Electronic Supplementary Information for The (Not So) Simple Prediction of Enantioselectivity — A Pipeline for High-Fidelity Computations

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Using Molassembler to generate conformational ensembles

Release 1.1 of the open source Molassembler code[1,2] can be obtained at `https://scine.ethz.ch/download/molassembler` or, alternatively, at `https://github.com/qcscine/molassembler`. Extensive documentation is available.

The python code (using the Molassembler python API) distributed here to generate the TS structures from templates is available at `https://github.com/lcmd-epfl/molassembler_script`. The script identifies the Cp rings in the provided template. The template is interpreted as a graph with stereopermutators. The identified CP ring is then replaced by the alternative Cp-derivative, which is provided as SMILES. The script then calls the Molassembler python API to generate 50 conformers while constraining the first coordination sphere of the metal center as in the 3D coordinates of the template. These system-specific steps of the process are customizeable for other purposes (vide infra). All the generated structures are available as separate Cartesian coordinates files (.xyz).

Table S1 collects timings for the execution of the steps in the protocol. We note that the timings for the entire Molassembler-handled part of the process, *i.e.*, functionalization and conformer generation, is negligible w.r.t. the subsequent steps.

Transferability of the proposed strategy

Molassembler can be used to generate conformational ensembles of transition metal homogeneous catalysts. Conveniently, Molassembler is capable of interpreting, editing and manipulating arbitrary molecular graphs containing any element of the periodic table (*e.g.*, without intrinsic limitations due to Lewis rules, chirality or bond type definitions). Thus, exhaustive conformational sampling of transition metal homogeneous catalysts can be performed using distance geometry methods with minimal cost. Information on the timing of the structures generated in the work can be found in Table S1. Molassembler is also capable of performing constrained conformer generation (incorporating fixed atomic positions or fixing the stereochemistry of particular centers) and of exhaustively enumerating conformers of complex molecules by iterating over stereopermutators. For more details, we refer the reader to the original Molassembler paper and documentation.[1,2]

As an example of transferability, we generate conformational ensembles for two exemplary Pd complexes containing Buchwald-type (dialkylbiaryl) phosphines XPhos (2-Dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl) and JohnPhos ((2-Biphenyl)di-tert-butylphosphine),[3] and present the superimposed conformational ensembles in Figures S1 and S2 respectively. Conformer generation on a single core Intel(R) Core(TM) i7-9700K @ 3.60GHz CPU took 2.119 and 2.190 seconds respectively.

An example script (`phosphine_conformer_generator.py`) to generate conformational ensembles of phosphine-bearing transition metal complexes using Molassembler is available at `https://github.com/lcmd-epfl/molassembler_script`.

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Cat./P.G.	Timing (min.)				
	Molassembler*	Semiempirical opt.	DFT TS opt.	DFT frequency comp.	Elec. Energy comp.
1A	0.78	43.27	331.61	127.68	54.48
1B	0.74	41.16	520.64	148.36	66.28
1C	0.69	36.57	326.91	106.51	48.88
2A	0.58	47.42	187.03	82.67	37.09
2B	0.48	39.38	330.20	93.01	42.84
2C	0.19	23.28	176.75	69.51	35.02
3A	0.05	28.46	155.79	60.17	29.29
3B	0.08	28.37	206.81	68.69	33.52
3C	0.09	24.47	123.68	46.78	24.97
4A	0.58	47.34	239.85	108.38	48.21
4B	0.65	46.59	368.91	107.12	46.60
4C	0.37	32.11	196.64	75.42	31.24

Table S1. Average real-time timings in minutes for the steps of the procedure on 24 Intel(R) Xeon(R) CPU E5-2650 v4 @ 2.20GHz cores. * : Functionalization and conformer generation were performed using Molassembler on a single workstation CPU; timing as average over pathways (four executions) instead of over structures.

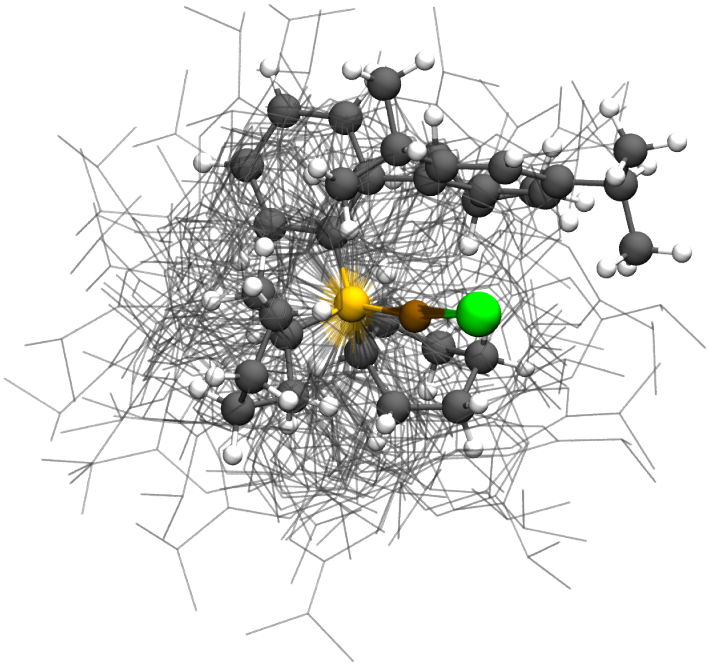

Figure S1. Conformational ensemble of Pd(XPhos)(Cl).

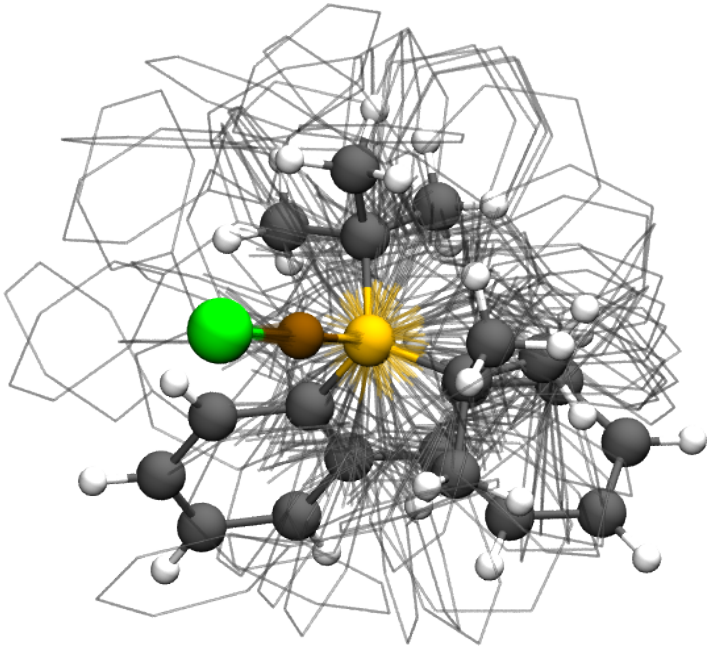

Figure S2. Conformational ensemble of Pd(JohnPhos)(Cl).

Boltzmann-weighted enantiomeric ratios

For each selectivity (R/S), effective relative free energies $\Delta G^{TS}_{eff,R/S}$ were computed as

$$\Delta G^{TS}_{eff,R/S} = -RT \ln\left(\sum_i e^{\Delta G^{TS}_{i,R/S}/RT}\right)$$

where T=296.15 K and R is the gas constant and $\Delta G^{TS}_{i,R/S}$ runs over the relative energies of all TS in the pathway with respect to the lowest energy conformer, assuming Curtin-Hammett conditions. Enantiomeric ratios (*er*) were then computed from the theoretical kinetic constants, given by

$$k_{R/S} = exp(\frac{-\Delta G^{TS}_{eff,R/S}}{kT})$$

as

$$er_{R/S} = 100 \times \frac{k_{R/S}}{k_R + k_S}$$

in which we assume identical concentrations and pre-exponential factors for all pathways. For an in-depth discussion on Boltzmann-weighting of conformers and activation energies, we refer the reader to a recent publication by Williams.[4]

Density Functional Theory computations

The B3PW91 exchange-correlation functional was used based on previous reports indicating its accuracy for geometry optimizations[5] as well as extensive benchmarking that showed its accuracy for energy computations.[6,7]

Figure S3 gives *er* values obtained using solvated electronic energies (*i.e.*, without free energy corrections, Figure S3a), free energy corrections but no solvation corrections (Figure S3b) and electronic energies (Figure S3c). Figure S4a shows *er* values obtained from free energies at the PBE0-D3/def2-TZVP SMD(ethanol)[8–12]//PBE0-D3/def2-SVP level. Figures S4b and S4c provide *er* values obtained from solvated electronic energies at the ωB97xd/def2-TZVP SMD(ethanol)[13]//B3PW91/def2-SVP and M06/def2-TZVP SMD(ethanol)[14]//B3PW91/def2-SVP levels. A comparison between Figure S4a and panel a from Figure 6 in the main text is given in Figure S5. B3PW91/def2-TZVP SMD(ethanol)//B3PW91-D3BJ/def2-SVP results are collected in Tables S2-S13.

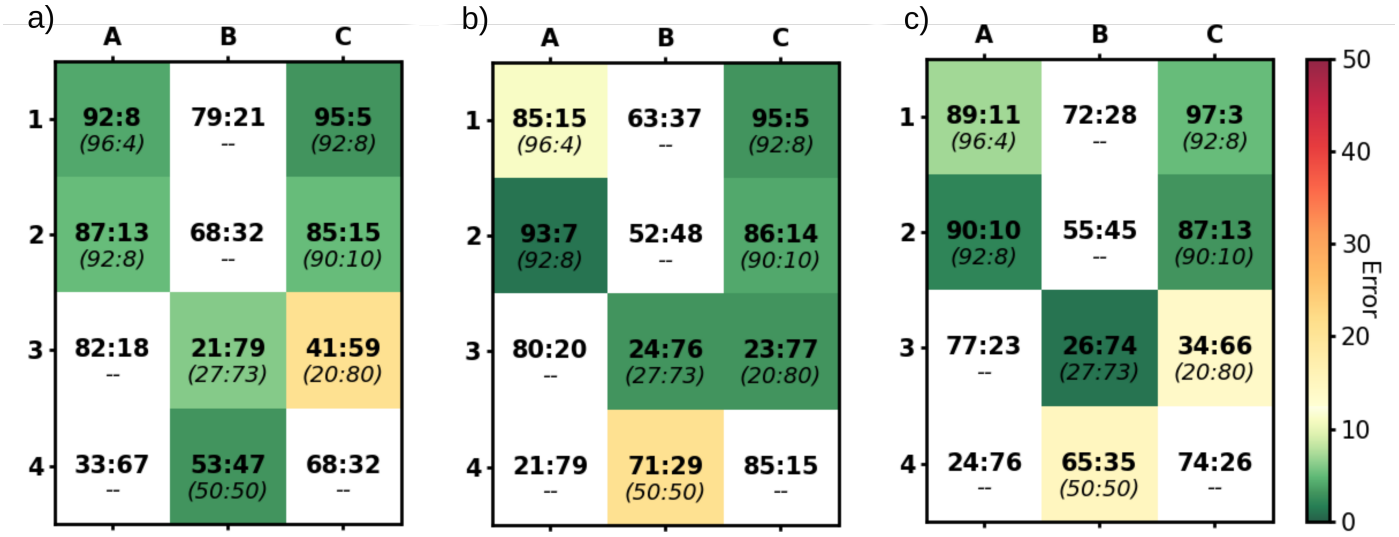

Figure S3. Comparison between predicted (top, bold) and experimental (bottom, italic) pro-*R* *er* colored by error for each catalyst and protecting group combination (Boltzmann weighting all TS). a) Solvated electronic energies computed at the B3PW91-D3BJ/def2-TZVP SMD(ethanol)//B3PW91-D3BJ/def2-SVP level. b) Free energies computed at the B3PW91-D3BJ/def2-TZVP//B3PW91-D3BJ/def2-SVP level. c) Electronic energies computed at the B3PW91-D3BJ/def2-TZVP//B3PW91-D3BJ/def2-SVP level.

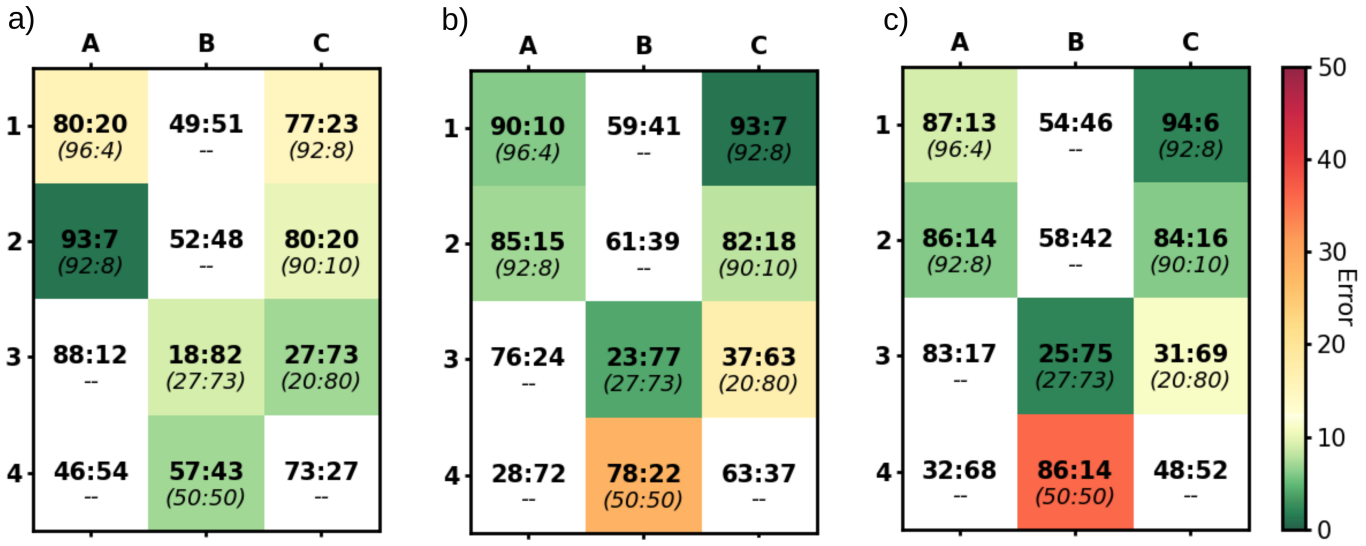

Figure S4. Comparison between predicted (top, bold) and experimental (bottom, italic) pro-*R er* colored by error for each catalyst and protecting group combination (Boltzmann weighting all TS). a) Free energies computed at the PBE0-D3/def2-TZVP SMD(ethanol)//PBE0-D3/def2-SVP level. b) Solvated electronic energies computed at the ωB97xd/def2-TZVP SMD(ethanol)//B3PW91-D3BJ/def2-SVP level. c) Solvated electronic energies computed at the M06/def2-TZVP SMD(ethanol)//B3PW91-D3BJ/def2-SVP level.

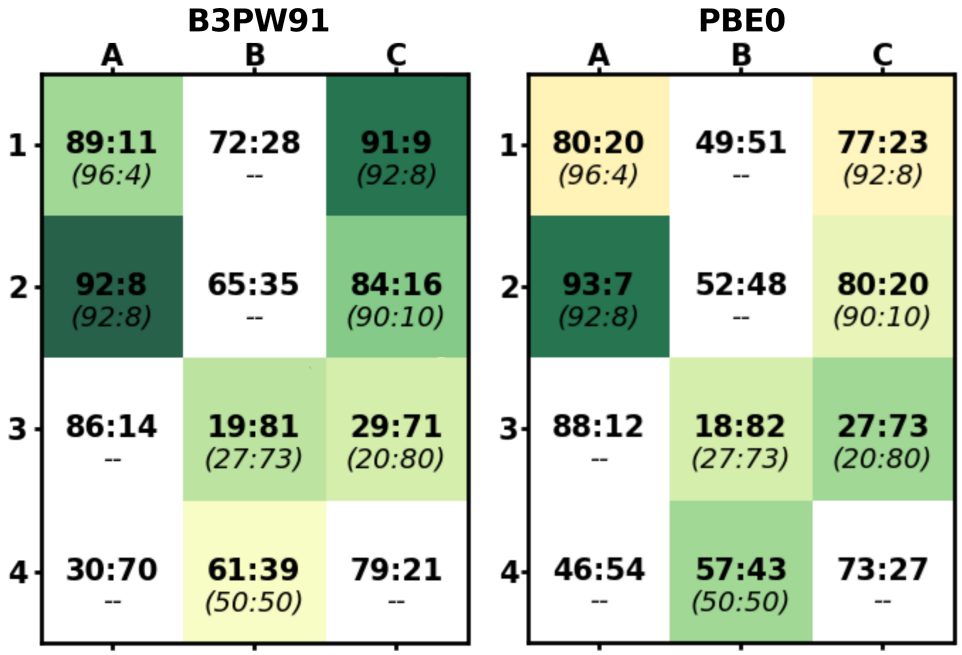

Figure S5. Comparison between predicted (top, bold) and experimental (bottom, italic) pro-*R er* colored by error for each catalyst and protecting group combination (Boltzmann weighting all TS) computed at the B3PW91-D3/def2-TZVP SMD(ethanol)//B3PW91-D3/def2-SVP and PBE0-D3/def2-TZVP SMD(ethanol)//PBE0-D3/def2-SVP levels.

Structure	G (Ha)	G (kcal/mol)	E (Ha)	E (kcal/mol)	ΔG_{sol} (Ha)	ΔG_{sol} (kcal/mol)
US-15	-2319.447505	-1455474.18	-2320.164173	-1455923.90	-0.003060	-1.92
US-9	-2319.441222	-1455470.24	-2320.156766	-1455919.25	-0.002167	-1.36
DR-11	-2319.444252	-1455472.14	-2320.159449	-1455920.94	-0.002853	-1.79
DR-12	-2319.439374	-1455469.08	-2320.154782	-1455918.01	-0.003554	-2.23
DR-2	-2319.447771	-1455474.35	-2320.165306	-1455924.61	-0.004351	-2.73
DR-5	-2319.44425	-1455472.14	-2320.159451	-1455920.94	-0.002853	-1.79
DR-6	-2319.447771	-1455474.35	-2320.165306	-1455924.61	-0.004351	-2.73
DR-7	-2319.443765	-1455471.84	-2320.159565	-1455921.01	-0.003522	-2.21
DS-13	-2319.44572	-1455473.06	-2320.161671	-1455922.33	-0.002821	-1.77
DS-14	-2319.434267	-1455465.88	-2320.148183	-1455913.87	-0.003729	-2.34
DS-2	-2319.435778	-1455466.83	-2320.152445	-1455916.54	-0.005769	-3.62
DS-8	-2319.447894	-1455474.43	-2320.164866	-1455924.33	-0.003426	-2.15
UR-11	-2319.445002	-1455472.61	-2320.161309	-1455922.10	-0.004685	-2.94
UR-2	-2319.451664	-1455476.79	-2320.168553	-1455926.65	-0.002677	-1.68
UR-3	-2319.451663	-1455476.79	-2320.168553	-1455926.65	-0.002677	-1.68

Table S2. Results for **1A**.

Structure	G (Ha)	G (kcal/mol)	E (Ha)	E (kcal/mol)	ΔG_{sol} (Ha)	ΔG_{sol} (kcal/mol)
US-10	-2244.221569	-1408269.23	-2244.934404	-1408716.54	-0.004988	-3.13
US-12	-2244.217161	-1408266.47	-2244.929497	-1408713.46	-0.004127	-2.59
US-1	-2244.220164	-1408268.35	-2244.932575	-1408715.40	-0.004558	-2.86
US-2	-2244.21804	-1408267.02	-2244.930543	-1408714.12	-0.004382	-2.75
US-4	-2244.218922	-1408267.57	-2244.932171	-1408715.14	-0.004860	-3.05
US-5	-2244.19301	-1408251.31	-2244.90491	-1408698.04	-0.003139	-1.97
US-6	-2244.221569	-1408269.23	-2244.934404	-1408716.54	-0.004988	-3.13
US-8	-2244.217158	-1408266.46	-2244.929496	-1408713.46	-0.004127	-2.59
US-9	-2244.221566	-1408269.23	-2244.934402	-1408716.54	-0.004988	-3.13
DR-10	-2244.219427	-1408267.89	-2244.931982	-1408715.02	-0.004797	-3.01
DR-18	-2244.219426	-1408267.89	-2244.931982	-1408715.02	-0.004797	-3.01
DR-5	-2244.216152	-1408265.83	-2244.92806	-1408712.56	-0.004924	-3.09
DR-9	-2244.197848	-1408254.35	-2244.909343	-1408700.82	-0.004032	-2.53
DS-3	-2244.220017	-1408268.26	-2244.932424	-1408715.30	-0.004558	-2.86
DS-5	-2244.220022	-1408268.26	-2244.93243	-1408715.30	-0.004558	-2.86
UR-11	-2244.201117	-1408256.40	-2244.913878	-1408703.66	-0.003442	-2.16
UR-15	-2244.224616	-1408271.14	-2244.936743	-1408718.01	-0.004271	-2.68
UR-2	-2244.207268	-1408260.26	-2244.921474	-1408708.43	-0.004255	-2.67
UR-6	-2244.21476	-1408264.96	-2244.925681	-1408711.07	-0.003857	-2.42
UR-7	-2244.214761	-1408264.96	-2244.925683	-1408711.07	-0.003857	-2.42

Table S3. Results for **1B**.

Structure	G (Ha)	G (kcal/mol)	E (Ha)	E (kcal/mol)	ΔG_{sol} (Ha)	ΔG_{sol} (kcal/mol)
US-0	-2126.337906	-1334296.17	-2126.969591	-1334692.56	-0.003458	-2.17
US-14	-2126.332851	-1334293.00	-2126.963759	-1334688.90	-0.001578	-0.99
US-15	-2126.341112	-1334298.18	-2126.971865	-1334693.99	-0.003315	-2.08
US-4	-2126.337908	-1334296.17	-2126.969592	-1334692.56	-0.003458	-2.17
US-7	-2126.341109	-1334298.18	-2126.971865	-1334693.99	-0.003315	-2.08
DR-15	-2126.337123	-1334295.68	-2126.967395	-1334691.18	-0.002040	-1.28
DR-3	-2126.340611	-1334297.87	-2126.970217	-1334692.95	-0.002805	-1.76
DR-4	-2126.339449	-1334297.14	-2126.970411	-1334693.08	-0.004892	-3.07
DR-6	-2126.335052	-1334294.38	-2126.967349	-1334691.15	-0.004653	-2.92
DR-7	-2126.340631	-1334297.88	-2126.970219	-1334692.96	-0.002805	-1.76
DS-10	-2126.339972	-1334297.47	-2126.971739	-1334693.91	-0.002151	-1.35
DS-12	-2126.337413	-1334295.86	-2126.96777	-1334691.42	-0.001880	-1.18
DS-15	-2126.337403	-1334295.86	-2126.967771	-1334691.42	-0.001896	-1.19
DS-1	-2126.33743	-1334295.87	-2126.96777	-1334691.42	-0.001880	-1.18
DS-2	-2126.338634	-1334296.63	-2126.969536	-1334692.53	-0.002932	-1.84
DS-4	-2126.338635	-1334296.63	-2126.969536	-1334692.53	-0.002932	-1.84
DS-5	-2126.331548	-1334292.18	-2126.964286	-1334689.23	-0.003617	-2.27
UR-0	-2126.33923	-1334297.00	-2126.97062	-1334693.21	-0.001482	-0.93
UR-10	-2126.342025	-1334298.76	-2126.974304	-1334695.52	-0.001880	-1.18
UR-11	-2126.339231	-1334297.00	-2126.97062	-1334693.21	-0.001482	-0.93
UR-12	-2126.339228	-1334297.00	-2126.970619	-1334693.21	-0.001482	-0.93
UR-6	-2126.346617	-1334301.64	-2126.978066	-1334697.88	-0.002327	-1.46

Table S4. Results for **1C**.

Structure	G (Ha)	G (kcal/mol)	E (Ha)	E (kcal/mol)	ΔG_{sol} (Ha)	ΔG_{sol} (kcal/mol)
US-10	-1936.049579	-1214888.54	-1936.665440	-1215274.99	-0.000749	-0.47
US-12	-1936.043706	-1214884.85	-1936.658945	-1215270.92	0.000080	0.05
US-13	-1936.049579	-1214888.54	-1936.665441	-1215274.99	-0.000749	-0.47
US-15	-1936.051202	-1214889.55	-1936.667127	-1215276.05	-0.000861	-0.54
US-16	-1936.048407	-1214887.80	-1936.664377	-1215274.33	-0.000701	-0.44
US-2	-1936.048410	-1214887.80	-1936.664380	-1215274.33	-0.000701	-0.44
US-6	-1936.046473	-1214886.59	-1936.662299	-1215273.02	-0.000908	-0.57
US-9	-1936.049336	-1214888.38	-1936.665236	-1215274.87	-0.001116	-0.70
DR-0	-1936.049591	-1214888.54	-1936.666810	-1215275.85	-0.001705	-1.07
DR-10	-1936.043094	-1214884.47	-1936.659713	-1215271.40	-0.002279	-1.43
DR-11	-1936.043273	-1214884.58	-1936.658507	-1215270.64	-0.001434	-0.90
DR-14	-1936.042143	-1214883.87	-1936.658211	-1215270.46	-0.001179	-0.74
DR-15	-1936.053556	-1214891.03	-1936.669683	-1215277.66	-0.002741	-1.72
DR-1	-1936.045157	-1214885.76	-1936.659937	-1215271.54	-0.001610	-1.01
DR-4	-1936.047904	-1214887.48	-1936.662096	-1215272.90	-0.000829	-0.52
DS-11	-1936.048044	-1214887.57	-1936.664657	-1215274.50	-0.002215	-1.39
DS-4	-1936.048300	-1214887.73	-1936.663485	-1215273.77	-0.000622	-0.39
DS-6	-1936.038299	-1214881.46	-1936.654263	-1215267.98	-0.001594	-1.00
UR-0	-1936.052699	-1214890.49	-1936.668657	-1215277.01	-0.000175	-0.11
UR-4	-1936.054002	-1214891.31	-1936.670842	-1215278.38	-0.000414	-0.26
UR-5	-1936.046888	-1214886.85	-1936.663872	-1215274.01	-0.001657	-1.04
UR-9	-1936.037869	-1214881.19	-1936.654089	-1215267.87	-0.000175	-0.11

Table S5. Results for **2A**.

Structure	G (Ha)	G (kcal/mol)	E (Ha)	E (kcal/mol)	ΔG_{sol} (Ha)	ΔG_{sol} (kcal/mol)
US-10	-1860.822619	-1167682.94	-1861.434193	-1168066.71	-0.002598	-1.63
US-16	-1860.825164	-1167684.54	-1861.437550	-1168068.82	-0.002359	-1.48
US-1	-1860.801468	-1167669.67	-1861.414387	-1168054.28	-0.001291	-0.81
US-2	-1860.825162	-1167684.54	-1861.437550	-1168068.82	-0.002359	-1.48
US-3	-1860.816564	-1167679.14	-1861.428038	-1168062.85	-0.001928	-1.21
US-9	-1860.817108	-1167679.48	-1861.426971	-1168062.18	-0.001466	-0.92
DR-11	-1860.813474	-1167677.20	-1861.425888	-1168061.50	-0.002135	-1.34
DR-13	-1860.803372	-1167670.86	-1861.416061	-1168055.33	-0.001976	-1.24
DR-15	-1860.802254	-1167670.16	-1861.413643	-1168053.81	-0.001801	-1.13
DR-16	-1860.820958	-1167681.90	-1861.432078	-1168065.38	-0.001849	-1.16
DR-17	-1860.791747	-1167663.57	-1861.403301	-1168047.32	-0.001625	-1.02
DR-18	-1860.797350	-1167667.08	-1861.410349	-1168051.75	-0.002550	-1.60
DR-19	-1860.820949	-1167681.89	-1861.434210	-1168066.72	-0.003108	-1.95
DR-1	-1860.823226	-1167683.32	-1861.434331	-1168066.80	-0.002151	-1.35
DR-22	-1860.803384	-1167670.87	-1861.416073	-1168055.34	-0.001976	-1.24
DR-4	-1860.820949	-1167681.89	-1861.434210	-1168066.72	-0.003108	-1.95
DR-6	-1860.802256	-1167670.16	-1861.413644	-1168053.81	-0.001801	-1.13
DS-0	-1860.802381	-1167670.24	-1861.414049	-1168054.07	-0.001912	-1.20
DS-10	-1860.815486	-1167678.46	-1861.426448	-1168061.85	-0.002343	-1.47
DS-11	-1860.820001	-1167681.30	-1861.432431	-1168065.60	-0.002884	-1.81
DS-12	-1860.826496	-1167685.37	-1861.438843	-1168069.63	-0.002183	-1.37
DS-13	-1860.824862	-1167684.35	-1861.435800	-1168067.72	-0.001785	-1.12
DS-1	-1860.805877	-1167672.44	-1861.418280	-1168056.72	-0.002359	-1.48
DS-2	-1860.802379	-1167670.24	-1861.414051	-1168054.07	-0.001912	-1.20
DS-9	-1860.791311	-1167663.29	-1861.404586	-1168048.13	-0.002566	-1.61
UR-10	-1860.817442	-1167679.69	-1861.428683	-1168063.25	-0.001657	-1.04
UR-12	-1860.817443	-1167679.69	-1861.428682	-1168063.25	-0.001657	-1.04
UR-1	-1860.820686	-1167681.73	-1861.431998	-1168065.33	-0.002645	-1.66
UR-2	-1860.827493	-1167686.00	-1861.439374	-1168069.96	-0.002024	-1.27
UR-3	-1860.827492	-1167686.00	-1861.439374	-1168069.96	-0.002024	-1.27
UR-8	-1860.817443	-1167679.69	-1861.428684	-1168063.25	-0.001657	-1.04

Table S6. Results for **2B**.

Structure	G (Ha)	G (kcal/mol)	E (Ha)	E (kcal/mol)	ΔG_{sol} (Ha)	ΔG_{sol} (kcal/mol)
US-6	-1742.940624	-1093710.93	-1743.471941	-1094044.33	0.000016	0.01
DR-0	-1742.940629	-1093710.93	-1743.470501	-1094043.43	0.000048	0.03
DR-2	-1742.943723	-1093712.87	-1743.473110	-1094045.07	-0.000669	-0.42
DR-4	-1742.946653	-1093714.71	-1743.477711	-1094047.95	-0.002056	-1.29
DS-10	-1742.942709	-1093712.24	-1743.473127	-1094045.08	-0.001817	-1.14
DS-11	-1742.931211	-1093705.02	-1743.462328	-1094038.30	-0.001243	-0.78
DS-12	-1742.946421	-1093714.57	-1743.477246	-1094047.66	-0.000526	-0.33
DS-1	-1742.938471	-1093709.58	-1743.469636	-1094042.89	-0.001450	-0.91
DS-5	-1742.941249	-1093711.32	-1743.471426	-1094044.01	0.000335	0.21
UR-10	-1742.937030	-1093708.67	-1743.468525	-1094042.19	0.000781	0.49
UR-11	-1742.931405	-1093705.14	-1743.462546	-1094038.44	-0.000733	-0.46
UR-12	-1742.941578	-1093711.53	-1743.472540	-1094044.71	0.000988	0.62
UR-16	-1742.949122	-1093716.26	-1743.480162	-1094049.49	-0.000143	-0.09
UR-3	-1742.945630	-1093714.07	-1743.476321	-1094047.08	-0.000510	-0.32
UR-4	-1742.940610	-1093710.92	-1743.471700	-1094044.18	-0.000032	-0.02
UR-7	-1742.939527	-1093710.24	-1743.470689	-1094043.55	-0.000048	-0.03

Table S7. Results for **2C**.

Structure	G (Ha)	G (kcal/mol)	E (Ha)	E (kcal/mol)	ΔG_{sol} (Ha)	ΔG_{sol} (kcal/mol)
US-12	-1668.923170	-1047264.31	-1669.471433	-1047608.35	-0.001801	-1.13
US-13	-1668.924990	-1047265.45	-1669.472765	-1047609.19	-0.002327	-1.46
US-15	-1668.926462	-1047266.38	-1669.474894	-1047610.52	-0.002279	-1.43
US-6	-1668.913662	-1047258.34	-1669.461231	-1047601.95	-0.001450	-0.91
US-7	-1668.919899	-1047262.26	-1669.468583	-1047606.56	-0.001928	-1.21
US-8	-1668.922595	-1047263.95	-1669.471470	-1047608.37	-0.002183	-1.37
DR-0	-1668.921683	-1047263.38	-1669.469662	-1047607.24	-0.002534	-1.59
DR-10	-1668.921674	-1047263.37	-1669.469008	-1047606.83	-0.002390	-1.50
DR-11	-1668.919289	-1047261.87	-1669.467729	-1047606.03	-0.002438	-1.53
DR-3	-1668.919808	-1047262.20	-1669.467151	-1047605.66	-0.002104	-1.32
DR-4	-1668.919288	-1047261.87	-1669.467728	-1047606.02	-0.002438	-1.53
DR-5	-1668.916368	-1047260.04	-1669.464832	-1047604.21	-0.002757	-1.73
DR-7	-1668.928403	-1047267.59	-1669.475820	-1047611.10	-0.003649	-2.29
DS-11	-1668.917934	-1047261.02	-1669.466545	-1047605.28	-0.003139	-1.97
DS-13	-1668.924482	-1047265.13	-1669.471774	-1047608.56	-0.002598	-1.63
DS-14	-1668.921379	-1047263.19	-1669.470224	-1047607.59	-0.003586	-2.25
DS-17	-1668.907527	-1047254.49	-1669.456463	-1047598.96	-0.002948	-1.85
DS-19	-1668.924446	-1047265.11	-1669.473148	-1047609.43	-0.003203	-2.01
DS-5	-1668.924950	-1047265.43	-1669.472796	-1047609.20	-0.002789	-1.75
UR-11	-1668.925329	-1047265.66	-1669.474536	-1047610.30	-0.002311	-1.45
UR-13	-1668.919330	-1047261.90	-1669.468475	-1047606.49	-0.001689	-1.06
UR-14	-1668.924813	-1047265.34	-1669.473832	-1047609.85	-0.001801	-1.13
UR-2	-1668.921883	-1047263.50	-1669.470794	-1047607.95	-0.002247	-1.41
UR-4	-1668.928990	-1047267.96	-1669.476680	-1047611.64	-0.002072	-1.30
UR-5	-1668.925329	-1047265.66	-1669.474535	-1047610.30	-0.002311	-1.45
UR-7	-1668.922165	-1047263.68	-1669.471078	-1047608.13	-0.001100	-0.69
UR-8	-1668.916678	-1047260.24	-1669.465045	-1047604.34	-0.001673	-1.05

Table S8. Results for **3A**.

Structure	G (Ha)	G (kcal/mol)	E (Ha)	E (kcal/mol)	ΔG_{sol} (Ha)	ΔG_{sol} (kcal/mol)
US-10	-1593.668069	-1000041.06	-1594.212221	-1000382.52	-0.002566	-1.61
US-11	-1593.694918	-1000057.90	-1594.238618	-1000399.08	-0.003219	-2.02
US-12	-1593.675792	-1000045.90	-1594.221598	-1000388.40	-0.002629	-1.65
US-13	-1593.690820	-1000055.33	-1594.235274	-1000396.98	-0.003315	-2.08
US-3	-1593.685832	-1000052.20	-1594.229723	-1000393.50	-0.003394	-2.13
US-9	-1593.696760	-1000059.06	-1594.241056	-1000400.61	-0.003602	-2.26
DR-0	-1593.689988	-1000054.81	-1594.233624	-1000395.95	-0.003713	-2.33
DR-12	-1593.674250	-1000044.93	-1594.218290	-1000386.32	-0.003155	-1.98
DR-15	-1593.693350	-1000056.92	-1594.238425	-1000398.96	-0.003745	-2.35
DR-3	-1593.670660	-1000042.68	-1594.215264	-1000384.43	-0.003315	-2.08
DR-4	-1593.686935	-1000052.89	-1594.231568	-1000394.66	-0.004032	-2.53
DR-5	-1593.692914	-1000056.65	-1594.237003	-1000398.07	-0.003139	-1.97
DS-0	-1593.669021	-1000041.65	-1594.213998	-1000383.63	-0.002900	-1.82
DS-3	-1593.690749	-1000055.29	-1594.235039	-1000396.84	-0.003809	-2.39
DS-7	-1593.679492	-1000048.22	-1594.224230	-1000390.05	-0.003108	-1.95
DS-8	-1593.696420	-1000058.85	-1594.240718	-1000400.40	-0.003028	-1.90
UR-6	-1593.694990	-1000057.95	-1594.239643	-1000399.72	-0.003012	-1.89

Table S9. Results for **3B**.

Structure	G (Ha)	G (kcal/mol)	E (Ha)	E (kcal/mol)	ΔG_{sol} (Ha)	ΔG_{sol} (kcal/mol)
US-11	-1475.816599	-926088.20	-1476.279119	-926378.43	-0.001068	-0.67
US-13	-1475.810753	-926084.53	-1476.273426	-926374.86	-0.001594	-1.00
US-14	-1475.815371	-926087.43	-1476.278523	-926378.06	-0.001801	-1.13
US-18	-1475.818262	-926089.24	-1476.281438	-926379.89	-0.001960	-1.23
US-1	-1475.817881	-926089.00	-1476.281614	-926380.00	-0.002374	-1.49
US-2	-1475.815242	-926087.35	-1476.278545	-926378.07	-0.002040	-1.28
US-3	-1475.809410	-926083.69	-1476.273017	-926374.60	-0.000861	-0.54
US-4	-1475.818262	-926089.24	-1476.281438	-926379.89	-0.001960	-1.23
DR-0	-1475.808007	-926082.81	-1476.271119	-926373.41	-0.002406	-1.51
DR-1	-1475.815705	-926087.64	-1476.279271	-926378.53	-0.001865	-1.17
DR-3	-1475.813854	-926086.48	-1476.277114	-926377.18	-0.002470	-1.55
DR-4	-1475.813857	-926086.48	-1476.277116	-926377.18	-0.002470	-1.55
DR-6	-1475.810295	-926084.24	-1476.273726	-926375.05	-0.003108	-1.95
DS-0	-1475.817329	-926088.66	-1476.280584	-926379.35	-0.001928	-1.21
DS-11	-1475.809208	-926083.56	-1476.272804	-926374.47	-0.001817	-1.14
DS-13	-1475.815872	-926087.74	-1476.278666	-926378.15	-0.001594	-1.00
DS-5	-1475.815284	-926087.37	-1476.278363	-926377.96	-0.001434	-0.90
DS-7	-1475.817260	-926088.61	-1476.279886	-926378.91	-0.002056	-1.29
UR-10	-1475.815247	-926087.35	-1476.278541	-926378.07	-0.001450	-0.91
UR-19	-1475.818562	-926089.43	-1476.281296	-926379.80	-0.001068	-0.67

Table S10. Results for **3C**.

Structure	G (Ha)	G (kcal/mol)	E (Ha)	E (kcal/mol)	ΔG_{sol} (Ha)	ΔG_{sol} (kcal/mol)
US-10	-1826.087113	-1145886.10	-1826.745238	-1146299.08	-0.002773	-1.74
US-9	-1826.080247	-1145881.79	-1826.738388	-1146294.78	-0.003331	-2.09
DR-6	-1826.084626	-1145884.54	-1826.741541	-1146296.76	-0.003092	-1.94
DR-7	-1826.089872	-1145887.83	-1826.745897	-1146299.49	-0.002837	-1.78
DR-9	-1826.082617	-1145883.28	-1826.740095	-1146295.85	-0.003363	-2.11
DS-10	-1826.084488	-1145884.45	-1826.741690	-1146296.85	-0.003570	-2.24
DS-13	-1826.091157	-1145888.64	-1826.748008	-1146300.82	-0.003076	-1.93
DS-17	-1826.075015	-1145878.51	-1826.731764	-1146290.62	-0.002996	-1.88
DS-18	-1826.071857	-1145876.52	-1826.730283	-1146289.69	-0.004319	-2.71
DS-1	-1826.078509	-1145880.70	-1826.736077	-1146293.33	-0.003984	-2.50
DS-2	-1826.070355	-1145875.58	-1826.728574	-1146288.62	-0.002821	-1.77
UR-0	-1826.082103	-1145882.95	-1826.739197	-1146295.29	-0.001992	-1.25
UR-13	-1826.083739	-1145883.98	-1826.741394	-1146296.67	-0.003219	-2.02
UR-1	-1826.088363	-1145886.88	-1826.744980	-1146298.92	-0.002693	-1.69

Table S11. Results for **4A**.

Structure	G (Ha)	G (kcal/mol)	E (Ha)	E (kcal/mol)	ΔG_{sol} (Ha)	ΔG_{sol} (kcal/mol)
US-10	-1750.849995	-1098674.13	-1751.503495	-1099084.21	-0.003761	-2.36
US-12	-1750.847235	-1098672.40	-1751.501242	-1099082.79	-0.003570	-2.24
US-14	-1750.860118	-1098680.48	-1751.512367	-1099089.77	-0.004064	-2.55
US-15	-1750.856967	-1098678.50	-1751.511445	-1099089.20	-0.003426	-2.15
US-4	-1750.857968	-1098679.13	-1751.512469	-1099089.84	-0.004398	-2.76
US-7	-1750.860576	-1098680.77	-1751.512924	-1099090.12	-0.003841	-2.41
DR-11	-1750.860594	-1098680.78	-1751.514088	-1099090.85	-0.004494	-2.82
DR-2	-1750.852011	-1098675.39	-1751.505457	-1099085.44	-0.004398	-2.76
DR-4	-1750.838373	-1098666.84	-1751.492483	-1099077.30	-0.004080	-2.56
DR-5	-1750.839621	-1098667.62	-1751.493729	-1099078.08	-0.003506	-2.20
DR-8	-1750.860598	-1098680.78	-1751.51409	-1099090.86	-0.004494	-2.82
DS-10	-1750.855494	-1098677.58	-1751.50951	-1099087.98	-0.003586	-2.25
DS-2	-1750.833039	-1098663.49	-1751.487088	-1099073.91	-0.003347	-2.10
UR-11	-1750.833866	-1098664.01	-1751.488213	-1099074.62	-0.002821	-1.77
UR-14	-1750.842542	-1098669.45	-1751.495709	-1099079.32	-0.003076	-1.93
UR-2	-1750.836515	-1098665.67	-1751.490781	-1099076.23	-0.003888	-2.44

Table S12. Results for **4B**.

Structure	G (Ha)	G (kcal/mol)	E (Ha)	E (kcal/mol)	ΔG_{sol} (Ha)	ΔG_{sol} (kcal/mol)
US-0	-1632.980384	-1024709.89	-1633.553634	-1025069.61	-0.002183	-1.37
US-15	-1632.966379	-1024701.10	-1633.539258	-1025060.59	-0.001275	-0.80
US-17	-1632.980457	-1024709.93	-1633.553261	-1025069.37	-0.002263	-1.42
US-21	-1632.980653	-1024710.06	-1633.552733	-1025069.04	-0.001020	-0.64
US-5	-1632.969219	-1024702.88	-1633.543420	-1025063.20	-0.002247	-1.41
US-9	-1632.977559	-1024708.12	-1633.550719	-1025067.78	-0.001562	-0.98
DR-0	-1632.978993	-1024709.01	-1633.550761	-1025067.80	-0.002008	-1.26
DR-11	-1632.977005	-1024707.77	-1633.549656	-1025067.11	-0.002964	-1.86
DR-15	-1632.977755	-1024708.24	-1633.549331	-1025066.91	-0.002406	-1.51
DR-17	-1632.983071	-1024711.57	-1633.555803	-1025070.97	-0.003888	-2.44
DR-3	-1632.979009	-1024709.02	-1633.552154	-1025068.68	-0.003108	-1.95
DR-5	-1632.98178	-1024710.76	-1633.553903	-1025069.78	-0.002741	-1.72
DR-8	-1632.982801	-1024711.40	-1633.555200	-1025070.59	-0.003522	-2.21
DS-0	-1632.980709	-1024710.09	-1633.552680	-1025069.01	-0.002725	-1.71
DS-14	-1632.978709	-1024708.84	-1633.550870	-1025067.87	-0.002996	-1.88
DS-1	-1632.967975	-1024702.10	-1633.540859	-1025061.59	-0.003968	-2.49
DS-4	-1632.954872	-1024693.88	-1633.527412	-1025053.15	-0.002104	-1.32
DS-7	-1632.975878	-1024707.06	-1633.548322	-1025066.27	-0.003490	-2.19
DS-8	-1632.973365	-1024705.48	-1633.546210	-1025064.95	-0.002773	-1.74
DS-9	-1632.982128	-1024710.98	-1633.553549	-1025069.55	-0.002853	-1.79
UR-11	-1632.979515	-1024709.34	-1633.552305	-1025068.77	-0.001530	-0.96
UR-12	-1632.979981	-1024709.63	-1633.552346	-1025068.80	-0.002311	-1.45
UR-13	-1632.973996	-1024705.88	-1633.546432	-1025065.09	-0.002088	-1.31
UR-15	-1632.979503	-1024709.33	-1633.551266	-1025068.12	-0.001562	-0.98
UR-1	-1632.975972	-1024707.12	-1633.548263	-1025066.24	-0.000829	-0.52
UR-3	-1632.981842	-1024710.80	-1633.554205	-1025069.97	-0.002295	-1.44
UR-4	-1632.968715	-1024702.57	-1633.541181	-1025061.79	-0.001705	-1.07
UR-7	-1632.978102	-1024708.46	-1633.550083	-1025067.38	-0.001450	-0.91

Table S13. Results for **4C**.

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