind, *et al. JACS* **2016**,138, 16345;

Hunger et al. ACS Catal. **2015**, 5, 6630; Gschwind, ACIE **2011**, 50, 6364.

Asymmetric Counteranion Directed Catalysis (ACDC)



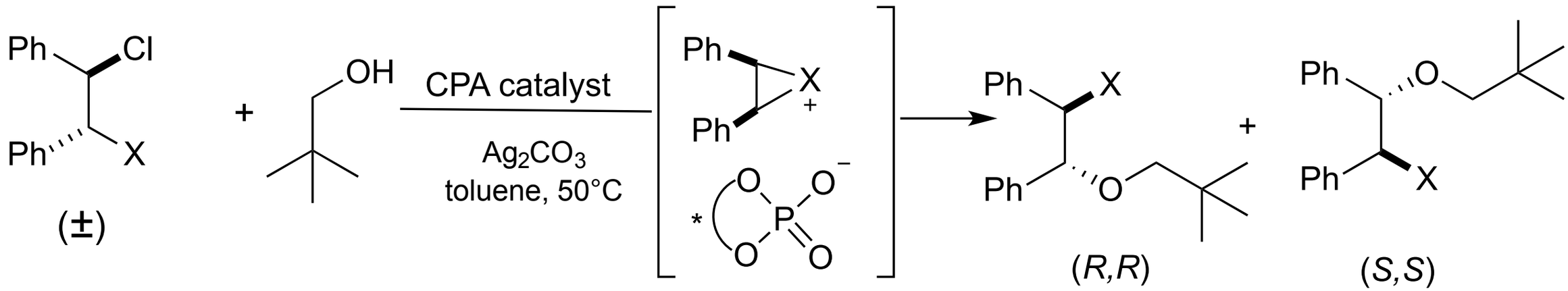


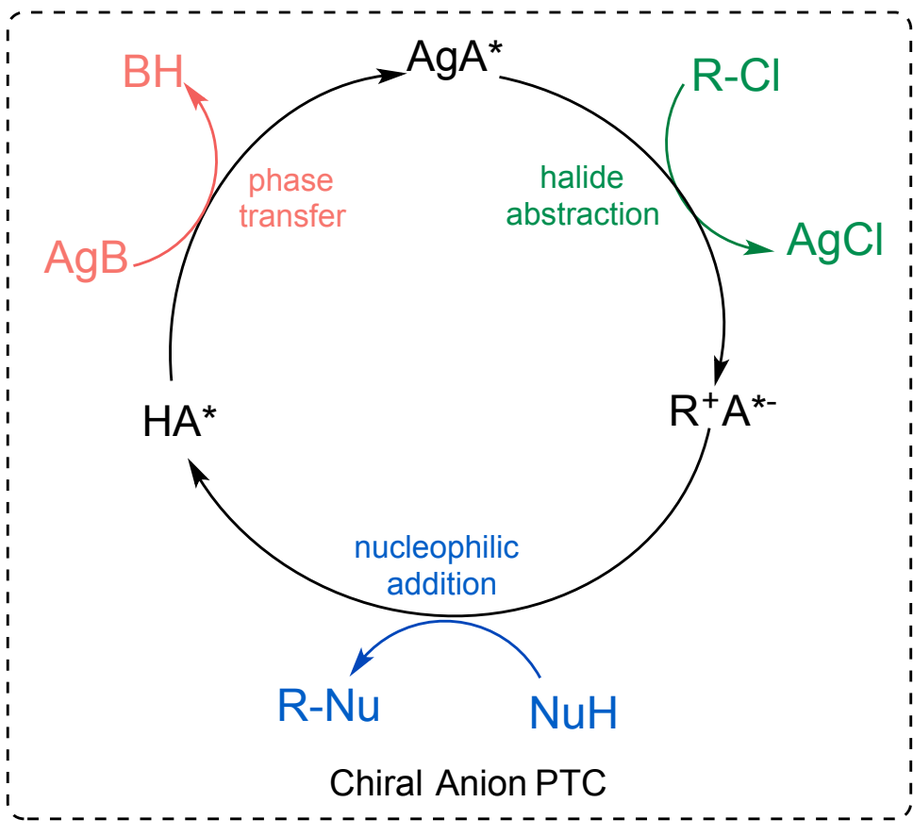


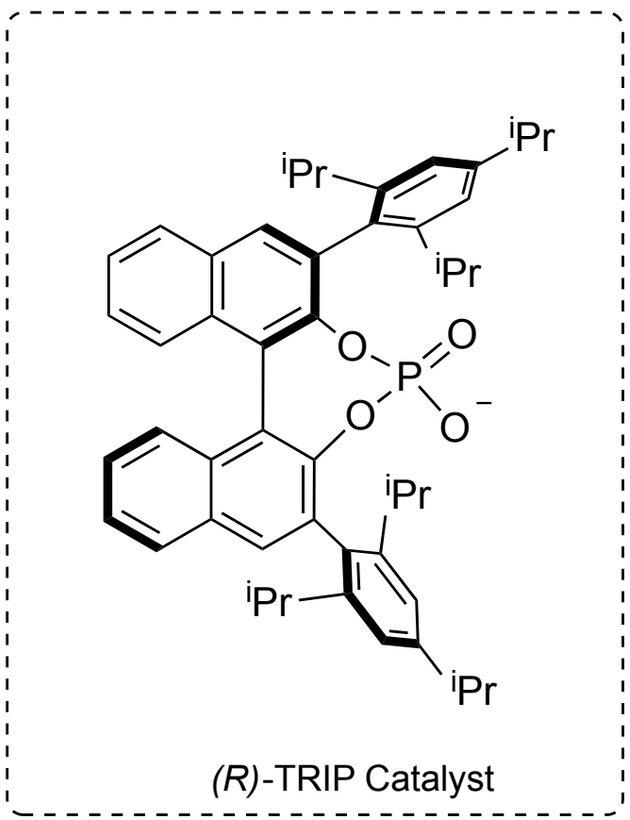
Rueping *et al.* JACS **2011**, 133, 3732; Terada *et al*. JACS **2009**, 131,3430;

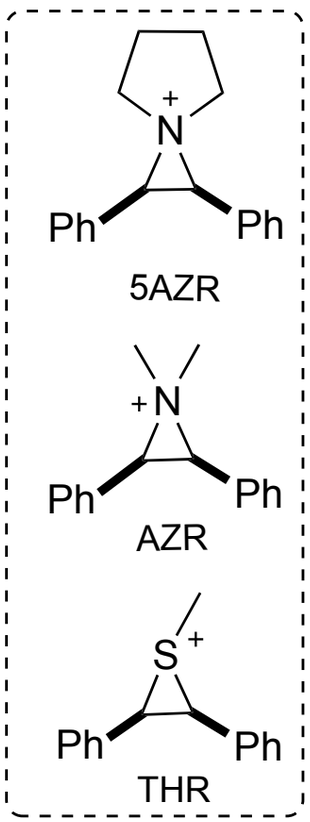
Hui *et al. Org. Lett.* **2012**, 14, 2010

Desymmetrization of a *meso*-cation *via* PTC



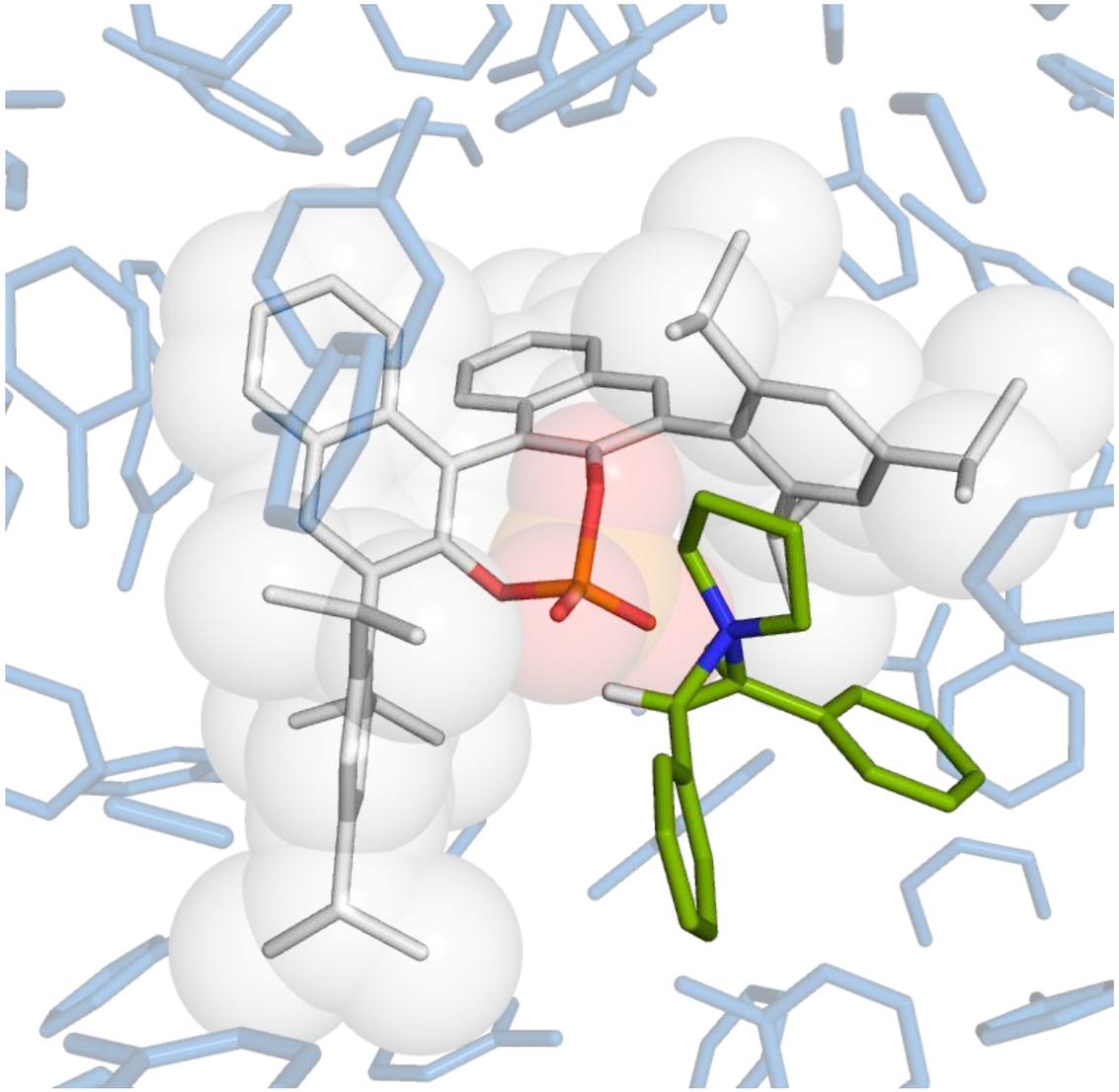






Toste et al. JACS, **2008**, 130, 14984

Ion-pair Binding Modes and Interaction Energies



Explicit Solvent:

Toluene

Dichloromethane (DCM)

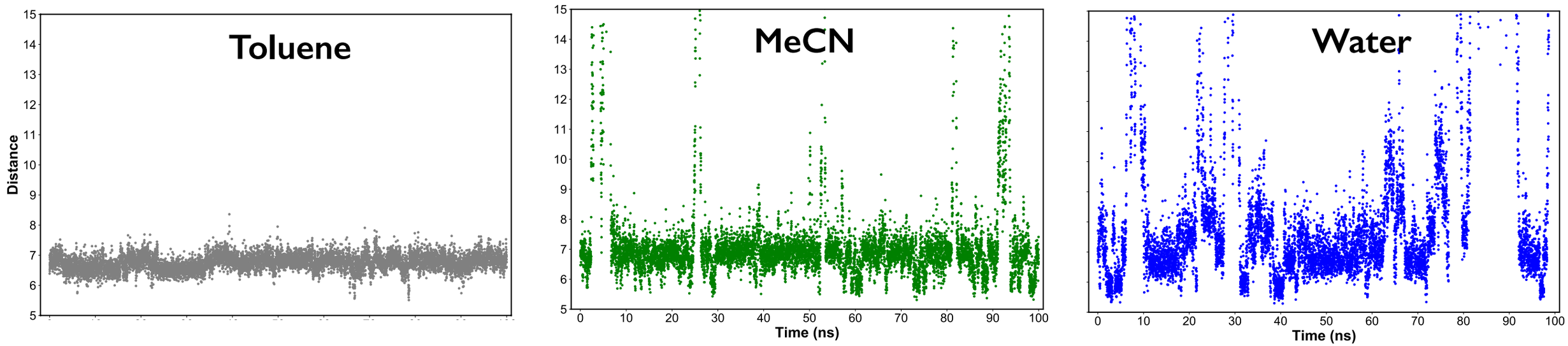
Acetonitrile (MeCN)

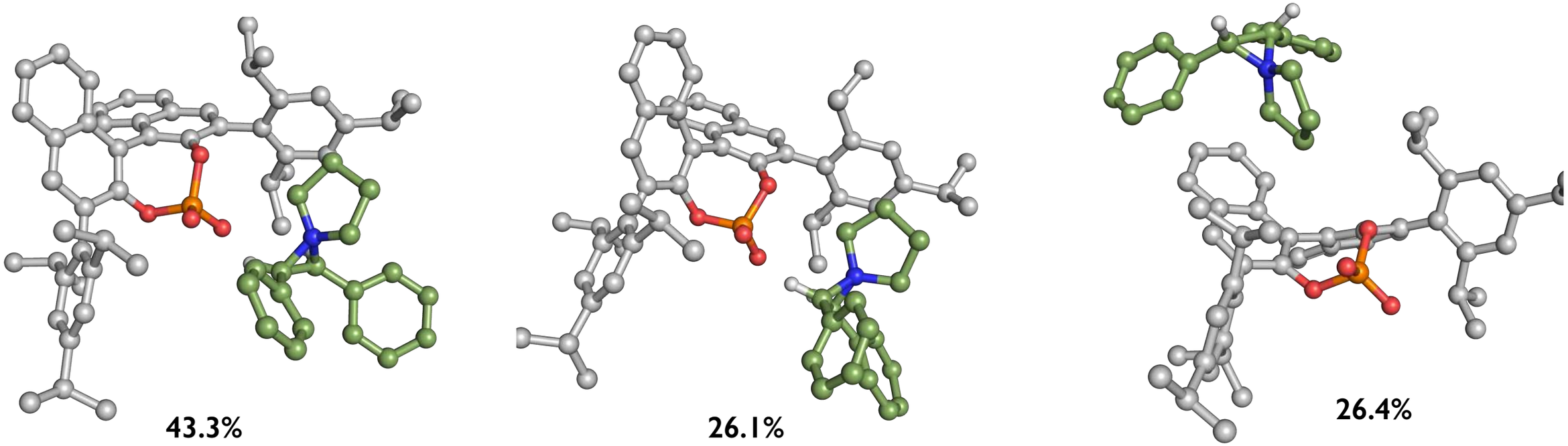
Water

(GROMACS Molecule & Liquid Database)

GROMACS 100 ns MD Simulations 298K

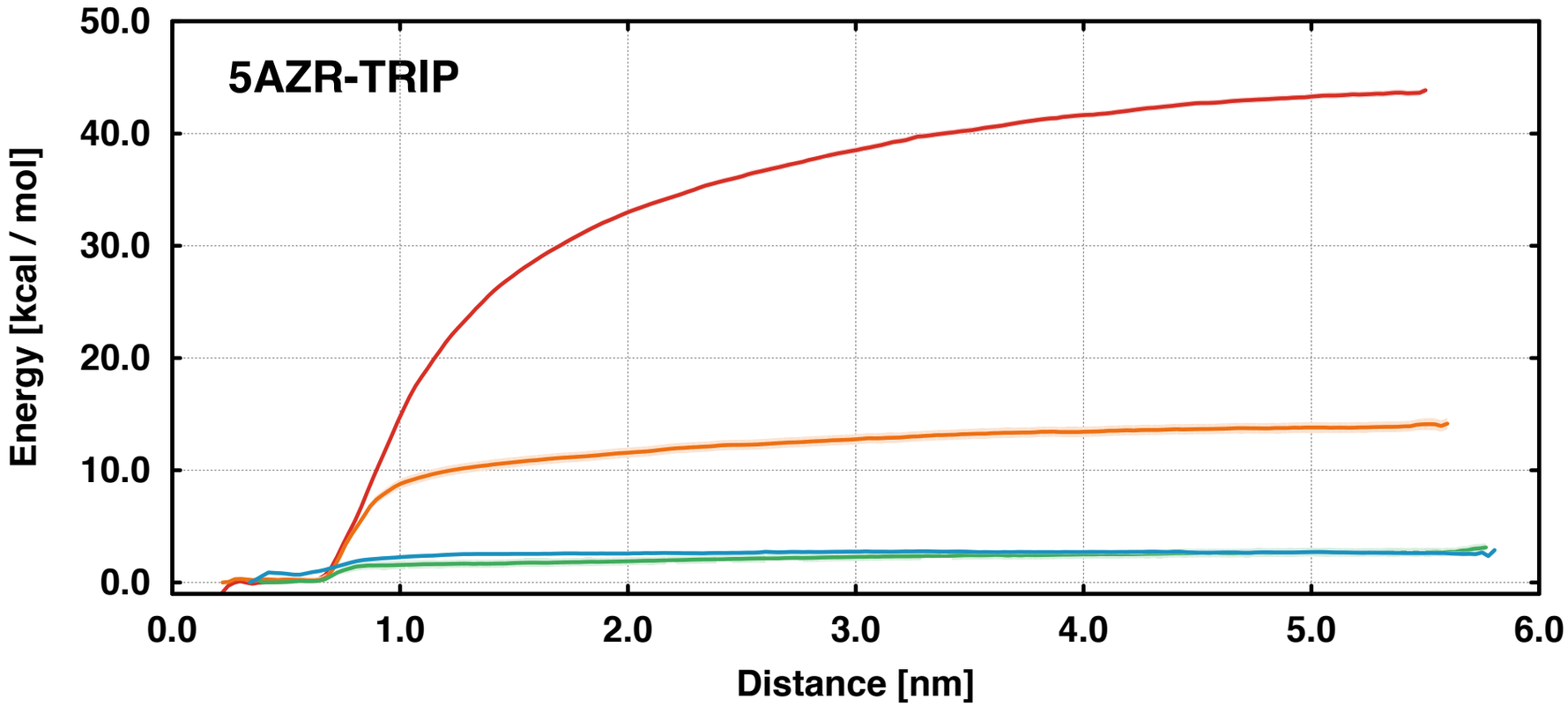
Ion-pair Binding Modes

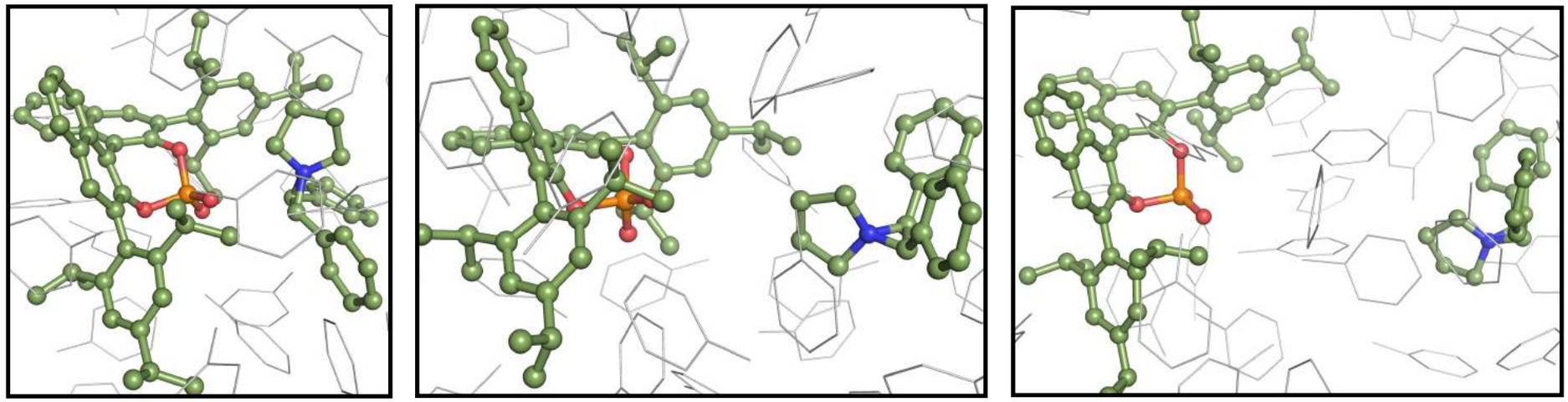




GROMACS MD Simulations 298K. Clustering RMSD criterion of 1.8 Å. Explicit Solvent: Toluene, dichloromethane (DCM), acetonitrile (MeCN), and water (GROMACS Molecule & Liquid Database)

Ion-pair Interaction Energies

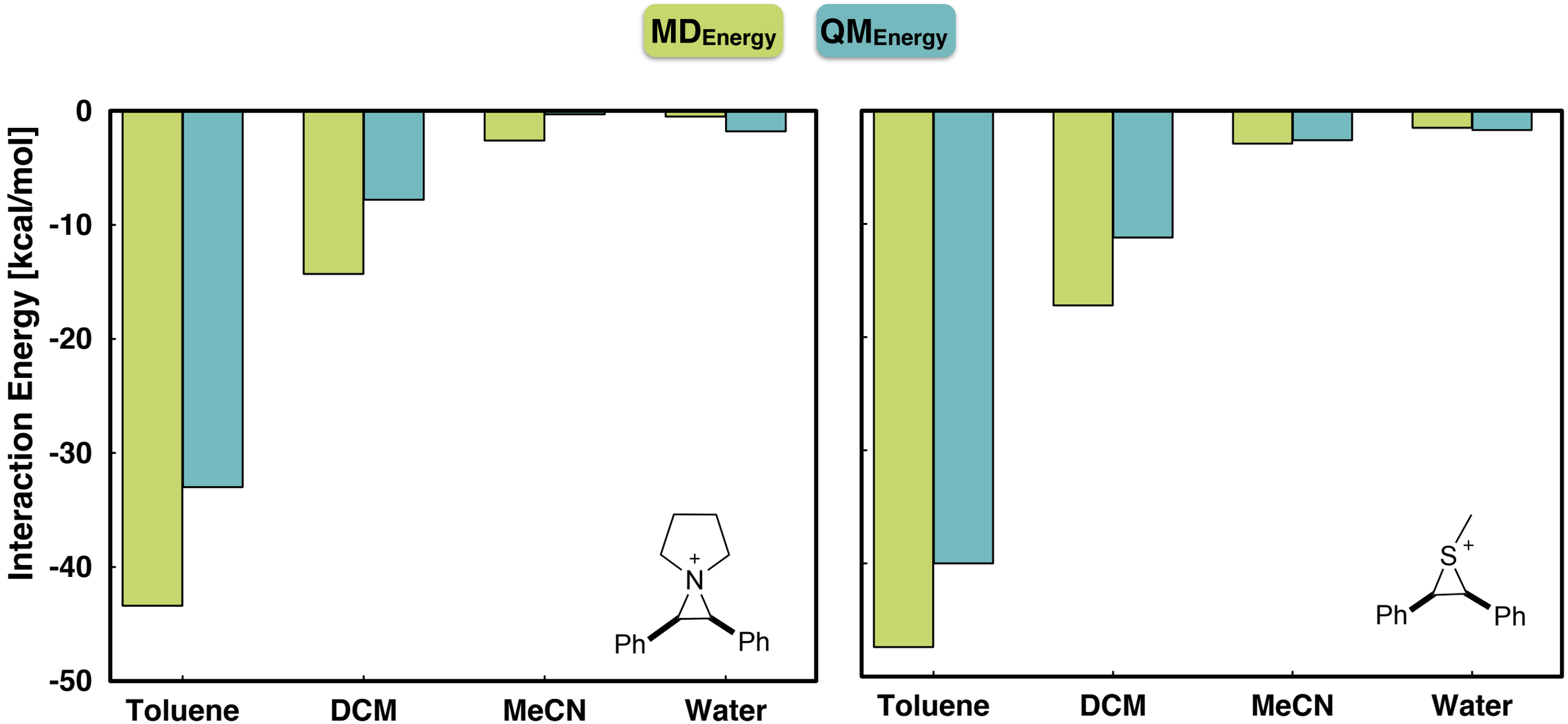




A tightly bind, but flexible, ion-pair complex is observed in nonpolar solvent.

GROMACS MD Simulations 298K. Explicit Solvent: Toluene, dichloromethane (DCM), acetonitrile (MeCN), and water (GROMACS Molecule & Liquid Database)

Ion-pair Binding Modes and Interaction Energies

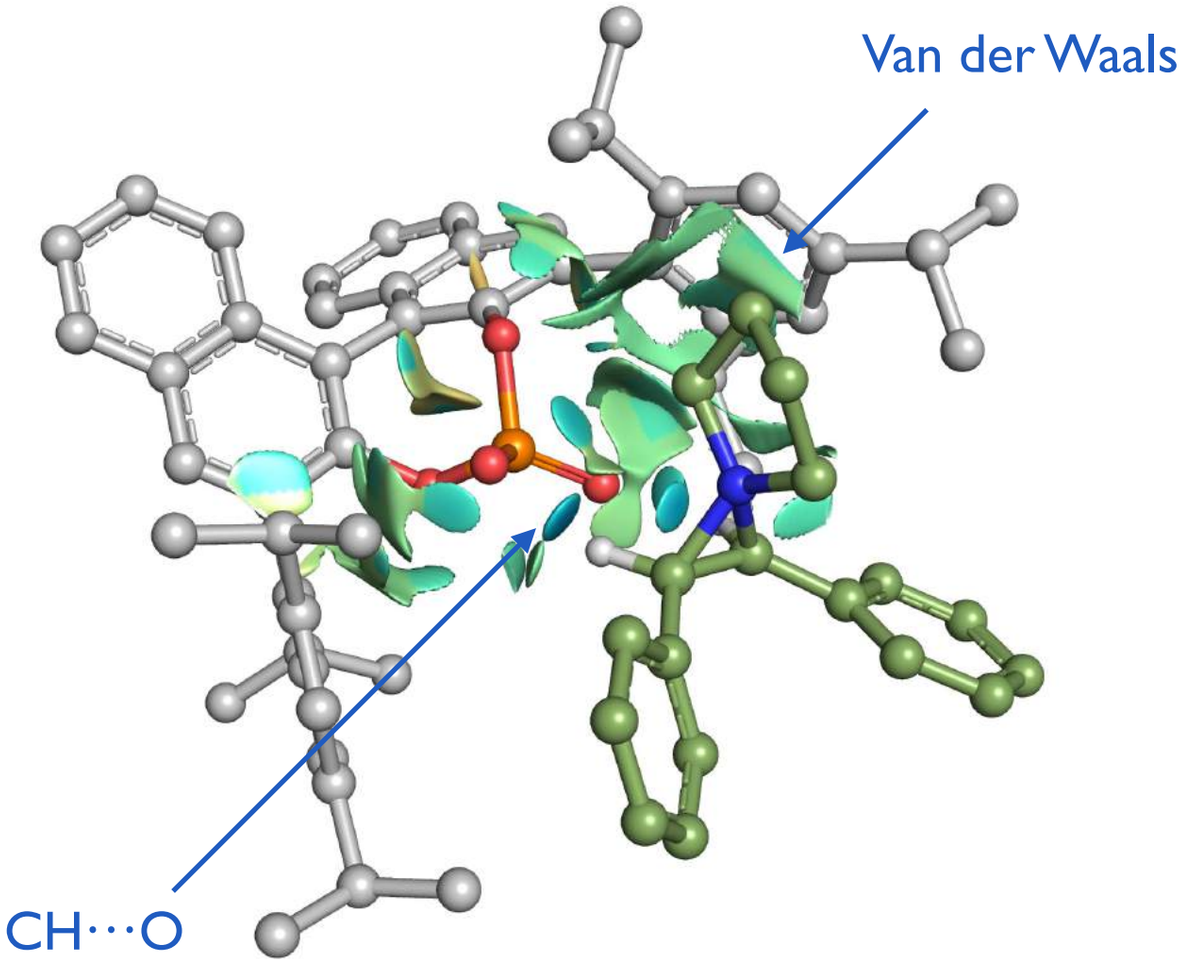


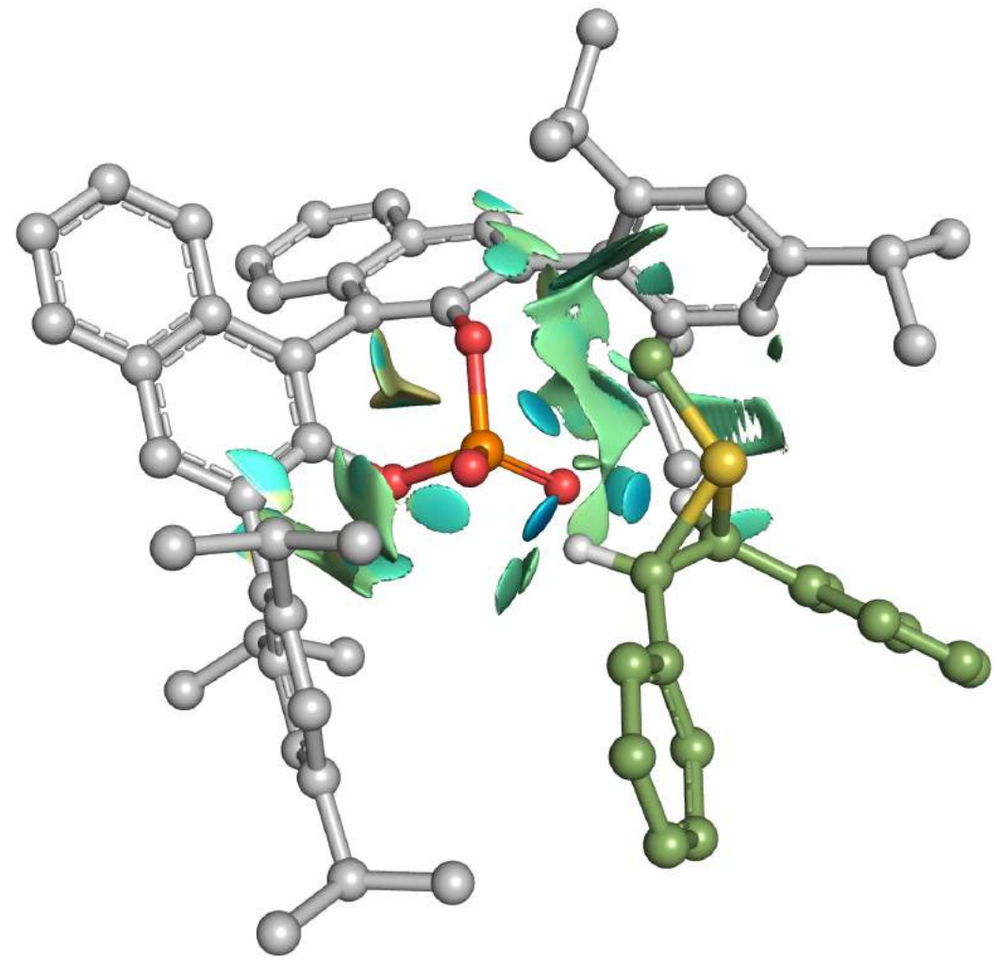
Dispersion effects in QM calculations increase as much as 8 kcal/mol the interaction energy value

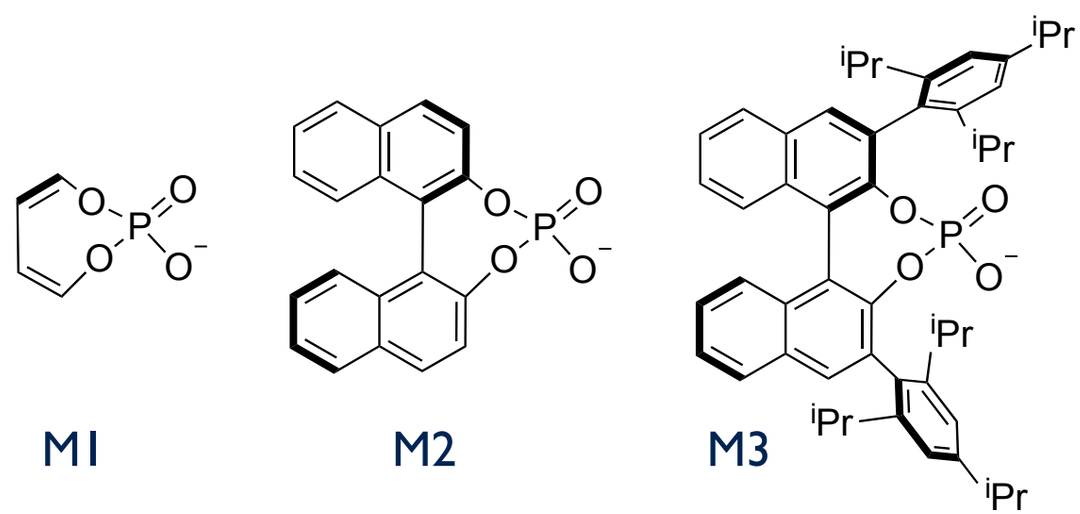
GROMACS MD Simulations 298K. Explicit Solvent: Toluene, DCM, MeCN, and water

(SMD)-ωB97X-D/6-311++G(d,p)//(SMD)-ωB97X-D/6-31G(d). M06L(D) and B97X(D) where tested

Ion-pair Binding Modes and Interaction Energies



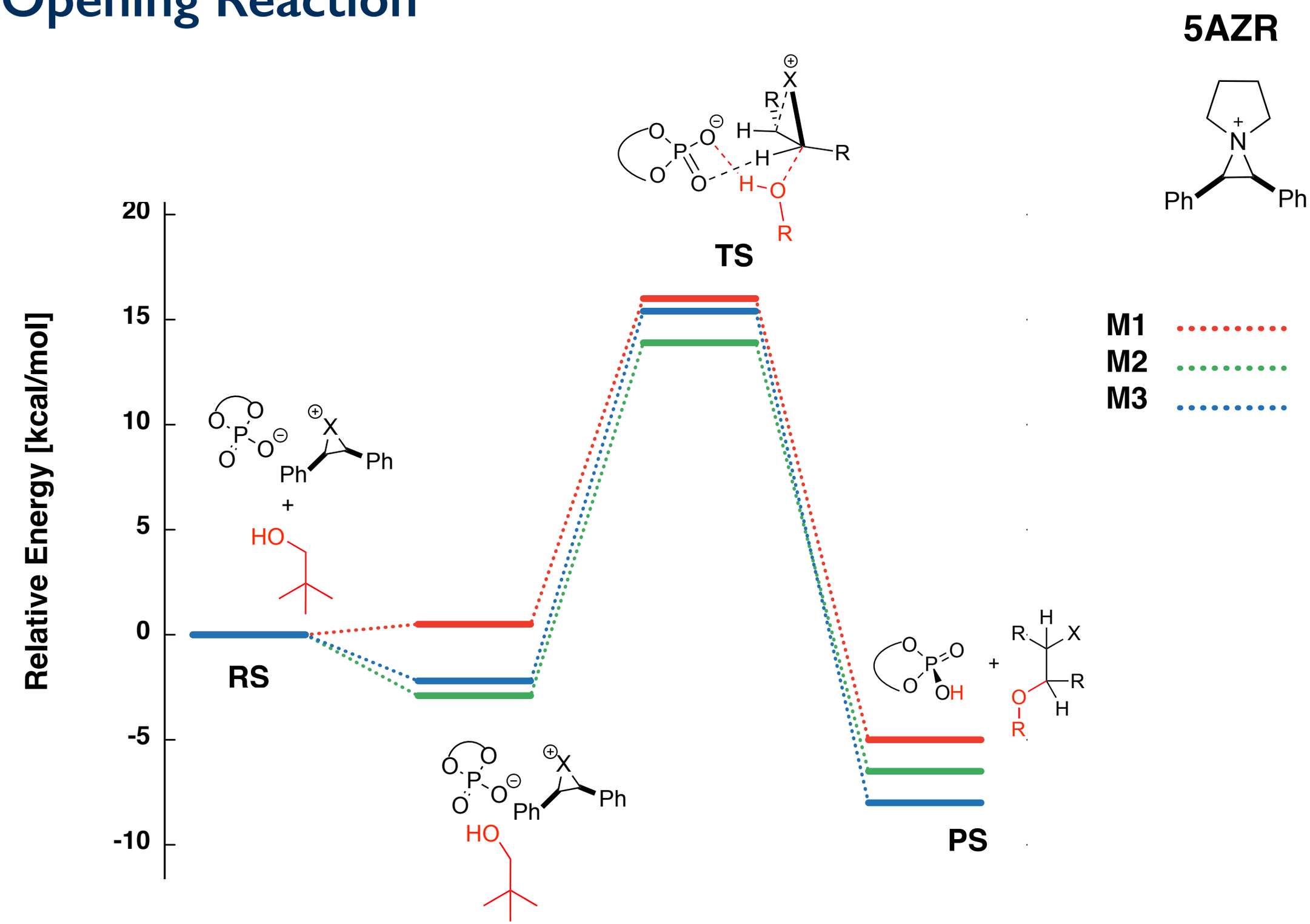




Noncovalent Interactions (NCI) plots obtained using the NCIPlot software

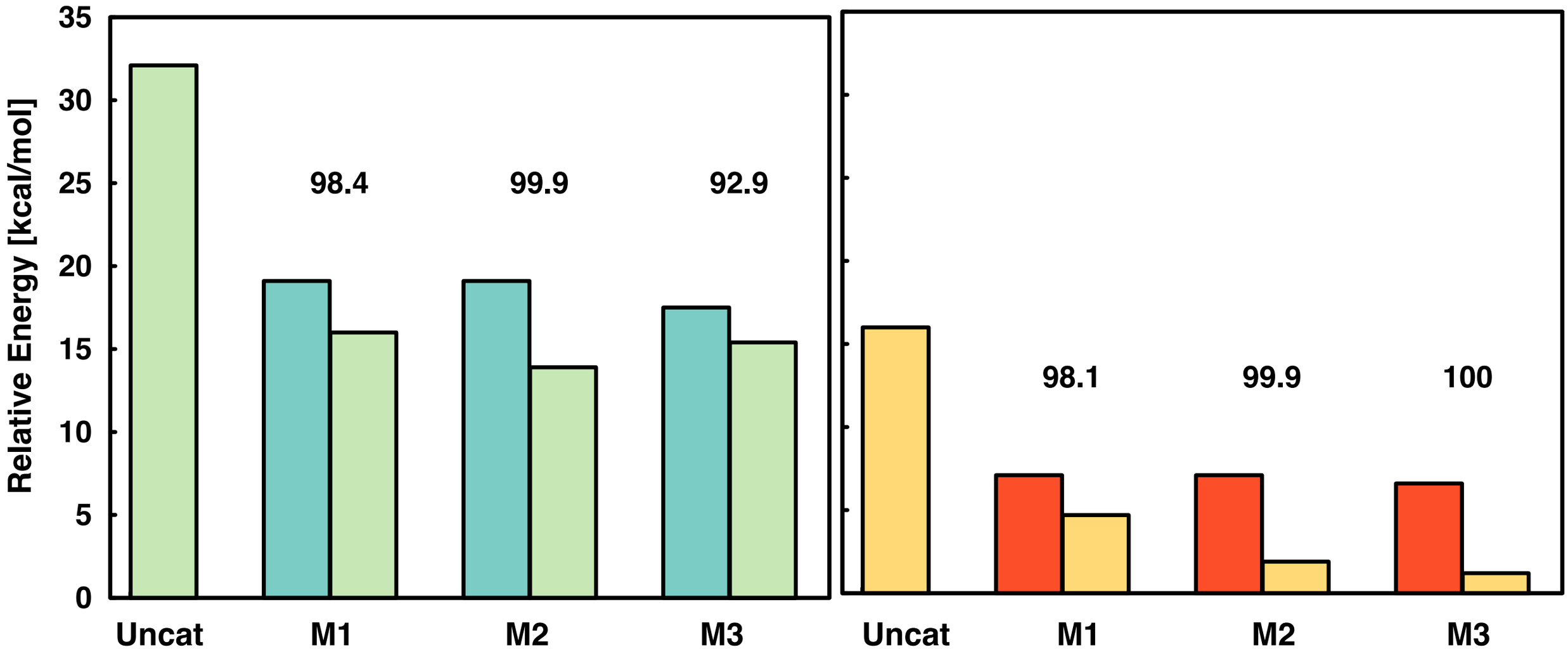
Johnson *et al.* JACS. 2010, 132, 6498; Contreras-Garcia *el al* JCTC **2011**, 7, 625

Ring-Opening Reaction



(SMD)-ωB97X-D/6-311++G(d,p)//(SMD)-ωB97X-D/6-31G(d). M06L(D) and B97X(D) where tested

Origin of Catalysis and Selectivity



(SMD)-ωB97X-D/6-311++G(d,p)//(SMD)-ωB97X-D/6-31G(d). M06L(D) and B97X(D) where tested

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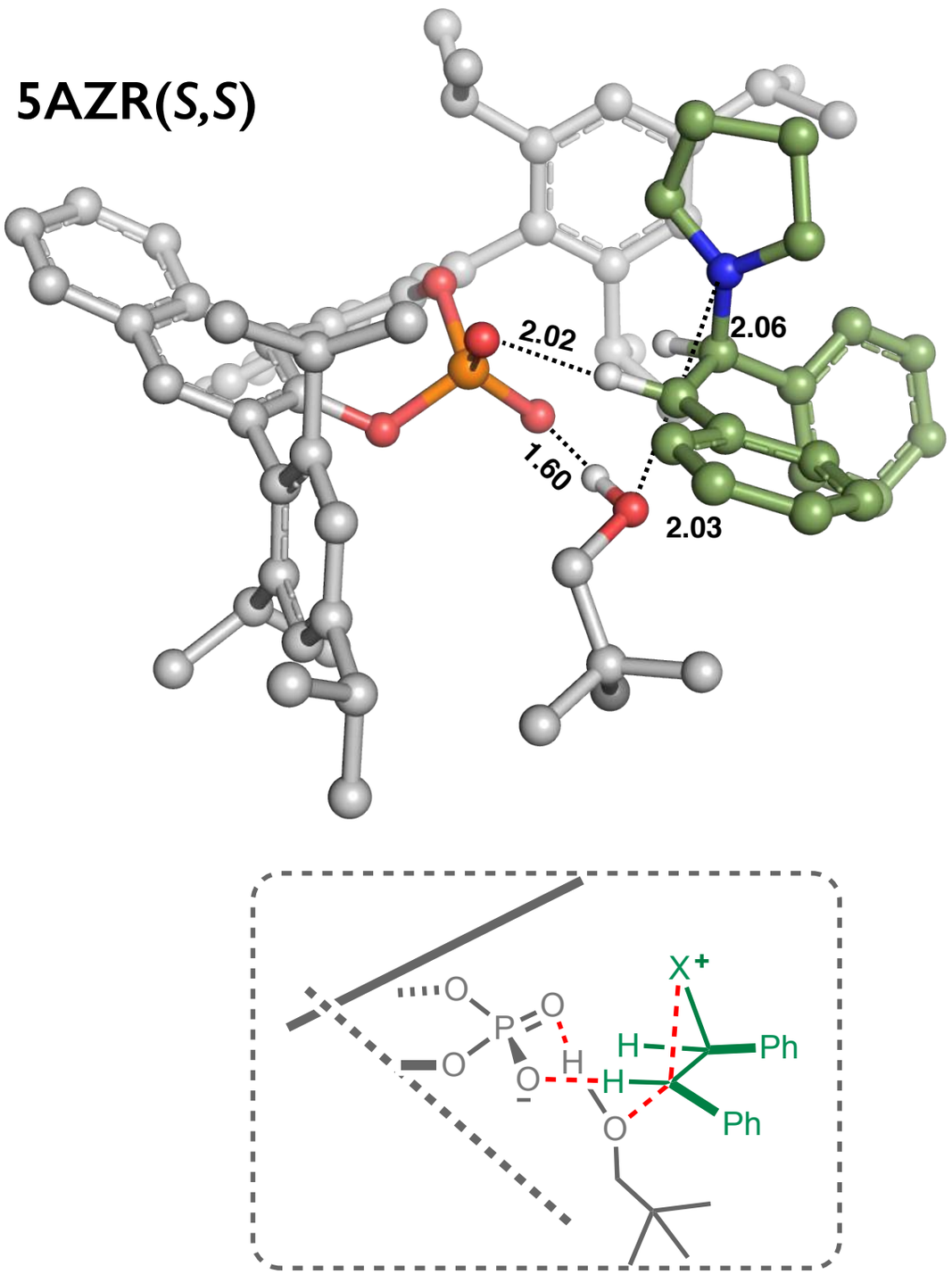

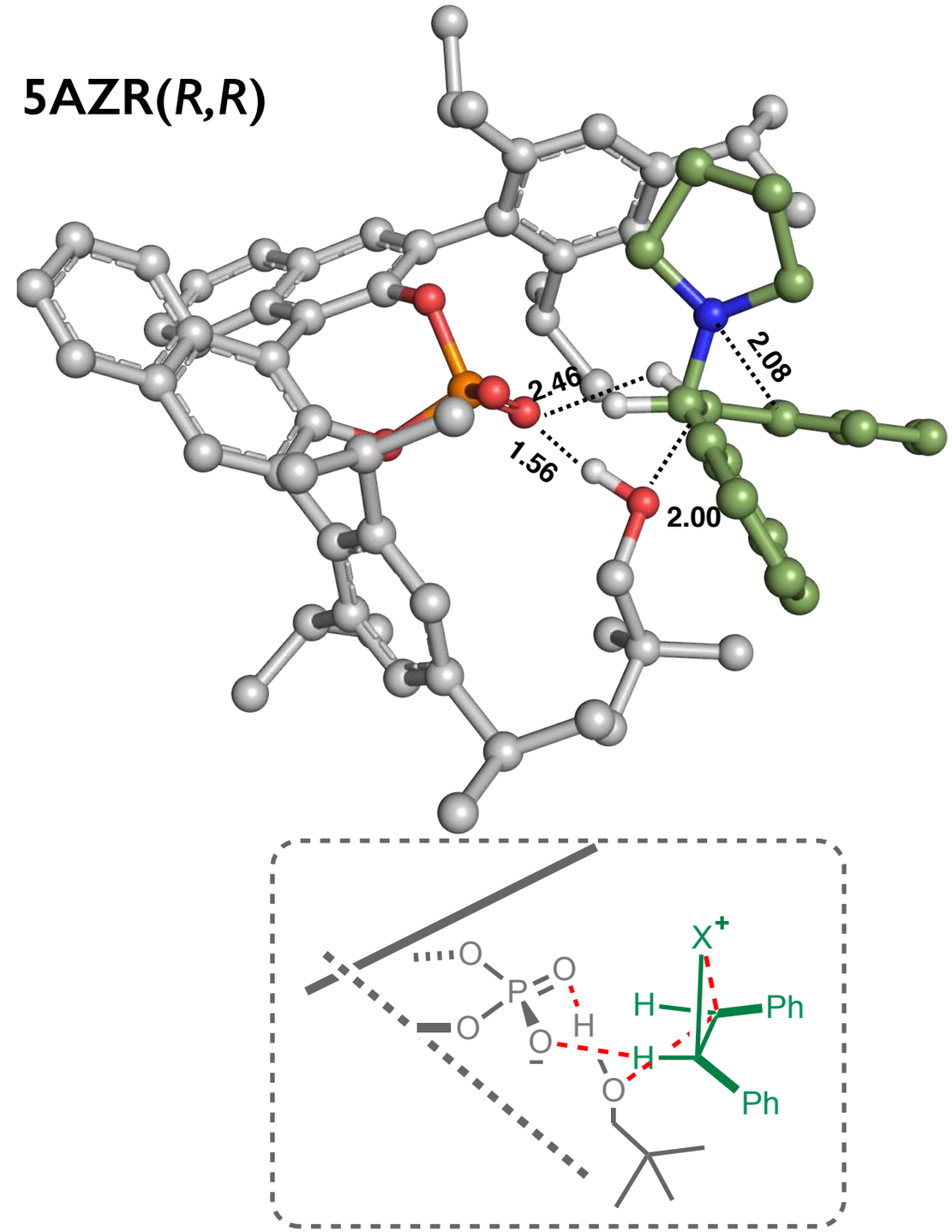

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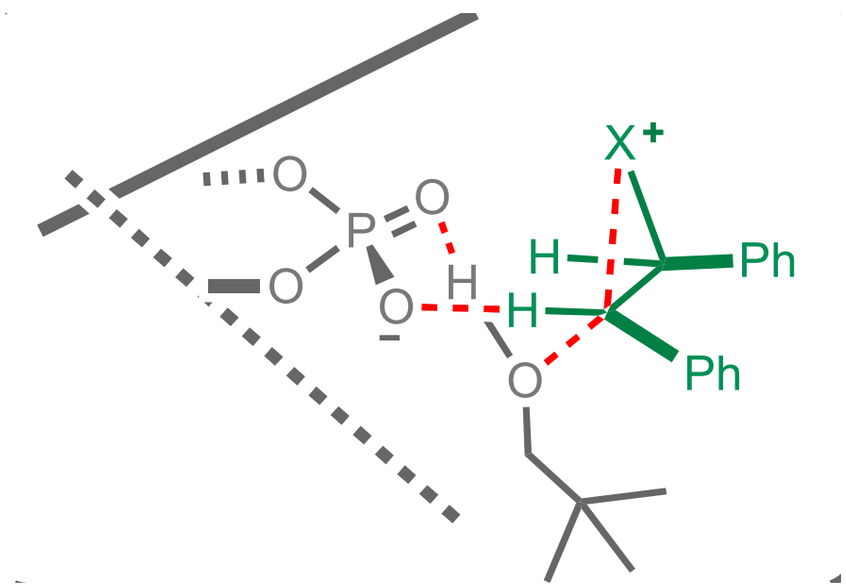
Origin of Catalysis and Selectivity

Distortion-Interaction Analysis

$$\Delta E^{\ddagger} = \Delta E^{\ddagger}_{dist} + \Delta E^{\ddagger}_{int}$$

$$\Delta E^{\ddagger}_{dist} = \Delta E^{\ddagger}_{dist\_cat} + \Delta E^{\ddagger}_{dist\_sub} + \Delta E^{\ddagger}_{dist\_nuc}$$



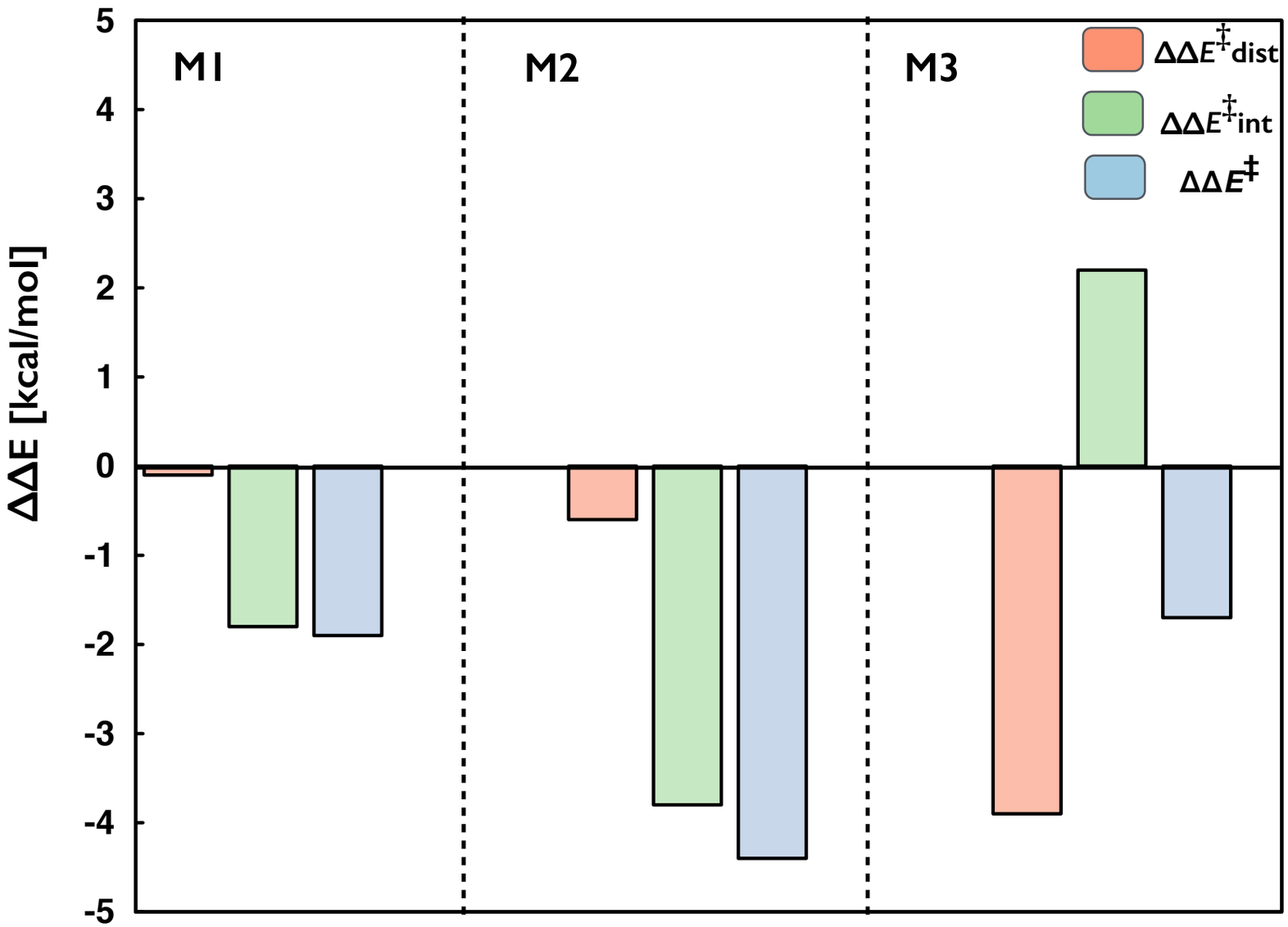
Ess, D. H.; Houk, K. N. *JACS* **2007**, 129, 10646

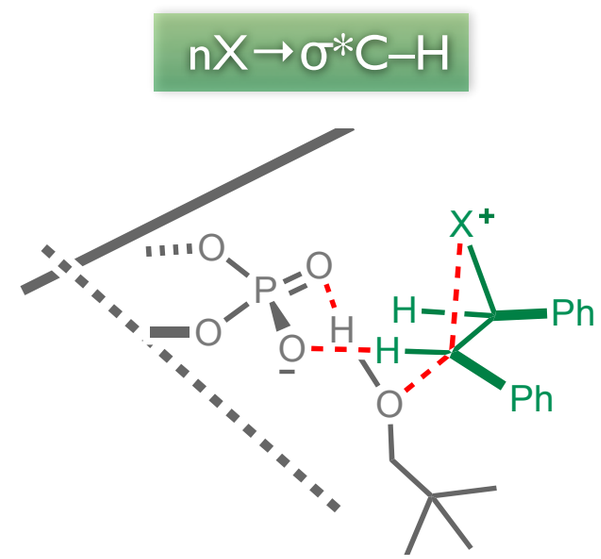
(SMD)-ωB97X-D/6-311++G(d,p)//(SMD)-ωB97X-D/6-31G(d). M06L(D) and B97X(D) where tested

Origin of Catalysis and Selectivity

$$\Delta E^{\ddagger} = \Delta E^{\ddagger}_{dist} + \Delta E^{\ddagger}_{int}$$

$$\Delta E^{\ddagger}_{dist} = \Delta E^{\ddagger}_{dist\_cat} + \Delta E^{\ddagger}_{dist\_sub} + \Delta E^{\ddagger}_{dist\_nuc}$$





Ess, D. H.; Houk, K. N. *JACS* **2007**, 129, 10646

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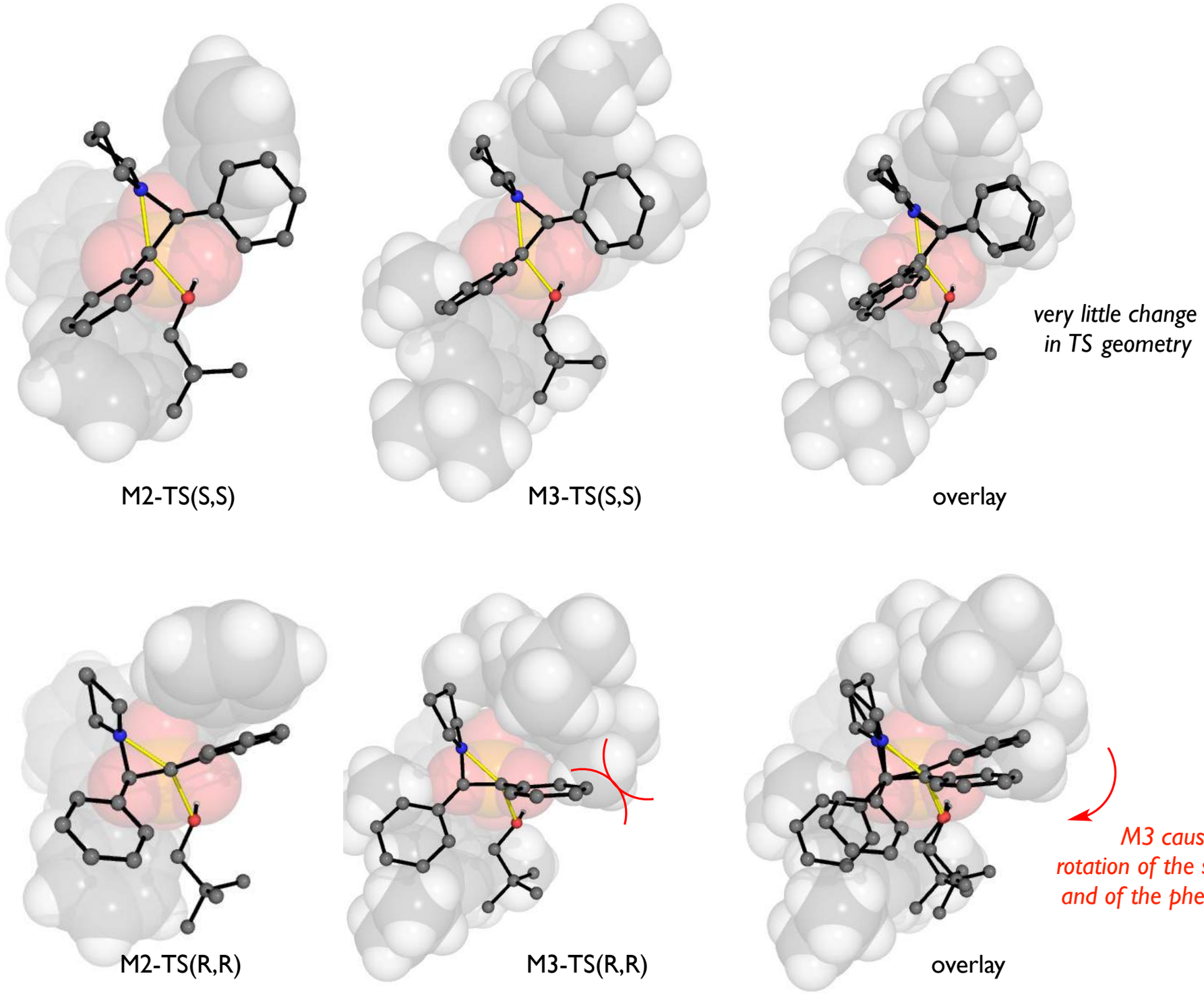
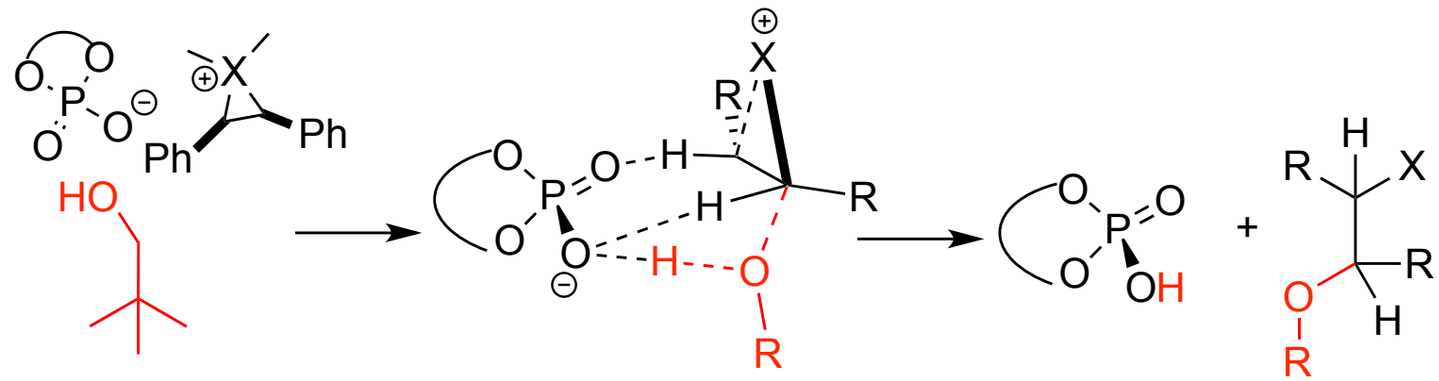
Origin of Catalysis and Selectivity



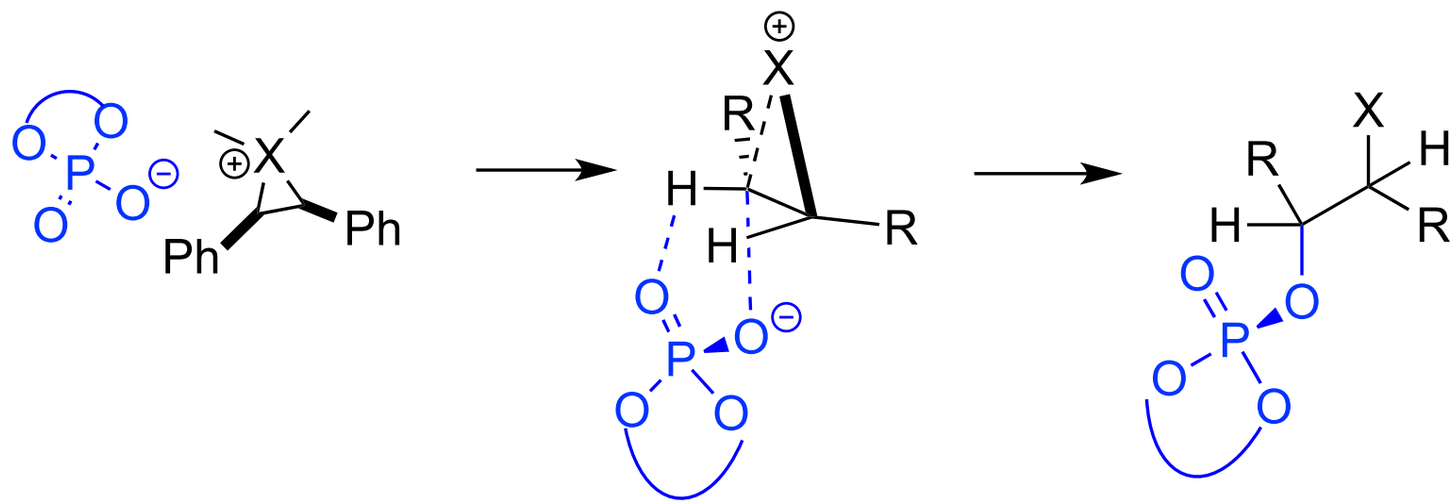
(SMD)-ωB97X-D/6-311++G(d,p)//(SMD)-ωB97X-D/6-31G(d). M06L(D) and B97X(D) where tested

Side-Reaction: Catalyst Deactivation

Path A



Path B

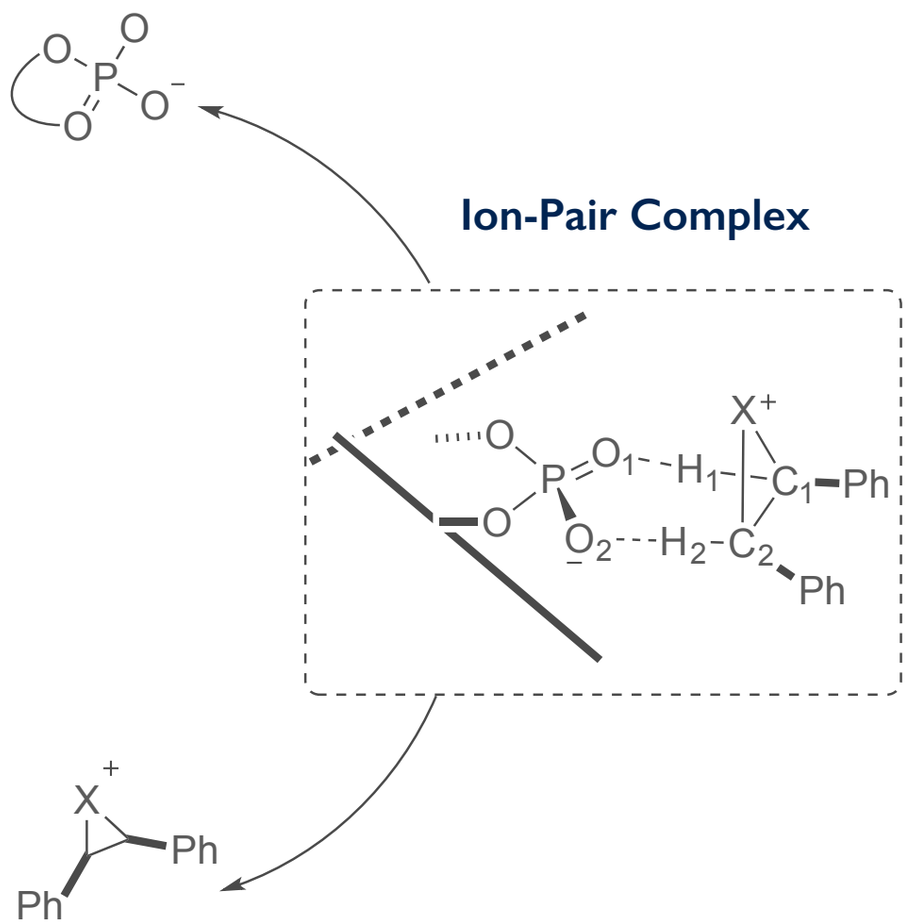


Even for the sterically hindered catalysts the decomposition pathway can dominate.

Under the experimental PTC conditions no alkylation of the catalyst was reported.

Rueping *et al.* Angew. Chem. Int. Ed. **2006**, 45, 7832; Li *et al.* *Org. Lett.* **2009** 11, 1075
Shi *et al.* ChemCatChem **2014** 6, 3309.

Summary



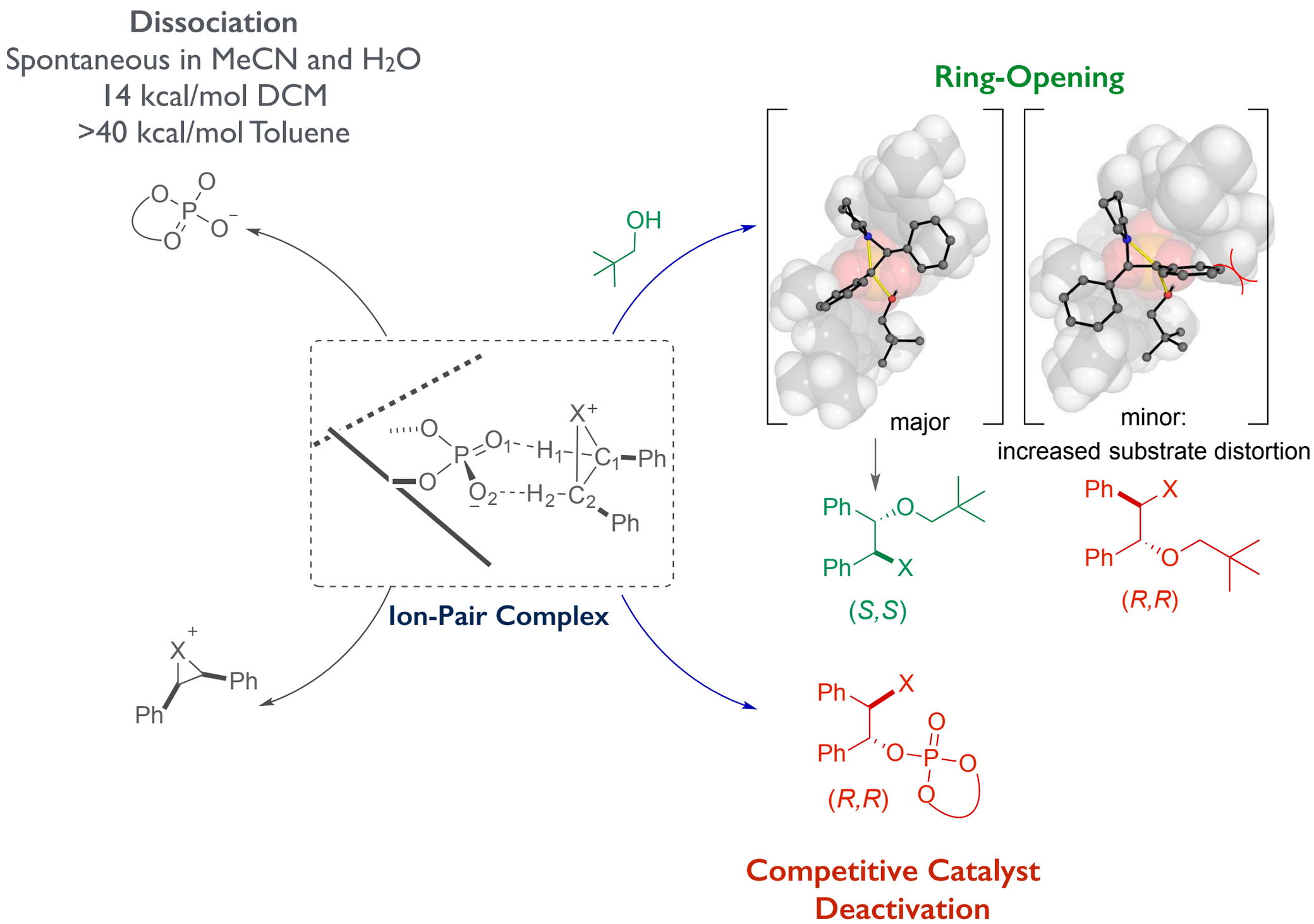
Dissociation

Spontaneous in MeCN and H_2O

14 kcal/mol DCM

>40 kcal/mol Toluene

Summary



Acknowledgements

THE ROYAL SOCIETY

Newton International Fellowship, Royal Society

School of Chemistry, University of Edinburgh

Paton Group, Department of Chemistry, Oxford