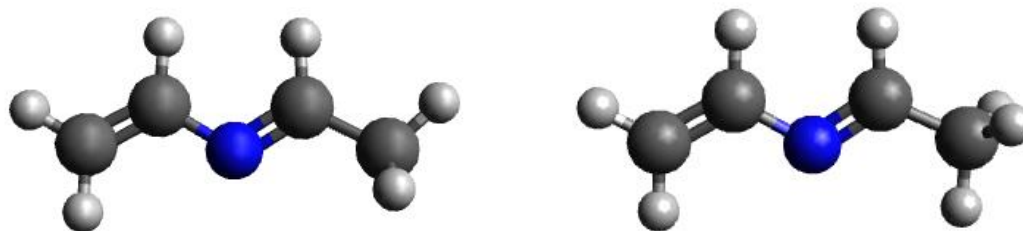
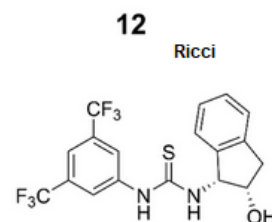
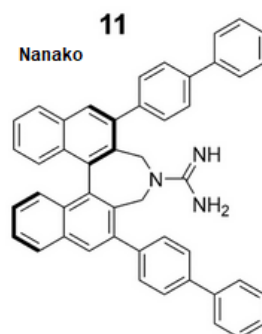
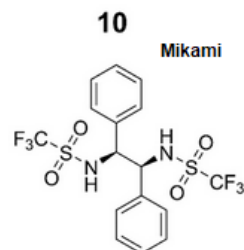
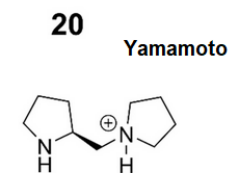
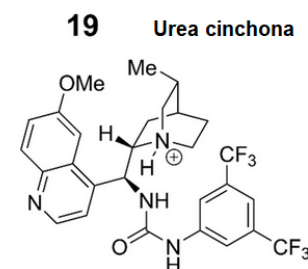
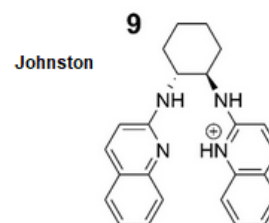
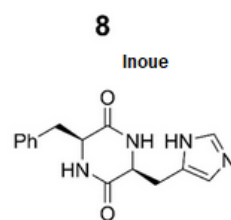
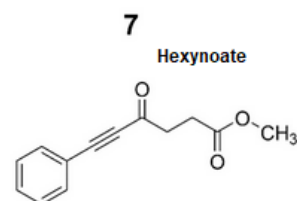
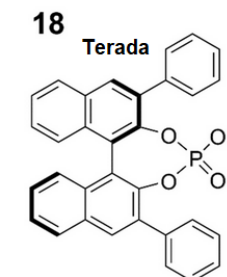
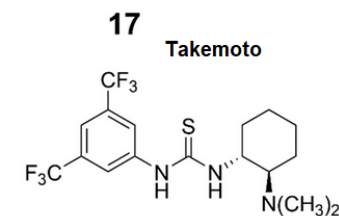
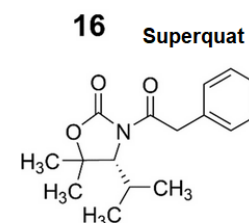
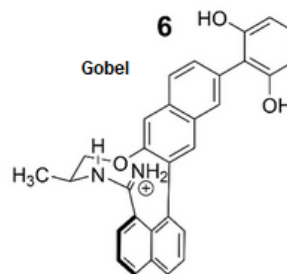
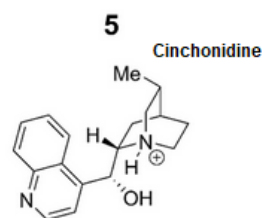
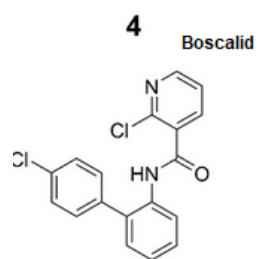
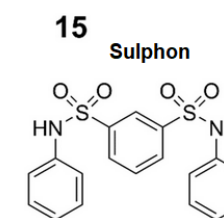
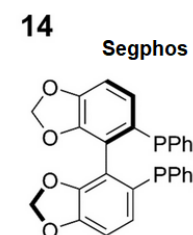
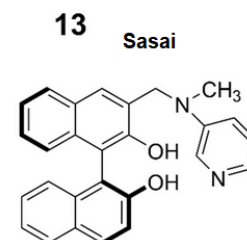
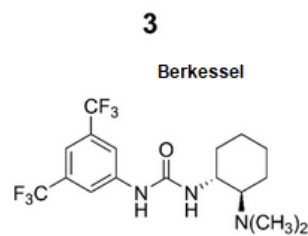
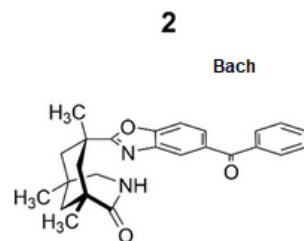
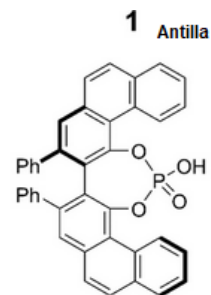


Performance comparisons for Gaussian16 geometry optimisation with Hessians



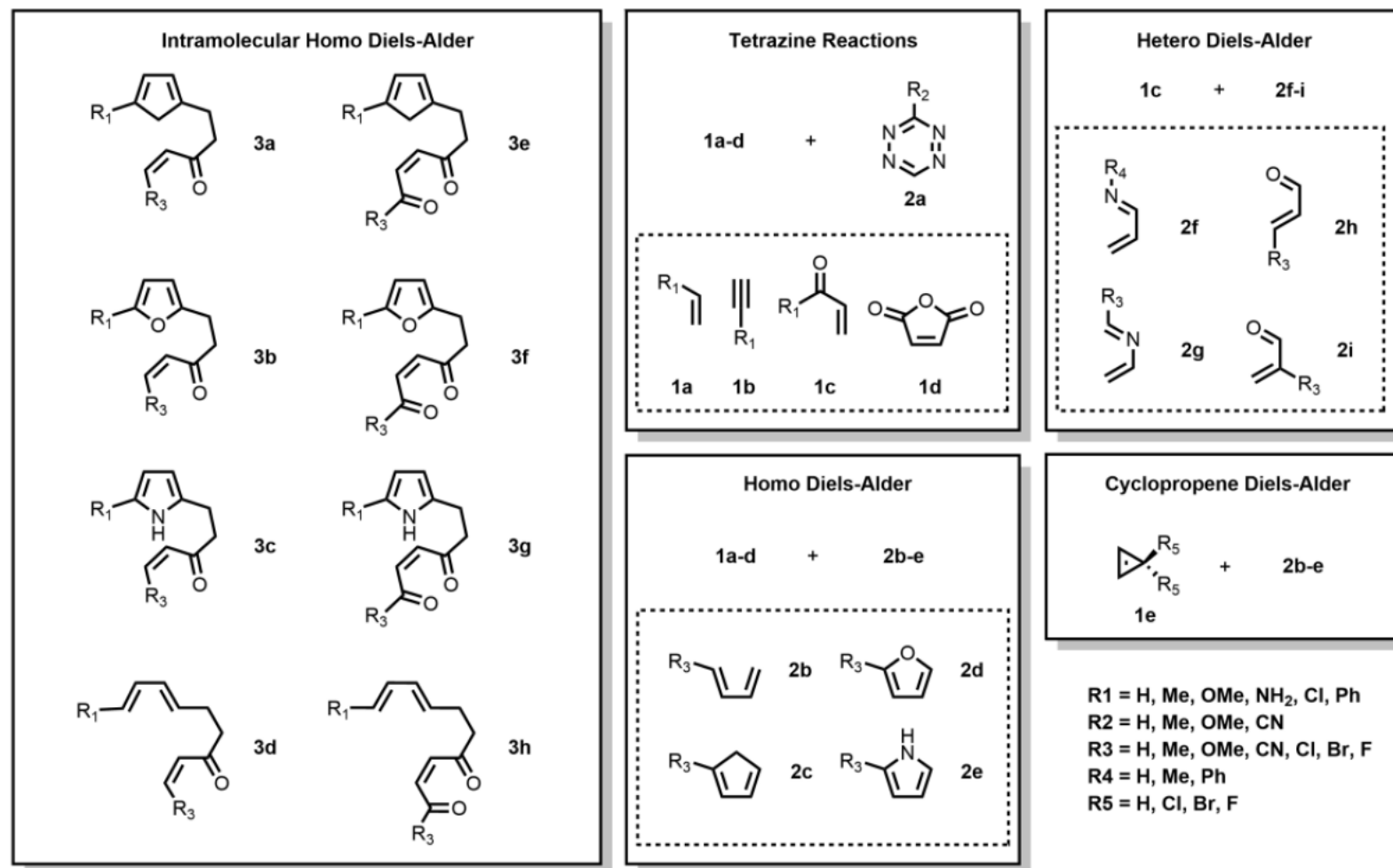
11 Dec 2023

Data: Catalyst-20 (OPLS3e)



Lewis-Atwell, T., Townsend, P.A. and Grayson, M.N., 2022. Comparing the Performances of Force Fields in Conformational Searching of Hydrogen-Bond-Donating Catalysts. *The Journal of Organic Chemistry*, 87(9), pp.5703-5712.

Data: Dienes-9, Dienophiles-5, Intra-8 (OPLS3e)



Dienes-9:
2x-2 (R3/R4=Me)

Dienophiles-5:
1x-2 (R1=Me)
1d

Intra-8:
3x-1 (R1=R3=H)

Espley, S.G., Farrar, E.H., Buttar, D.,
Tomasi, S. and Grayson, M.N., 2023.
Machine learning reaction barriers in
low data regimes: a horizontal and
diagonal transfer learning approach.
Digital Discovery.

Fig. S1 - Overview of the enumerations made to create the Diels-Alder dataset.

Level of theory: M062x/6-31G(d)

The same level of theory as used in JOC paper.

Lewis-Atwell, T., Townsend, P.A. and Grayson, M.N., 2022.
Comparing the Performances of Force Fields in Conformational
Searching of Hydrogen-Bond-Donating Catalysts. *The Journal
of Organic Chemistry*, 87(9), pp.5703-5712.

```
%chk=antilla_OPLS3e_1_freq.chk
%nprocshared=12
%mem=48GB
# m062x 6-31g(d) scrf=(iefpcm,solvent=benzene) freq=noraman
```

Structure3

O	1		
C		-2.28470	-2.41950
C		-1.41840	-3.50560
C		-0.18410	-3.37410
C		0.12520	-2.17640
H		-3.23870	-2.52480
O		1.29400	-2.15130
C		1.20440	-5.12200
C		0.80800	-4.51770
C		1.33430	-4.97830
C		2.16950	-6.08830
O		0.68850	-4.58190
H		2.57710	-6.44050
C		-0.74410	-1.02470
C		-1.97760	-1.19110
C		-2.90850	-0.13660
C		-2.65210	1.08050
H		-3.84130	-0.28490
H		-3.38380	1.87340
C		2.52930	-6.75750
C		2.05740	-6.29050
C		3.75600	-8.56760
C		3.37070	-7.88370

freq

```
%chk=antilla_OPLS3e_1_opt_freq.chk
%nprocshared=12
%mem=48GB
# m062x 6-31g(d) scrf=(iefpcm,solvent=benzene) opt=(maxcycles=50,maxstep=10)
freq=noraman
```

Structure3

O	1		
C		-2.28470	-2.41950
C		-1.41840	-3.50560
C		-0.18410	-3.37410
C		0.12520	-2.17640
H		-3.23870	-2.52480
O		1.29400	-2.15130
C		1.20440	-5.12200
C		0.80800	-4.51770
C		1.33430	-4.97830
C		2.16950	-6.08830
O		0.68850	-4.58190
H		2.57710	-6.44050
C		-0.74410	-1.02470
C		-1.97760	-1.19110
C		-2.90850	-0.13660
C		-2.65210	1.08050
H		-3.84130	-0.28490
H		-3.38380	1.87340
C		2.52930	-6.75750
C		2.05740	-6.29050
C		3.75600	-8.56760

opt_freq

```
%chk=antilla_OPLS3e_1_opt_hess.chk
%nprocshared=12
%mem=48GB
# m062x 6-31g(d) scrf=(iefpcm,solvent=benzene) opt=(calcf, maxcycles=50, maxstep=10)
freq=noraman
```

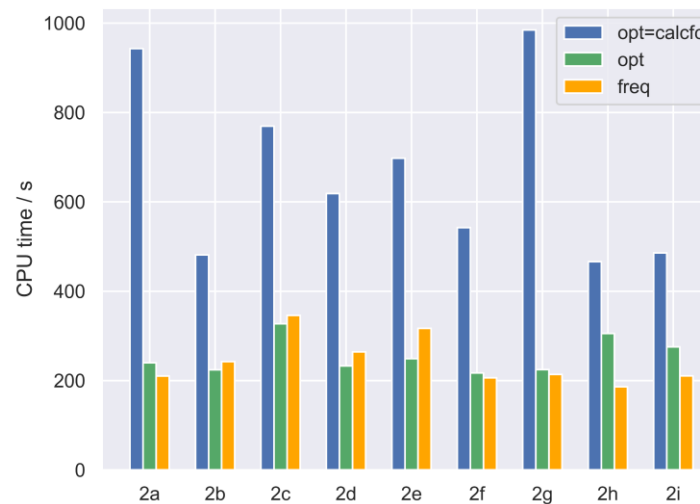
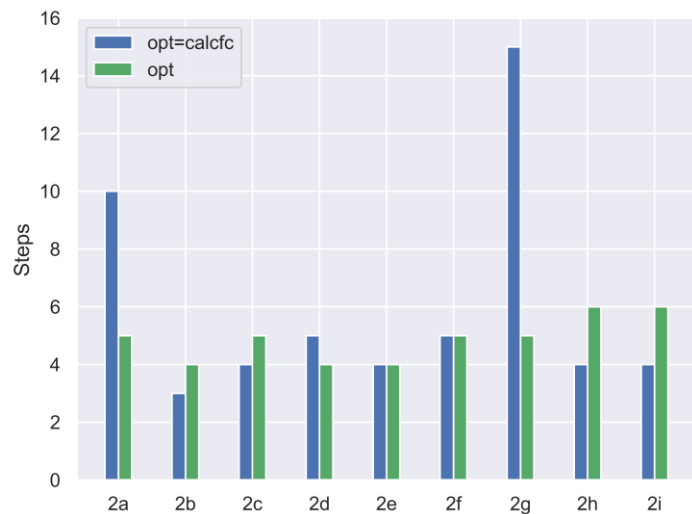
Structure3

O	1		
C		-2.28470	-2.41950
C		-1.41840	-3.50560
C		-0.18410	-3.37410
C		0.12520	-2.17640
H		-3.23870	-2.52480
O		1.29400	-2.15130
C		1.20440	-5.12200
C		0.80800	-4.51770
C		1.33430	-4.97830
C		2.16950	-6.08830
O		0.68850	-4.58190
H		2.57710	-6.44050
C		-0.74410	-1.02470
C		-1.97760	-1.19110
C		-2.90850	-0.13660
C		-2.65210	1.08050
H		-3.84130	-0.28490
H		-3.38380	1.87340
C		2.52930	-6.75750
C		2.05740	-6.29050
C		3.75600	-8.56760

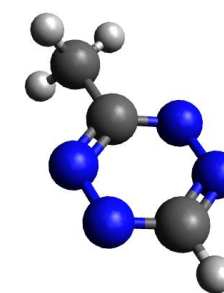
opt_hess

Dienes-9: results

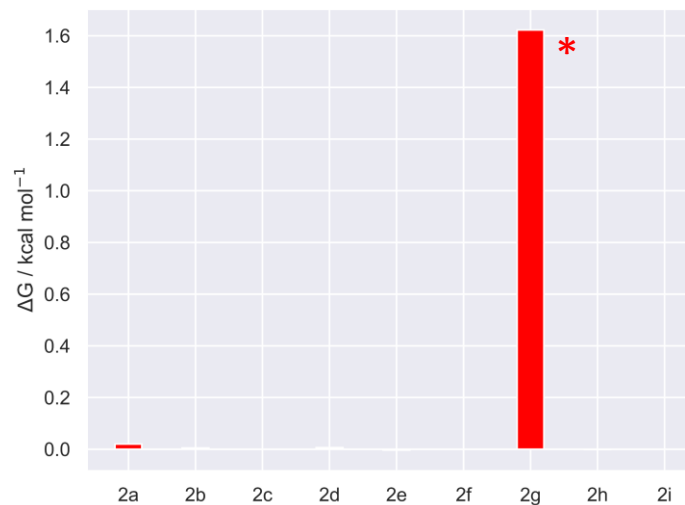
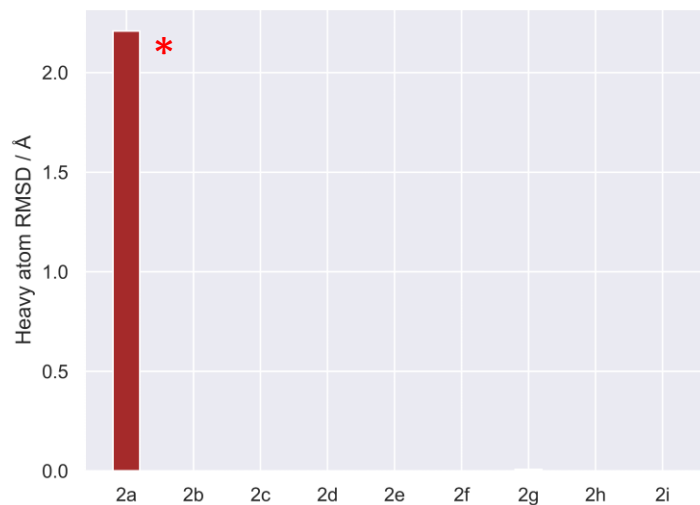
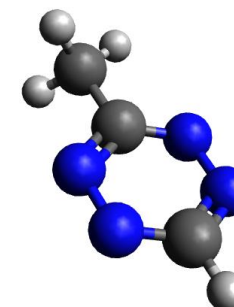
n.b in the following slides: $\Delta G = G_{(\text{opt})} - G_{(\text{opt=calcfc})}$



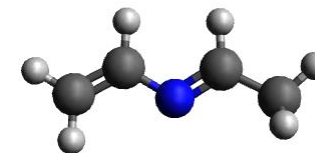
2a-opt



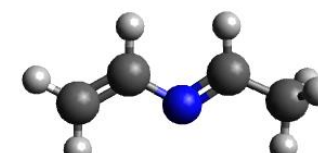
2a-opt=calcfc



2g-opt



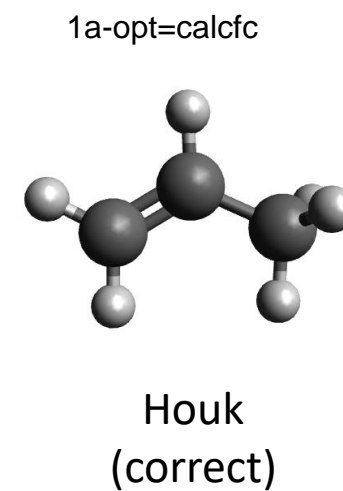
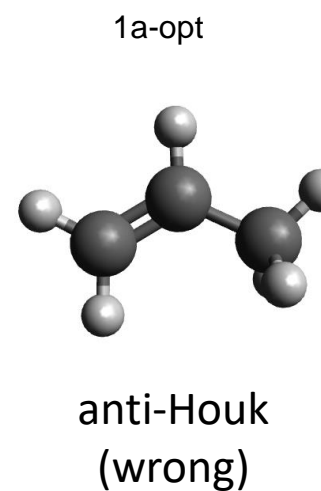
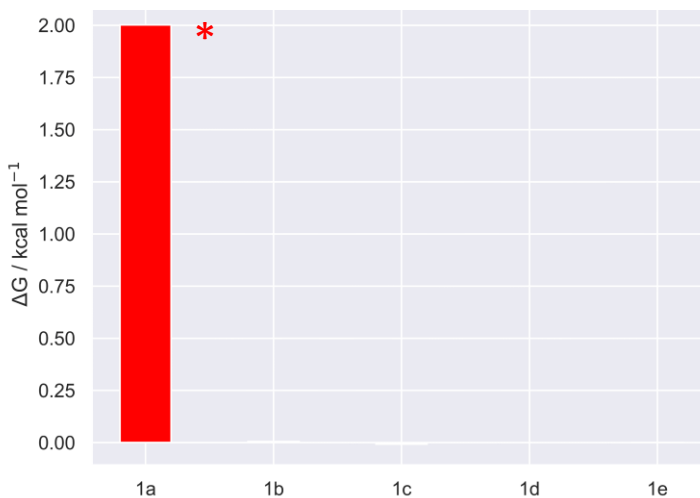
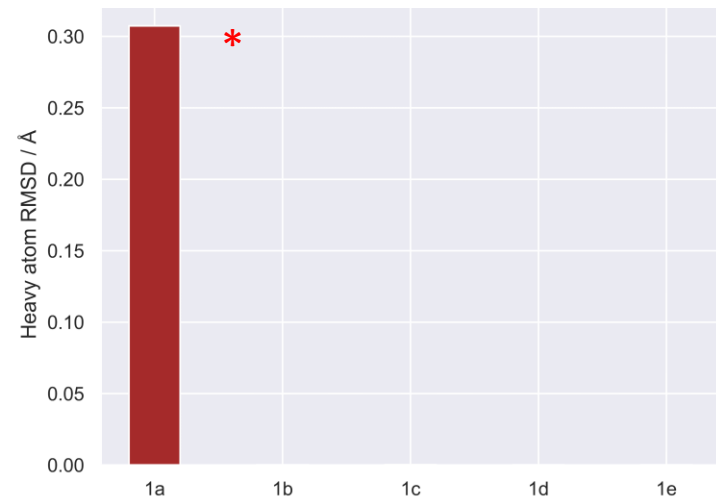
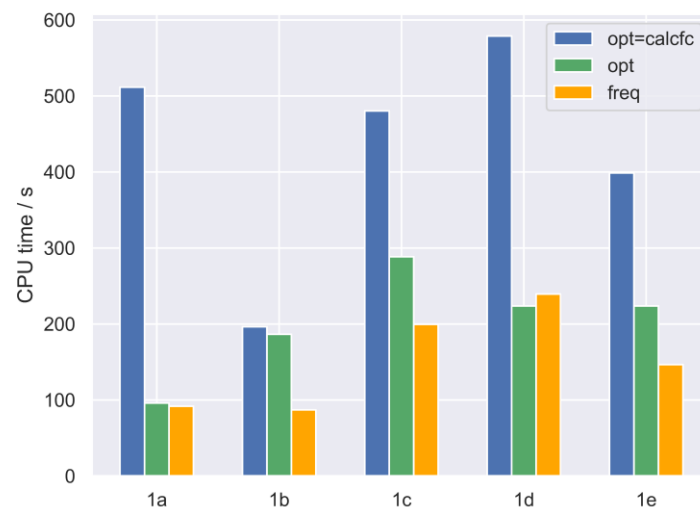
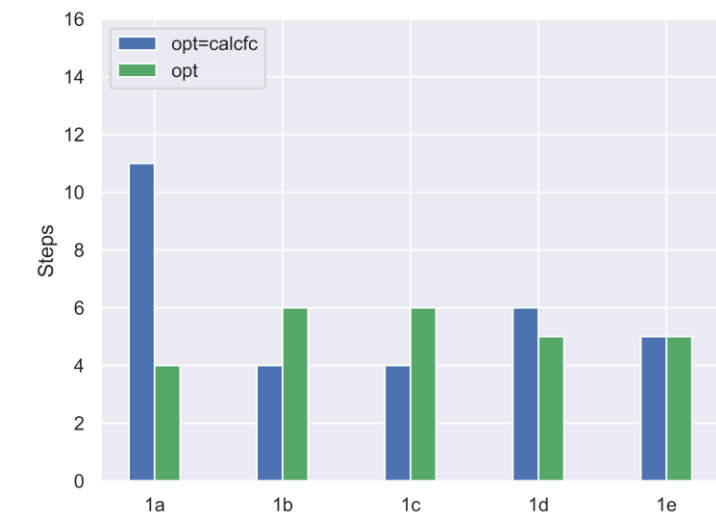
2g-opt=calcfc



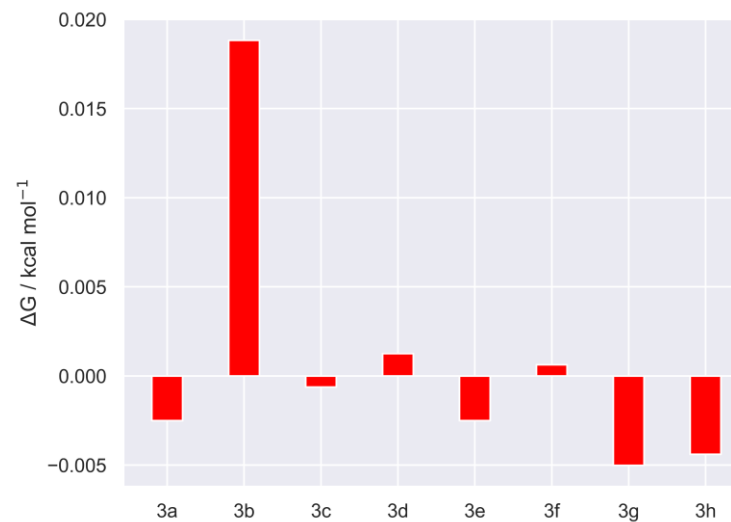
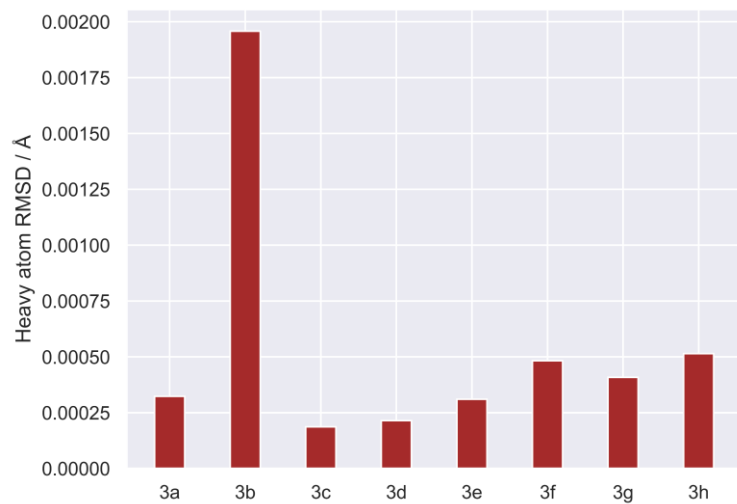
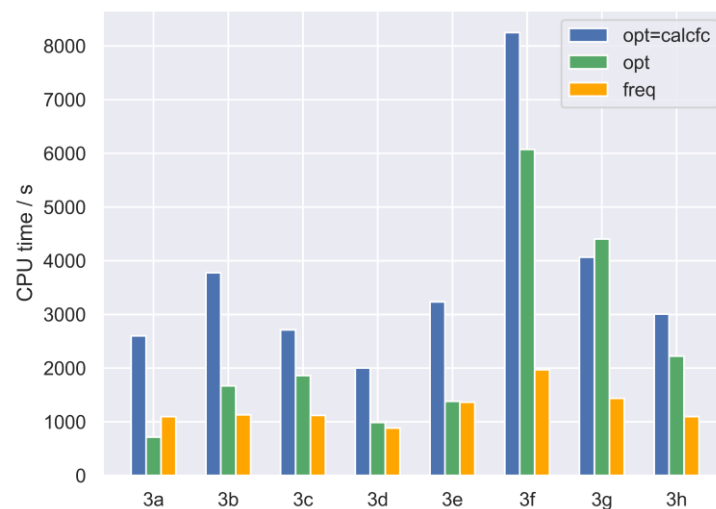
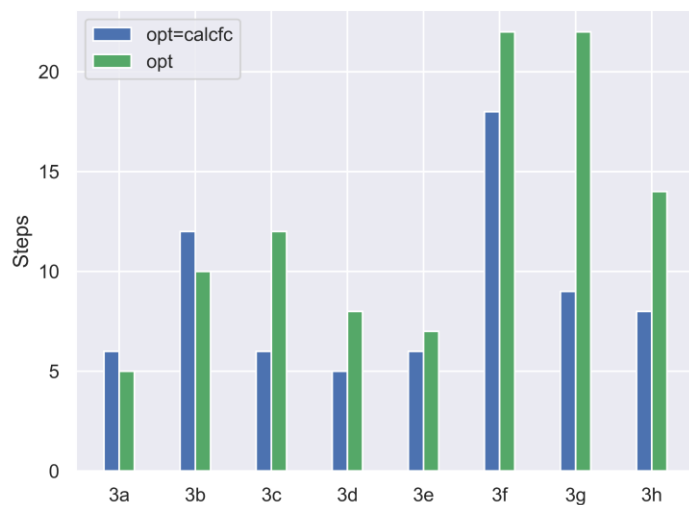
anti-Houk
(wrong)

Houk
(correct)

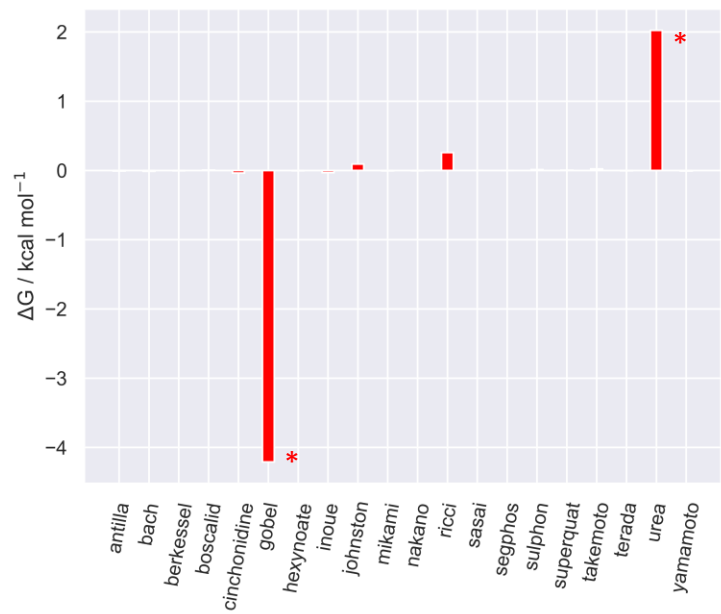
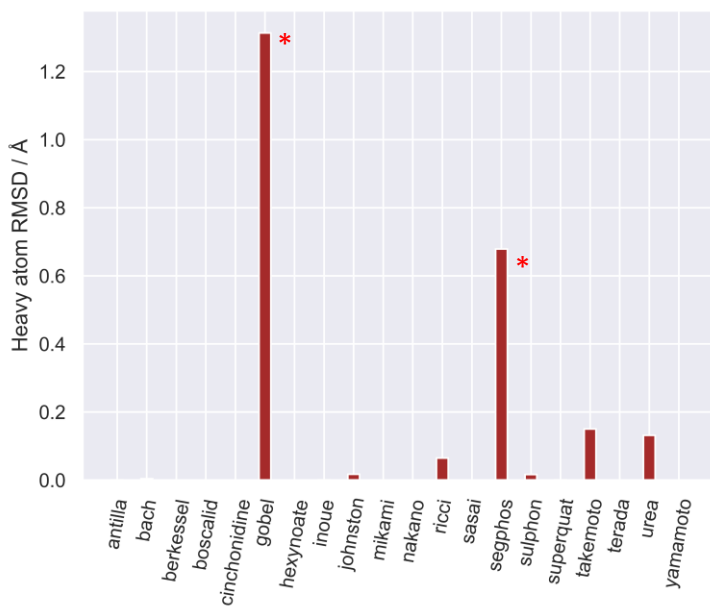
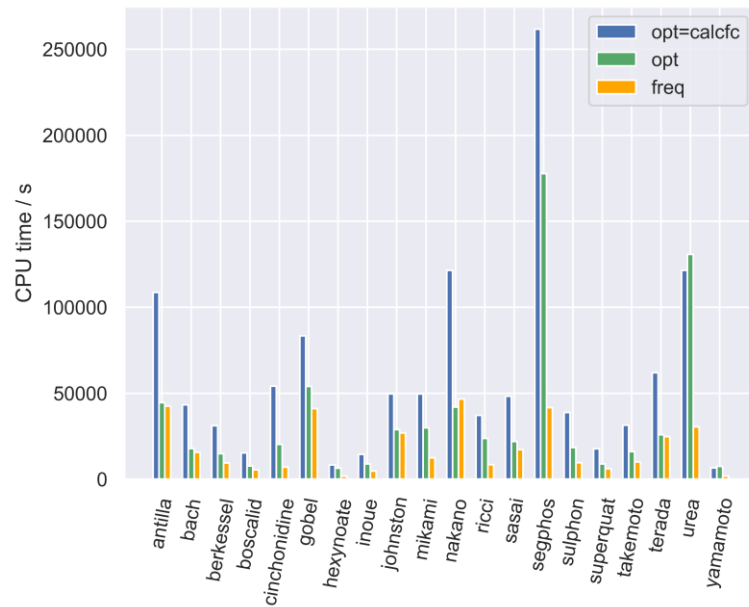
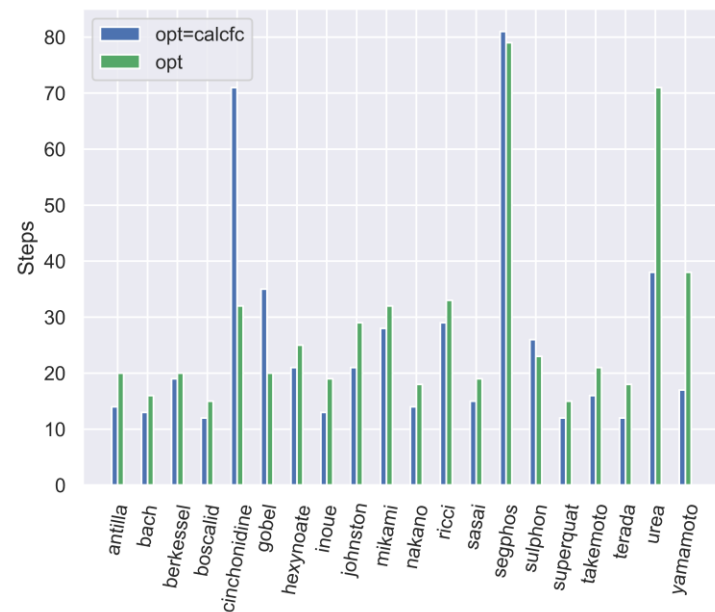
Dienophiles-5: results



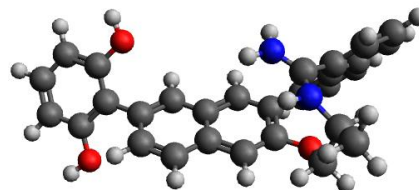
Intra-8: results



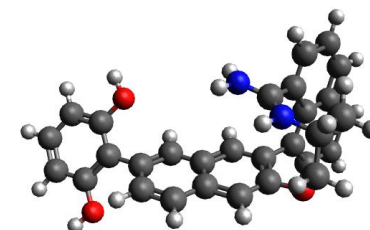
Catalysts-20: results



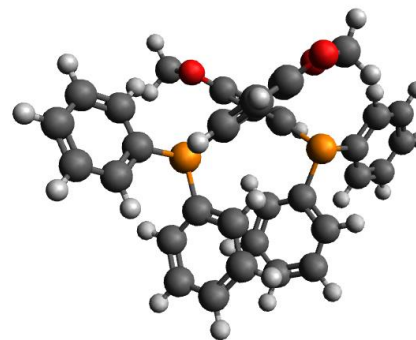
gobel-opt



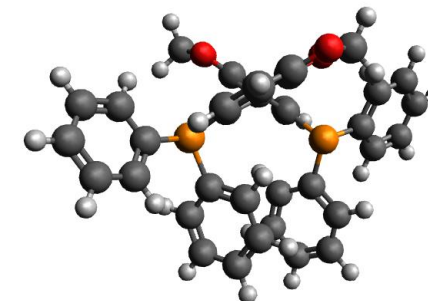
gobel-opt=calcfc



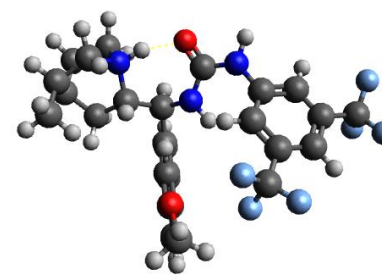
segphos-opt



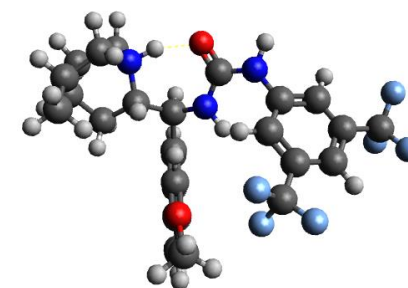
segphos-opt=calcfc



urea_cinchona-opt



urea_cinchona-opt=calcfc



Conclusions

1. `opt` usually takes a similar number of steps as `opt=calcfc`, although often slightly more steps
2. `opt` usually takes approximately half the CPU time as `opt=calcfc`, however it can sometimes take just as much time as the full calculation with an initial exact hessian
3. `opt` can sometimes optimise to a different local minima than `opt=calcfc`, as measured by ΔG and heavy atom RMSD, and this minima can be higher in free energy (e.g. anti-Houk) or lower in free energy (e.g. gobe1 – although DFT is not a variational method)
4. The `opt` approximate Hessian is based on a simple valence force field, therefore an SQM Hessian initial guess may be able to more closely approximate the DFT Hessian and potentially alleviate the problem of multiple conformers, to some extent