RxnEnumProfiler

Virtual high-throughput screening of reaction networks

RxnEnumProfiler is a fully automated, massively parallel, out-of-the-box workflow developed to systematically evaluate large libraries of chemical species within a fixed reaction topology—that is, a predefined sequence of mechanistic steps involving reactants, products, intermediates, and/or transition states that characterize a catalytic or chemical process. Easily organize and manage all your data through a single, intuitive graphical interface—and obtain results in days or weeks instead of months or years.

Applications:

- Homogeneous (molecular) catalyst design
- Chemical (non-catalytic) reaction and reactivity optimization
- Minimizing unwanted reactions or improving selectivity

Key features:

- Multi-site R-group enumeration
- Fragment swapping
- Conformational sampling (Monte Carlo/ force fields or metadynamics/xTB)
- Exact and approximate (energetic span model) automated TOF calculations, % ee calculations, selectivity
- Quantum mechanical descriptor generation for cheminformatics ML
- Dataset creation for training machine learning force fields
- Optional thermochemical properties refinement, including anharmonic corrections and solvation entropy adjustments (e.g., Garza model)

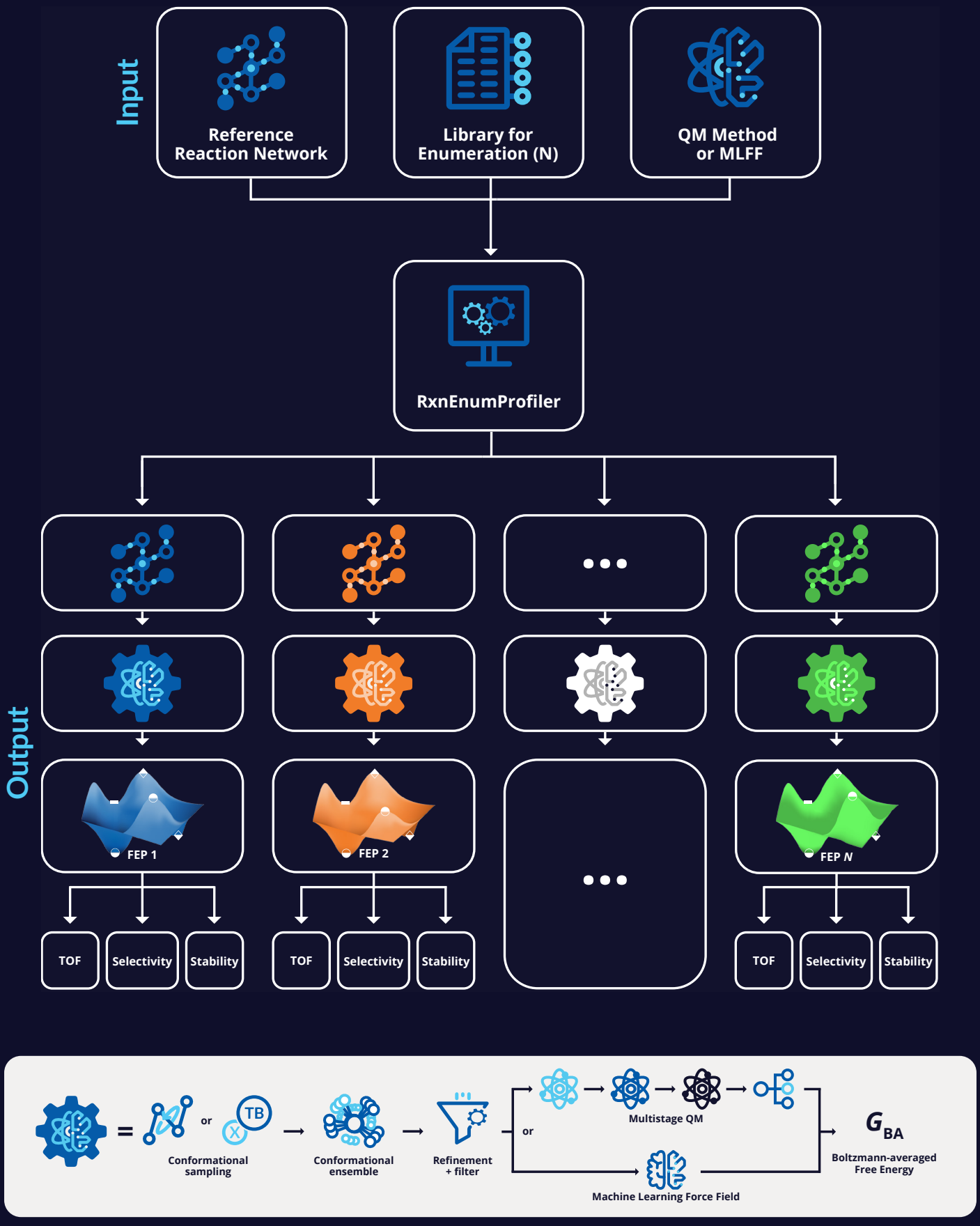
Methods:

- Classical force fields
- Extended tight-binding (GFN2-xTB)
- Pseudospectral density functional theory (PS-DFT)
- Machine Learning Force Fields (e.g. MPNICE, UMA_SM_OMOL)

Schrödinger

RxnEnumProfiler

Virtual high-throughput screening of reaction networks



Schematic workflow of virtual high-throughput screening of reaction networks

Case example 1

Virtual high-throughput screening of enantioselectivity (ee) and turnover frequency (TOF) to guide the design of FLP-based asymmetric hydrogenation catalysts

Google Cloud

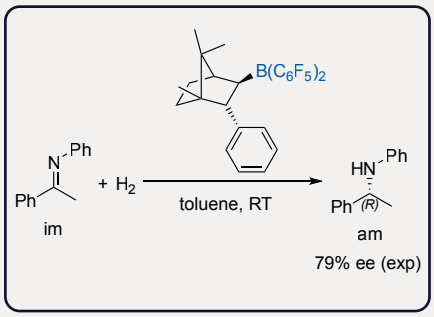
High Performance Computing (HPC) Cluster

Enantioselectivity screening:

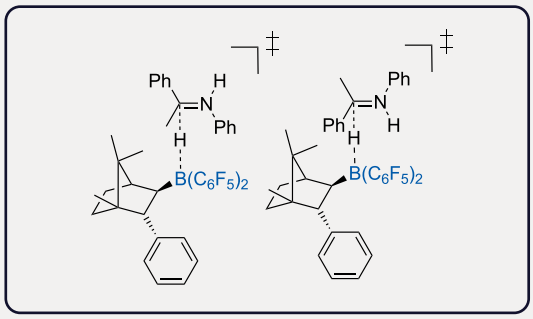
- 20 kcal/mol threshold for conformer selection
- ~400 transition states
- ~1600 DFT jobs
- 8 cores per DFT job
- ~2 weeks
- ~480,000 CPU hrs

TOF screening:

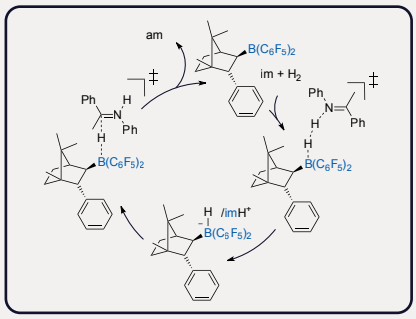
- Lowest conformer only
- 35 stationary points
- 10 transition states
- 175 DFT jobs
- 8 cores per DFT job
- ~5 days
- ~10,000 CPU hrs



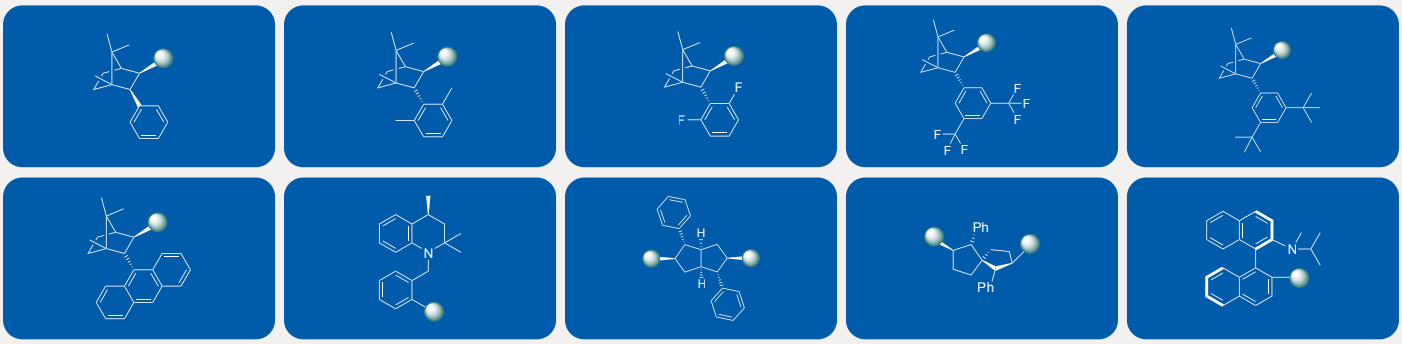
(a) asymmetric hydrogenation reaction



(b) reference network for enantioselectivity prediction



(c) reference network for TOF prediction



(d) library for single R-group enumeration (sphere indicates dummy atom)

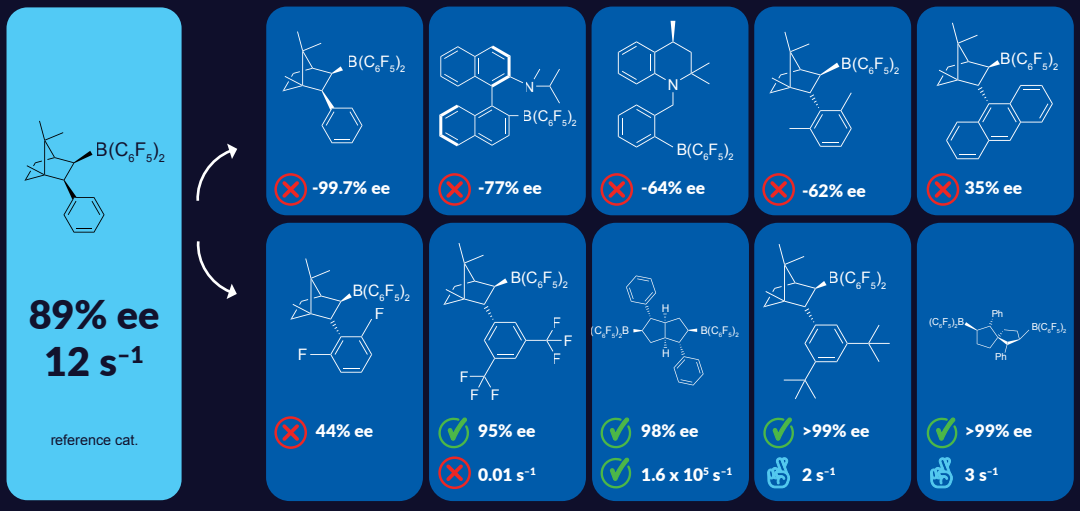
Predicted Boltzmann-averaged enantioselectivity (% ee) and turnover frequency (TOF in s^{-1})

ωB97X-D/C-PCM (toluene) with 6-311G++**//PS-6-31G*

UNSUITABLE

SUITABLE

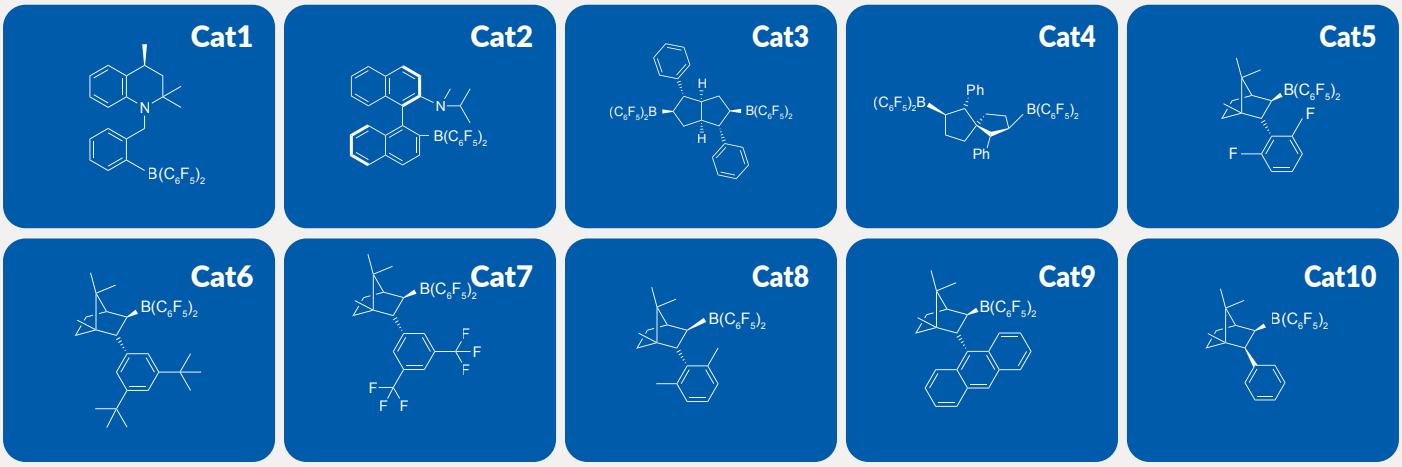
POSSIBLE CANDIDATE



Case example 1

DFT vs Machine Learning Force Fields for Catalyst Design: Accuracy–Efficiency Tradeoffs

394 cores requested on queuing system for MLFF
3152 cores used in parallel for DFT



Physics

Machine learning

Method	Established Trend	Failures	Time
ωB97X-D/C-PCM (toluene) with 6-311G++**// PS-6-31G*	cat10 < cat2 < cat1 < cat8 < cat9 < cat5 < ref < cat7 < cat3 < cat6 < cat4 -99.7% -77% -64% -62% 35% 44% 89% 95% 98% >99% >99%	33 of the 394 jobs failed	~ 2 weeks, ~480000 CPU hrs
UMA_SM_ OMOL v1.1	cat10 < cat2 < cat8 < cat1 < cat5 < cat9 < ref < cat7 < cat6 < cat4 < cat3 -99.6% -95% -72% -62% 35% 44% 89% 95% 98% >99% >99%	4 of the 394 jobs failed	~ 8 hrs, ~2600 CPU hrs
Organic_ MPNICE_tb (toluene)	cat2 < cat10 < cat1 < cat8 < cat7 < cat5 < cat9 < cat3 < ref < cat4 < cat6 -99.5% -98% -77% 10% 23% 27% 78% 92% 93% 99.5% 99.6%	24 of the 394 jobs failed	~ 9 hrs, ~2700 CPU hrs

Case example 2

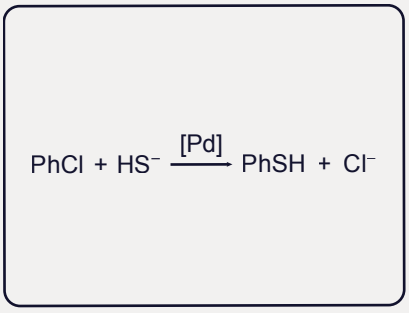
Virtual high-throughput screening of turnover frequency (TOF) to guide the design of Pd catalysts for C–O cross-coupling reaction

Google Cloud

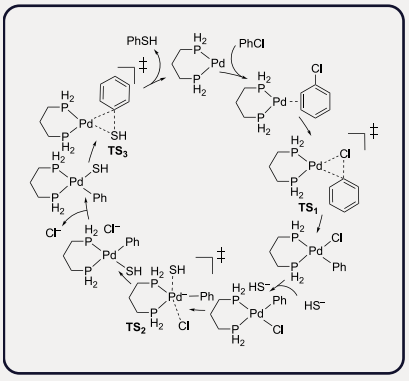
High Performance Computing (HPC) Cluster

- 10 conformers per stationary point
- 748 stationary points including
- 203 transition states
- 2992 DFT jobs

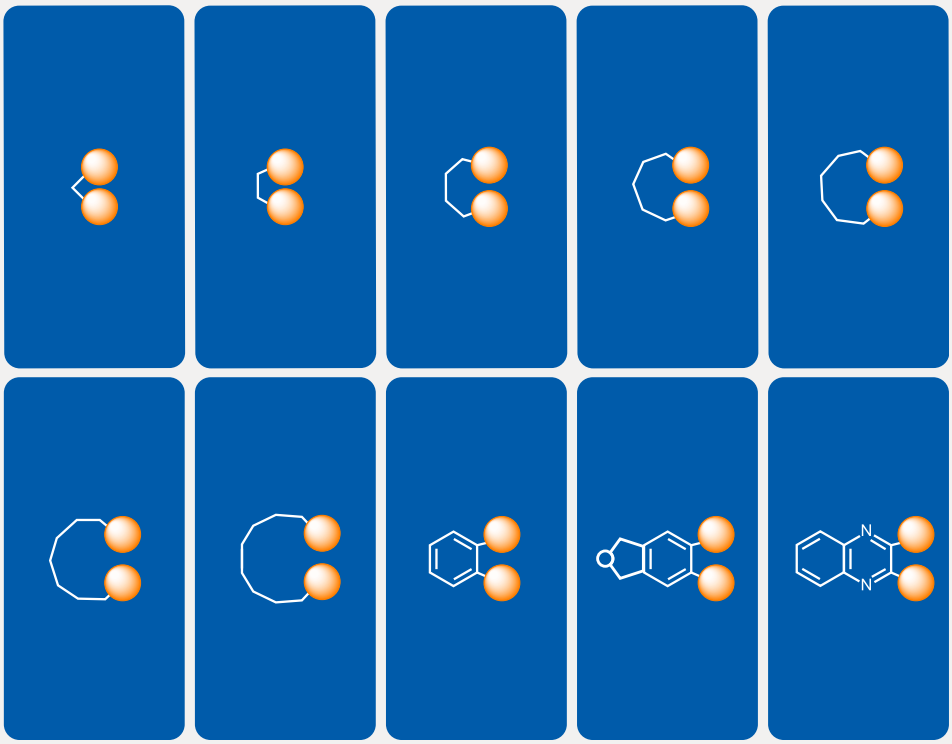
- 8 cores per DFT job
- ~2 days
- ~100,000 CPU hrs



(a) model C–O cross-coupling reaction



(b) reference network for TOF prediction



(c) virtual library for two R-group enumeration (spheres indicate dummy atoms)

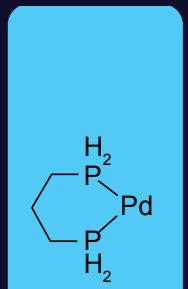
Predicted Boltzmann-averaged turnover frequency (TOF in s^{-1})

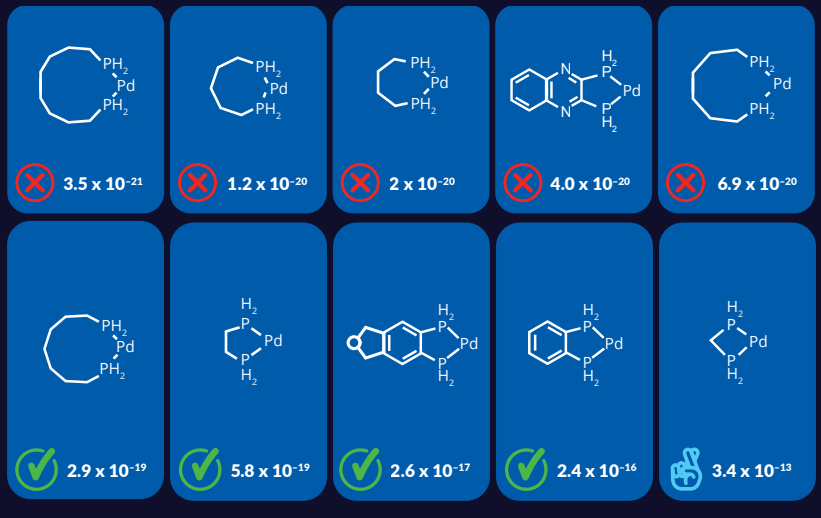
B3LYP-D3 with PS-LACV3P++**//PS-LACVP*

UNSUITABLE

SUITABLE

POSSIBLE CANDIDATE (POSSIBLE CHANGE IN MECHANISM DUE TO PARTIAL PP LIGAND DISSOCIATION)





Case example 3

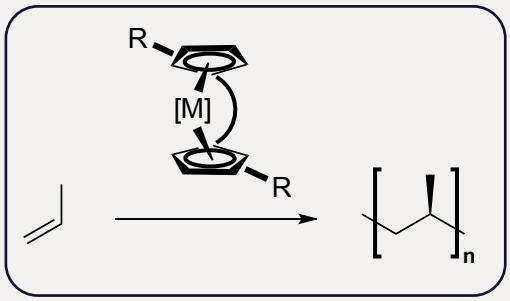
Designing an ansa-metallocene catalyst for enantiopure isotactic propylene polymerization, with the goals of minimizing stereochemical and regioselectivity errors while maximizing molecular weight and reaction rate

Google Cloud

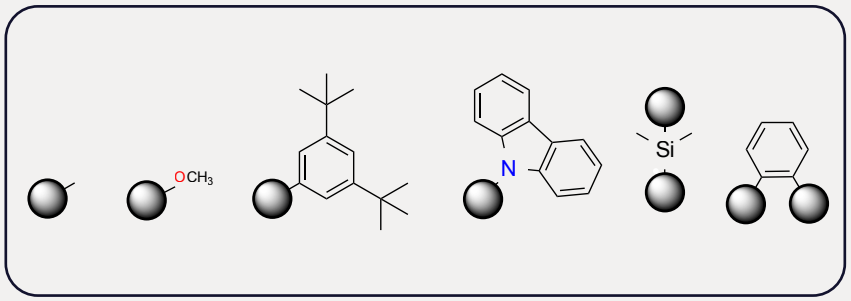
High Performance Computing (HPC) Cluster

- Lowest conformer only
- 55 stationary points
- 44 transition states
- 220 DFT jobs

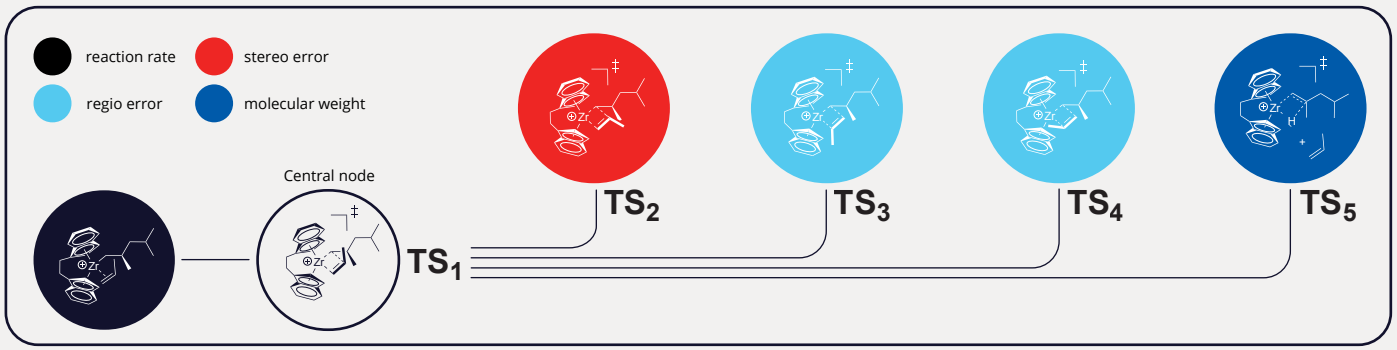
- 8 cores per DFT job
- ~2 days
- ~8,800 CPU hrs



(a) enantiopure isotactic propylene polymerization



(b) library for enumeration (sphere indicates dummy atom)

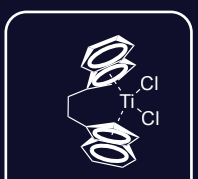
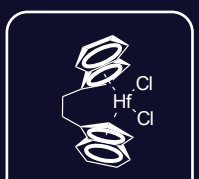
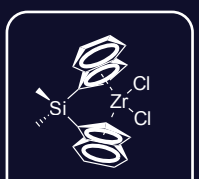
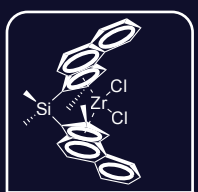
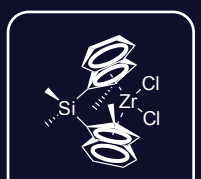
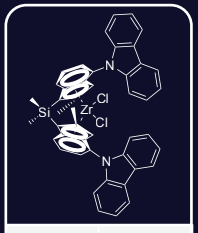
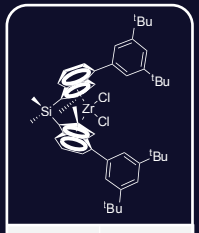
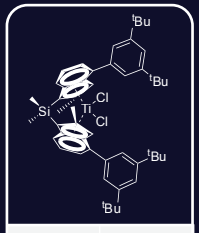
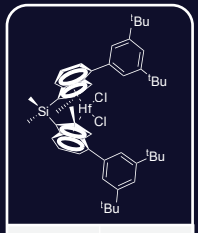
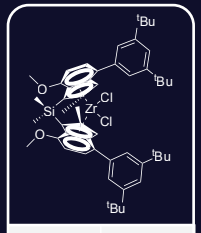


(c) reference network for catalyst design

Score functions for:

B3LYP-D3 with
PS-LACV3P++**//PS-LACVP*

- stereo error
- regio error
- molecular weight
- reaction rate

					
1.1 / 1.4	2.8 / 3.6	3.1 / 2.6	3.3 / 3.2	4.0 / 3.4	4.5 / 3.9
−7.3 / 1.3 × 10⁹	−1.9 / 2.7 × 10⁶	−3.4 / 3.4 × 10⁵	−2.4 / 3.6 × 10⁵	−0.2 / 1.5 × 10⁷	−2.3 / 1.3 × 10⁷
					
10 / 6.1	10 / 7.2	10.2 / 8.2	10.4 / 6.1	11.3 / 7.2	
5.2 / 1.8 × 10⁵	3.8 / 1.3 × 10⁷	6.0 / 1.7 × 10⁵	6.3 / 2.8 × 10⁴	2.2 / 5.1 × 10⁶	

Case Example 4

Screen substituents on the amine and epoxide in the epoxy–amine curing reaction and rank reactivity based on activation barrier

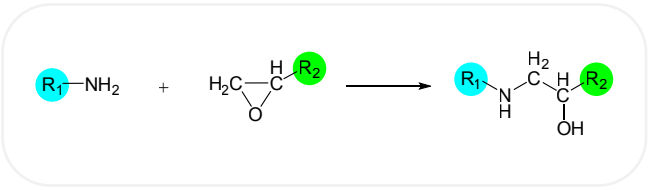
2500 reactions, 7500 stationary points including 2500 transition states

7500 CPU cores requested (queuing system)

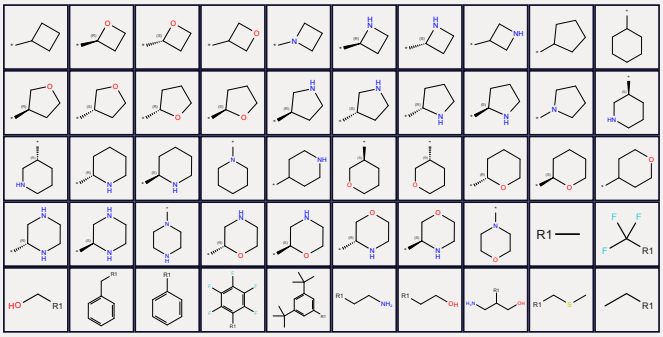
Macromodel engine, OPLS4 force field, lowest conformer only

~6.5 hrs walltime, ~ 2000 CPU hrs (estimate)

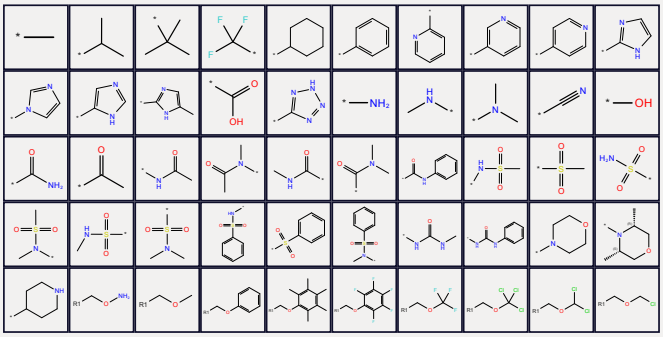
UMA_SM_OMOL v1.1



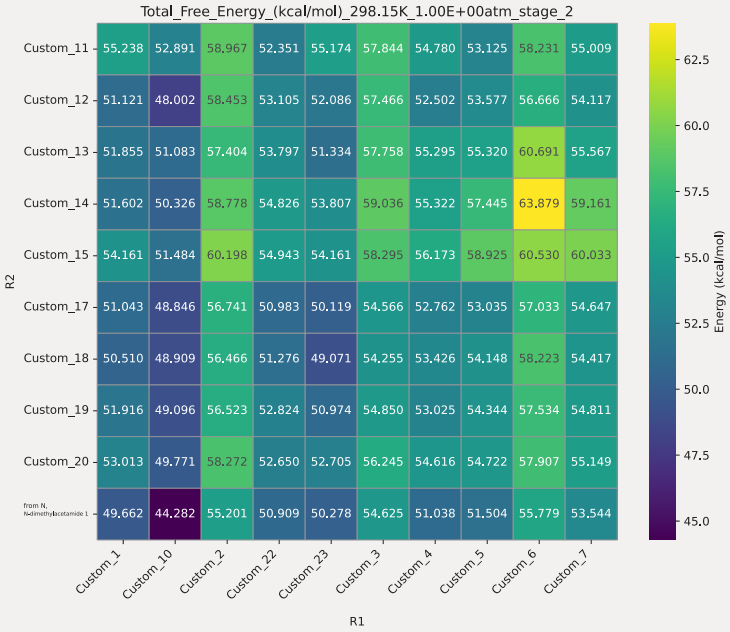
R_1-library



R_2-library



Total Free Energy



Activation barrier shown for 100 selected reactions (2486 of 2500 job(s) succeeded)

Contact us: ms-sales@schrodinger.com

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Learn more about RxnEnumProfiler