

Supporting information

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Computational methods

All energies and thermodynamic quantities reported in this work were obtained using ORCA (v. 4.2.1).¹ Minima and transition states (TSs) were initially identified using *autodE* (v. 1.0.0b3),² with low energy conformers located using the ETKDGv2 algorithm implemented in RDKit v. 2019.03.4,³ and optimised using GFN2-xTB implemented in xTB (v 6.2.2)⁴ followed by PBE0-D3BJ/def2-TZVP//PBE0-D3BJ/def2-SVP in ORCA (v. 4.2.1).^{1,5,6} Anionic reactions were run using the GBSA⁷ / CPCM⁸ solvent models for THF in xTB / ORCA, respectively. Geometries and energy were then refined in ORCA at the [DLPNO-CCSD(T)/def2-QZVPP (TightPNO)//B2PLYP-D3BJ/def2-TZVP] level of theory (CH_3^\bullet reactions) or [SMD(THF)-DLPNO-CCSD(T)/ma-def2-QZVPP (TightPNO)// SMD(THF)-B2PLYP-D3BJ/def2-TZVP (ma-def2-TZVP on N)] level of theory (NH_2^- reactions).^{5,6,9,10} All calculations used the resolution of the identity approximation (RIJCOSX),¹¹ with the appropriate auxiliary basis sets.¹² ‘Tight’ optimisation criteria (10^{-8} Ha tolerance for SCF, 10^{-6} Ha tolerance for optimisation step) were employed along with Grid6 / GridX6, corresponding to a Lebedev-590 angular grid, and a radial integral accuracy (IntAcc) of 5.34. Stationary points for the model systems were characterised through calculation of the Hessian. Minima were characterised by the absence of imaginary frequencies, and TSs by the presence of a single imaginary mode. Grimme’s quasi-RRHO method¹³ was used to calculate entropic corrections to obtain free energies at 298.15 K as implemented in the Python package *otherm*.¹⁴ For reactions calculated in the gas phase, a 1 atm standard state was employed. For reactions in implicit solvent, a 1 atm to 1 M standard state correction was applied by adding $RT \ln(24.5) = 1.89$ kcal mol⁻¹ to the calculated free energy of each species. NBO occupation numbers were calculated using the NBO program (v. 7.0), and ELF descriptors were calculated with Multiwfn (v. 3.6).¹⁵

All data processing was carried out using the Scikit-learn package in Python 3.7,¹⁶ and MLR plots were generated with Matplotlib.¹⁷ A Python script to generate plots is included as part of the Supporting Information. Individual figures can be generated interactively, or to plot all figures using the terminal run:

```
for i in {1..14}; do echo $i | python main.py -v; done
```

Enthalpies were chosen for a direct comparison with strain energies, which are commonly reported instead of Gibbs free energies. Trends in enthalpy and Gibbs free energy were found to be in excellent agreement for all reactions studied here. Values of $2 - N_{occ}$ were found to be in good agreement with an alternative density-based delocalisation parameter, $1 - ELF$, where ELF is the electron localisation function at the bond critical point (Fig. S3).¹⁸

S1 Hydrocarbon ring-opening reactivity

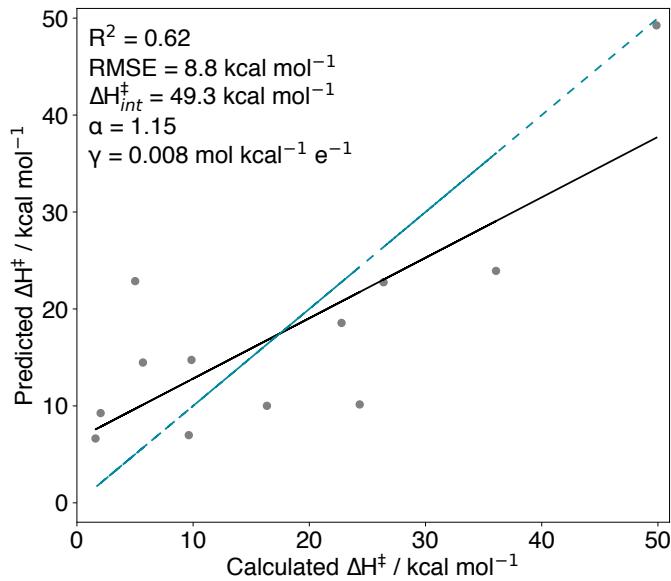


Figure S1: MLR plot ($\text{CH}_3\cdot + \text{hydrocarbon}$) for the prediction of ΔH^\ddagger from ΔH_r and ΔH_r^2 (Marcus) using $\Delta H^\ddagger = \Delta H_{int}^\ddagger + \alpha\Delta H_r + \beta\Delta H_r^2$, where α and β are optimised coefficients. The blue dashed line denotes perfect correlation.

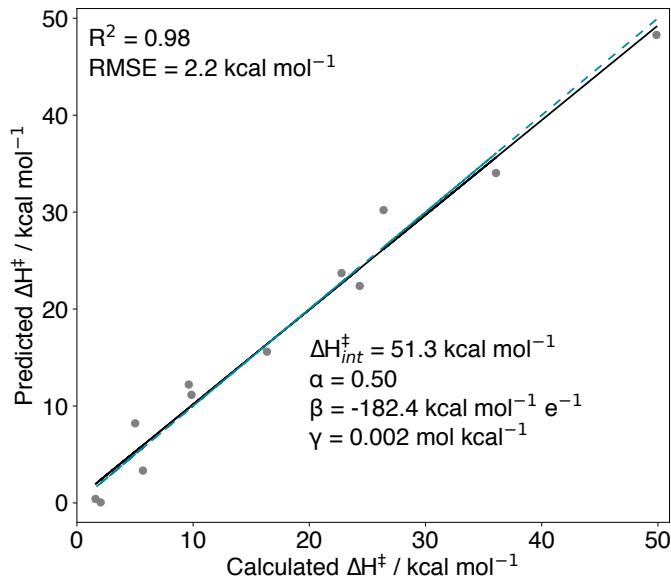


Figure S2: MLR plot ($\text{CH}_3\cdot + \text{hydrocarbon}$) for the prediction of ΔH^\ddagger from ΔH_r , ΔH_r^2 and $2 - N_{occ}$ (Marcus + delocalisation) using $\Delta H^\ddagger = \Delta H_{int}^\ddagger + \alpha\Delta H_r + \beta(2 - N_{occ}) + \gamma\Delta H_r^2$, where α , β and γ are optimised coefficients. The blue dashed line denotes perfect correlation.

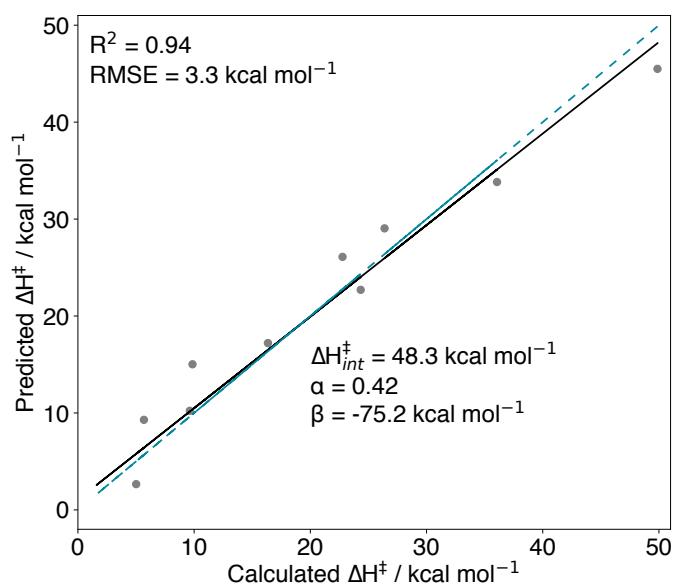


Figure S3: MLR plot ($\text{CH}_3\cdot + \text{hydrocarbon}$) for the prediction of ΔH^\ddagger from ΔH_r and $1-ELF$ using $\Delta H^\ddagger = \Delta H_{\text{int}}^\ddagger + \alpha \Delta H_r + \beta(1-ELF)$, where α and β are optimised coefficients. The blue dashed line denotes perfect correlation.

CCl_3^\bullet addition		B2PLYP-D3BJ					DLPNO-CCSD(T)		
		ΔE_{el}	ΔZPE	ΔH	$T\Delta S$	ΔG	ΔE	ΔH	ΔG
[1.1.1]Propellane, H	vdW complex	-2.7	0.3	-1.5	-10.5	9.1	-1.6	-0.4	10.2
	TS	-1.0	0.3	-0.6	-12.2	11.6	0.1	0.5	12.8
	rxn	-25.8	2.2	-24.0	-13.8	-10.2	-26.6	-24.8	-11.0
Bicyclo[1.1.0]butane, D	vdW complex	-2.9	0.4	-1.7	-9.9	8.3	-2.2	-0.9	9.0
	TS	2.5	0.3	2.8	-12.2	15.0	3.6	4.0	16.2
	rxn	-40.3	1.4	-39.0	-12.9	-26.1	-41.4	-40.1	-27.2
Bicyclo[2.1.0]pentane, E	vdW complex	-3.3	0.4	-2.1	-10.6	8.5	-2.5	-1.3	9.3
	TS	8.8	-0.1	8.8	-12.4	21.3	10.6	10.7	23.2
	rxn	-51.3	1.6	-49.8	-13.1	-36.7	-51.7	-50.2	-37.1

Table S1: Differences in thermodynamic quantities (kcal mol^{-1}) for the addition of CCl_3^\bullet to [1.1.1]propellane (**H**), bicyclo[1.1.0]butane (**D**) and bicyclo[2.1.0]pentane (**E**), optimised at the B2PLYP-D3BJ/def2-TZVP level, with single point energies calculated at the DLPNO-CCSD(T)/ma-def2-QZVPP (TightPNO) level. ΔH and ΔG at the DLPNO-CCSD(T) level calculated using thermal corrections from the B2PLYP level.

$\text{CH}_3\cdot$ addition	B2PLYP-D3BJ					DLPNO-CCSD(T)		
	ΔE_{el}	ΔZPE	ΔH	$T\Delta S$	ΔG	ΔE	ΔH	ΔG
Ethane, A	TS	49.2	1.2	49.5	-10.4	59.9	49.7	49.9
	rxn	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Cyclopropane, B	TS	25.2	1.6	25.9	-10.5	36.5	25.7	26.4
	rxn	-31.2	3.8	-28.3	-10.7	-17.7	-31.2	-28.4
Cyclobutane, C	TS	35.1	1.6	35.7	-11.0	46.6	35.5	36.1
	rxn	-30.1	3.1	-27.5	-9.8	-17.7	-29.4	-26.8
Bicyclo[1.1.0]butane, D	TS	7.8	1.9	8.9	-10.5	19.4	8.8	9.9
	rxn	-45.2	4.6	-41.8	-11.2	-30.6	-45.0	-41.6
Bicyclo[2.1.0]pentane, E	TS	14.4	1.6	15.3	-10.6	25.9	15.5	16.4
	rxn	-57.3	4.8	-53.6	-11.4	-42.2	-56.5	-52.9
Bicyclo[3.1.0]hexane, F	TS	21.0	2.0	22.0	-11.3	33.4	21.7	22.8
	rxn	-38.9	4.8	-35.3	15.4	-23.5	-38.3	-34.7
Bicyclo[2.2.0]hexane, G	TS	22.8	1.8	23.6	-11.1	34.8	23.5	24.3
	rxn	-57.9	5.5	-53.7	-11.9	-41.8	-56.7	-52.4
[1.1.1]Propellane, H	TS	2.9	1.7	3.9	-10.3	14.1	4.0	5.0
	rxn	-32.4	5.5	-28.4	-12.2	-16.2	-32.2	-28.2
[2.1.1]Propellane, I	TS	0.3	1.4	1.2	-9.9	11.1	1.1	2.0
	rxn	-59.7	6.2	-55.1	-12.6	-42.5	-59.8	-55.3
[3.1.1]Propellane, J	TS	3.4	1.8	4.4	-10.7	15.2	4.7	5.7
	rxn	-46.2	5.9	-41.9	-12.4	-29.5	-46.4	-42.1
[2.2.1]Propellane, K	TS	-0.4	1.4	0.5	-10.2	10.6	0.7	1.6
	rxn	-83.5	7.1	-78.2	-12.9	-65.3	-83.8	-78.5
[2.2.2]Propellane, L	TS	7.2	1.8	8.1	-11.1	19.3	8.6	9.6
	rxn	-88.6	7.8	-82.5	-13.1	-69.4	-88.1	-82.1

Table S2: Differences in thermodynamic quantities (kcal mol^{-1}) for the addition of a methyl radical to each of the molecules in the H12 set, optimised at the B2PLYP-D3BJ/def2-TZVP level, with single point energies calculated at the DLPNO-CCSD(T)/def2-QZVPP (TightPNO) level. ΔH and ΔG at the DLPNO-CCSD(T) level calculated using thermal corrections from the B2PLYP level.

NH_2^- addition		B2PLYP-D3BJ					DLPNO-CCSD(T)		
		ΔE_{el}	ΔZPE	ΔH	$T\Delta S$	ΔG	ΔE	ΔH	ΔG
Ethane, A	TS	66.2	-1.5	64.4	-8.1	72.5	68.5	66.7	74.8
	rxn	24.5	-0.2	24.3	0.8	23.5	22.4	22.3	21.4
Cyclopropane, B	TS	40.1	-0.3	39.3	-8.8	48.2	41.3	40.6	49.4
	rxn	1.7	3.3	4.1	-9.9	14.0	-2.2	0.2	10.0
Cyclobutane, C	TS	48.4	-0.2	47.5	-9.6	57.1	50.3	49.5	59.0
	rxn	3.8	2.8	6.0	-9.3	15.2	1.0	3.2	12.4
Bicyclo[1.1.0]butane, D	TS	19.7	1.2	20.2	-9.4	29.6	20.9	21.4	30.7
	rxn	-11.1	4.6	-8.0	-11.1	3.1	-15.2	-12.1	-1.0
Bicyclo[2.1.0]pentane, E	TS	27.2	-0.1	26.8	-9.0	35.8	29.0	28.6	37.6
	rxn	-18.4	4.4	-15.4	-11.0	-4.4	-21.2	-18.2	-7.2
Bicyclo[3.1.0]hexane, F	TS	36.4	-0.2	35.7	-9.4	45.1	39.3	38.7	48.0
	rxn	-3.5	4.0	-0.9	-11.5	10.6	-6.1	-3.5	8.0
Bicyclo[2.2.0]hexane, G	TS	32.6	0.4	32.4	-9.7	42.0	34.8	34.6	44.3
	rxn	-14.9	4.4	-11.7	-10.9	-0.8	-17.5	-14.3	-3.4
[1.1.1]Propellane, H	TS	12.1	1.0	12.4	-9.5	21.9	12.9	13.2	22.7
	rxn	-9.0	3.9	-6.5	-11.3	4.7	-13.1	-10.7	0.6
[2.1.1]Propellane, I	TS	6.5	1.0	6.9	-9.4	16.3	7.0	7.5	16.8
	rxn	-32.7	4.7	-29.6	-11.7	-18.0	-37.2	-34.1	-22.4
[3.1.1]Propellane, J	TS	17.0	0.8	17.1	-9.8	26.9	18.1	18.2	28.1
	rxn	-10.4	4.1	-7.7	-11.3	3.6	-14.9	-12.2	-0.9
[2.2.1]Propellane, K	TS	5.2	1.0	5.8	-9.0	14.8	6.0	6.6	15.6
	rxn	-54.1	5.7	-50.2	-12.1	-38.1	-58.2	-54.3	-42.2
[2.2.2]Propellane, L	TS	19.0	0.7	19.1	-9.8	28.8	21.1	21.2	30.9
	rxn	-54.5	6.1	-50.1	-12.0	-38.1	-57.0	-52.6	-40.7

Table S3: Differences in thermodynamic quantities (kcal mol^{-1}) for the addition of an amide anion (NH_2^-) to each of the molecules in the H12 set, optimised at the SMD(THF)-B2PLYP-D3BJ/def2-TZVP (ma-def2-TZVP on N) level, with single point energies calculated at the SMD(THF)-DLPNO-CCSD(T)/ma-def2-QZVPP (TightPNO) level. ΔH and ΔG at the DLPNO-CCSD(T) level calculated using thermal corrections from the B2PLYP level.

S2 Heterocycle ring-opening reactivity

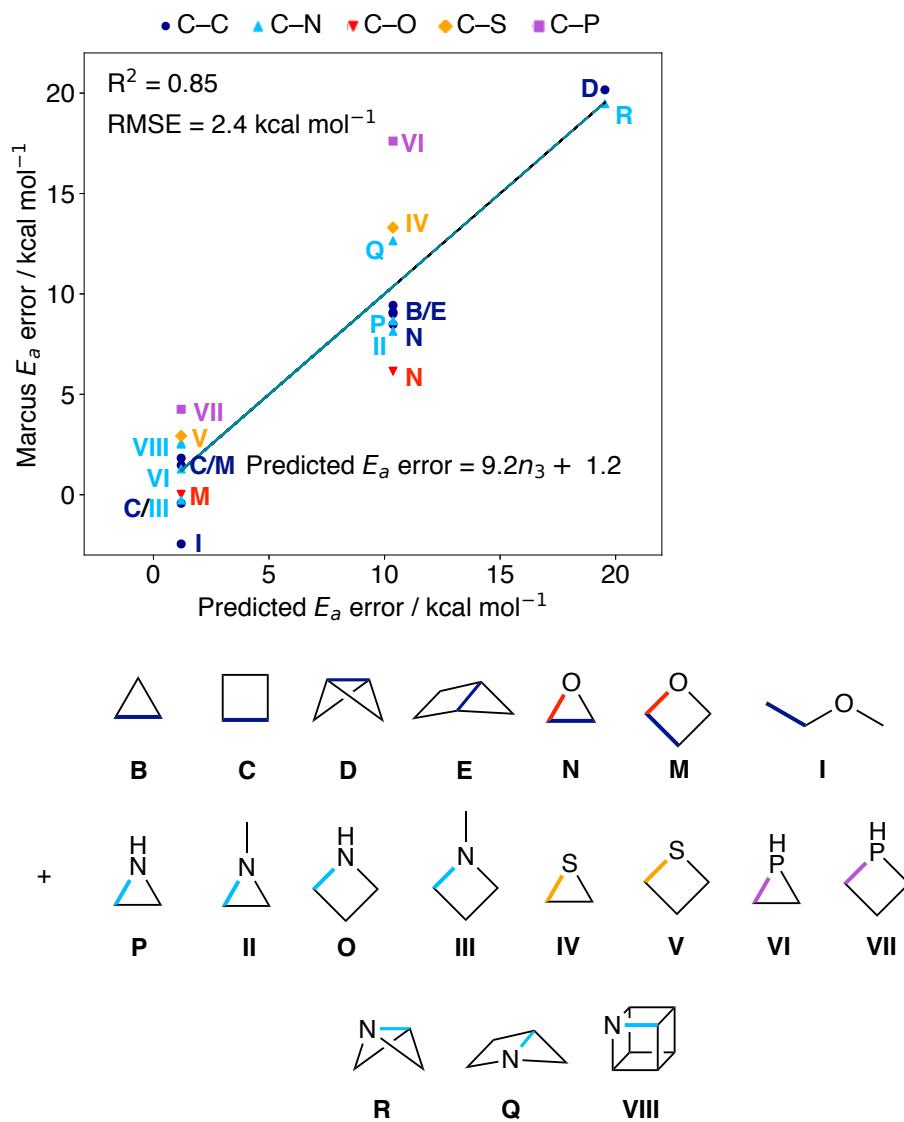


Figure S4: Anionic and radical additions to a set of 18 heterocyclic molecules (Fig. S5, and the error in activation energy (E_a) predicted by Marcus theory vs $2 - N_{occ}$. Reaction data from refs. [19, 20].

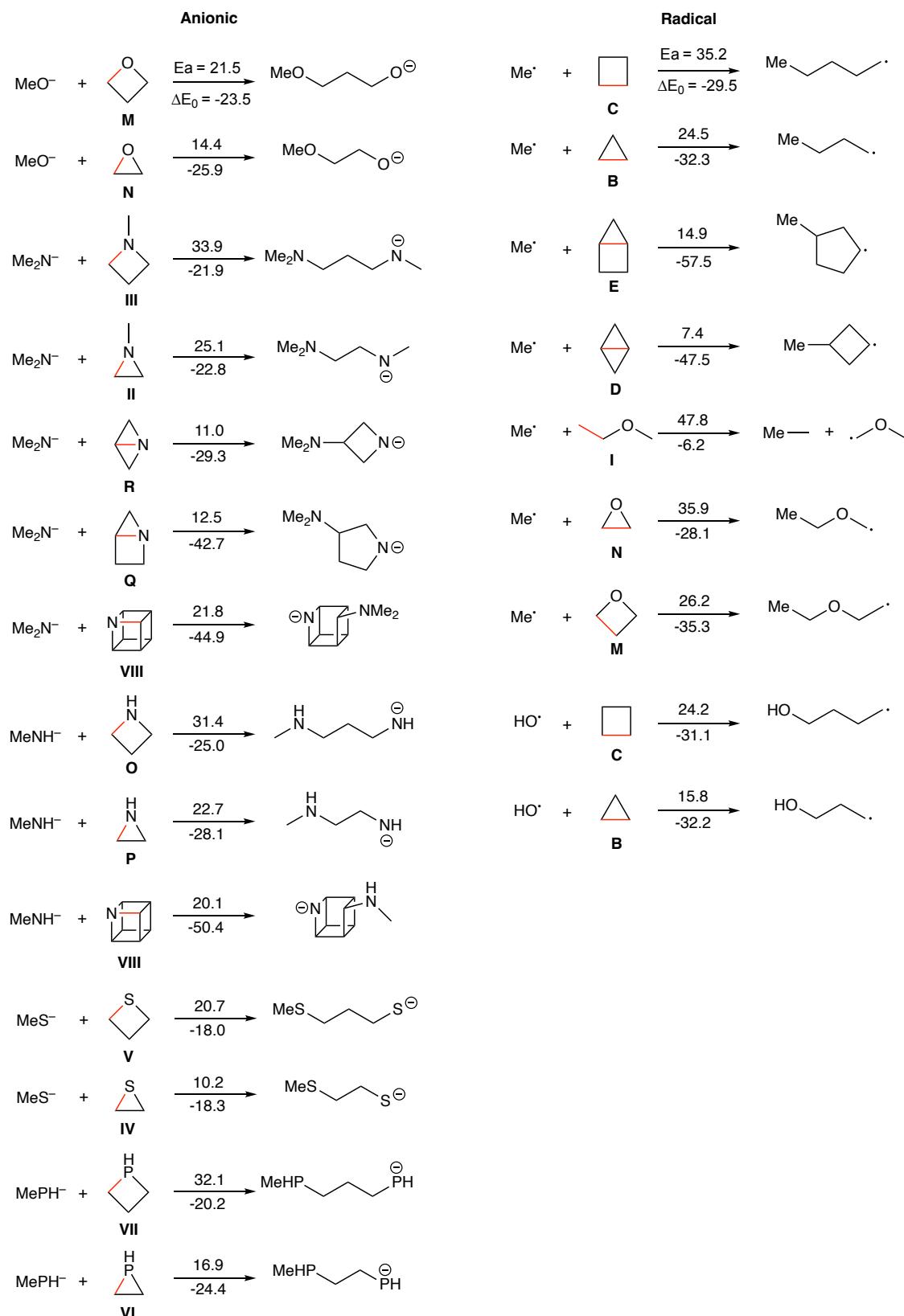


Figure S5: Anionic and radical reactions used to generate Fig. S14, with data taken from refs. [19, 20].

S3 Tabulated strain release energies and delocalisation values

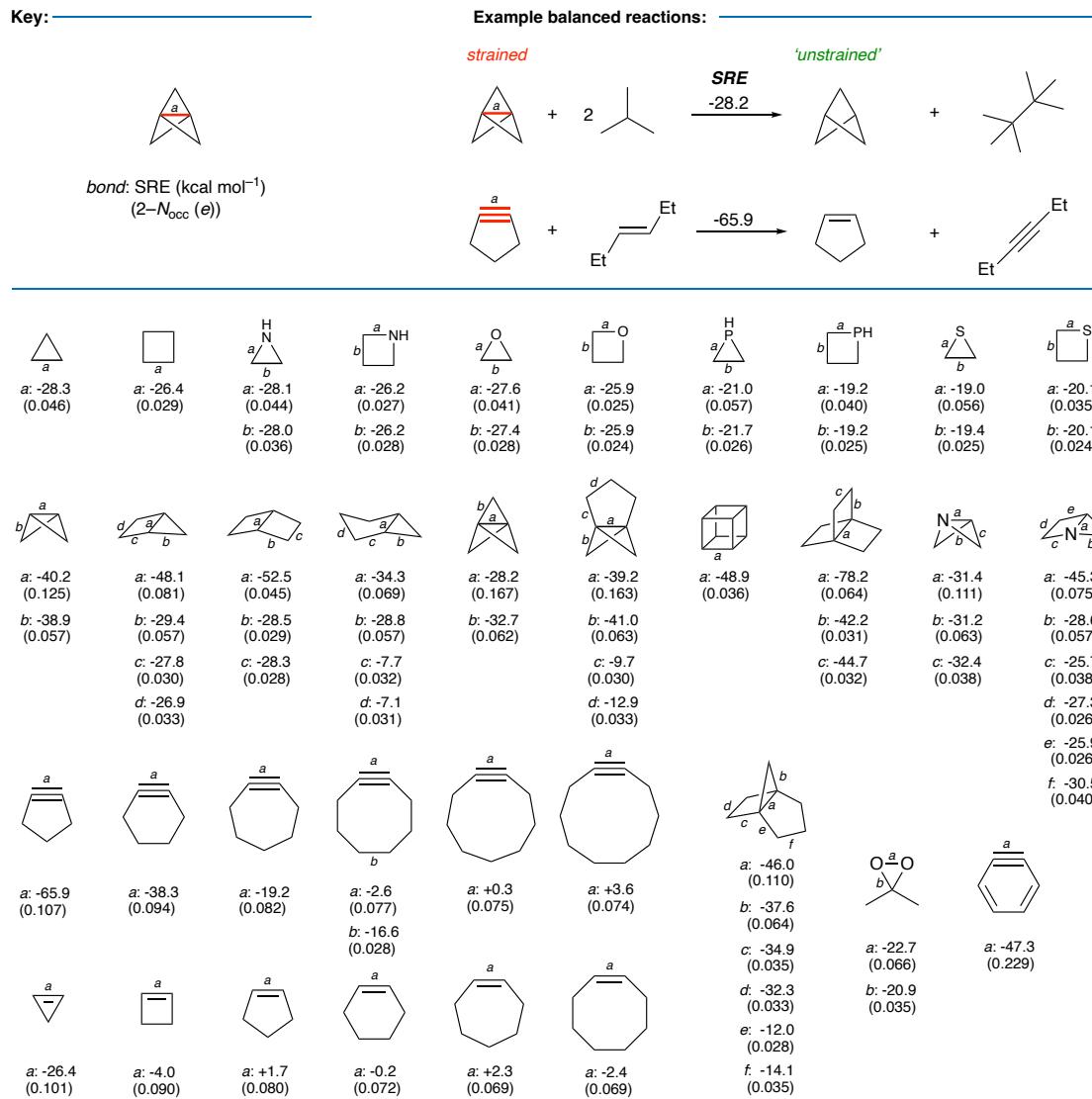
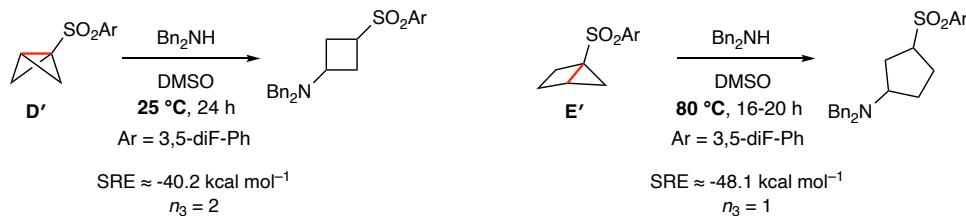


Figure S6: Set of strain release energies (SREs, kcal mol⁻¹) and $2 - N_{occ}$ values (e) per bond type for a range of mono-, bi- and tricyclic ring systems, cyclic alkynes and alkenes.

'Rule of thumb' worked example

Shown in Fig. 4c, and reproduced here, is the addition of Bn_2NH to a sulfonyl bicyclo[1.1.0]butane (**D'**) or bicyclo[2.1.0]pentane (**E'**). While the former reaction takes place at 25 °C (298 K), the latter requires heating to 80 °C (353 K).

'Strain-release' amination (ref. 30 in main text)



Using the 'rule of thumb' of $\Delta\Delta H^\ddagger \approx 0.5\Delta\text{SRE} - 10\Delta n_3$, for these reactions $\Delta\text{SRE} = -7.9 \text{ kcal mol}^{-1}$ and $\Delta n_3 = -1$. Based on strain release alone, **E'** should have an activation enthalpy $\approx 4 \text{ kcal mol}^{-1}$ lower than **D'** – therefore a reaction rate $\approx 10^3$ times greater than **D'** at 298 K. However, barrier lowering due to three-membered ring delocalisation should independently lower the intrinsic barrier for **D'** by $\approx 10 \text{ kcal mol}^{-1}$ relative to **E'**. The net effect is a prediction of a $\approx 6 \text{ kcal mol}^{-1}$ lower enthalpic barrier to the reaction for **D'** than **E'**, with delocalisation overturning the strain release bias.

Based on the experimental data, we can roughly estimate the relative reaction rates for the two reactions at a given temperature ($k_{\text{rel}} = k_{D'}(T)/k_{E'}(T)$) using the Eyring equation, if we assume that the experimental conditions are identical except for changes in temperature, that the two mechanisms are identical, and that the reactions occur at identical rates at the two different temperatures used in the reactions (*i.e.*, $k_{D'}(T)/k_{E'}(T') = 1$).

Using the latter condition, the relationship between the free energy barriers of the two reactions and the two reaction temperatures is

$$\Delta G_{E'}^\ddagger = \frac{T'}{T} \Delta G_{D'}^\ddagger + RT' \ln \frac{T'}{T}$$

where R is the gas constant. Using $T'/T = 1.2$, we obtain $\Delta G_{E'}^\ddagger = 1.2\Delta G_{D'}^\ddagger + 0.1 \text{ kcal mol}^{-1}$. Based on the reported reaction time of 24 h for **D'** at 298 K, we can estimate a value of $\Delta G_{D'}^\ddagger \approx 24 \text{ kcal mol}^{-1}$ ($t_{1/2} = 12 \text{ h}$). The resulting estimate for $\Delta G_{E'}^\ddagger$ is then 29 kcal mol $^{-1}$ – therefore the free energy barrier is $\approx 5 \text{ kcal mol}^{-1}$ lower for **D'** than **E'**, a difference of only 1 kcal mol $^{-1}$ from the rule of thumb prediction. Despite completely neglecting entropic effects and avoiding any electronic structure calculations or experiments, the rule of thumb gives a good estimate of the expected reactivity difference based only on tabulated data and visual inspection.

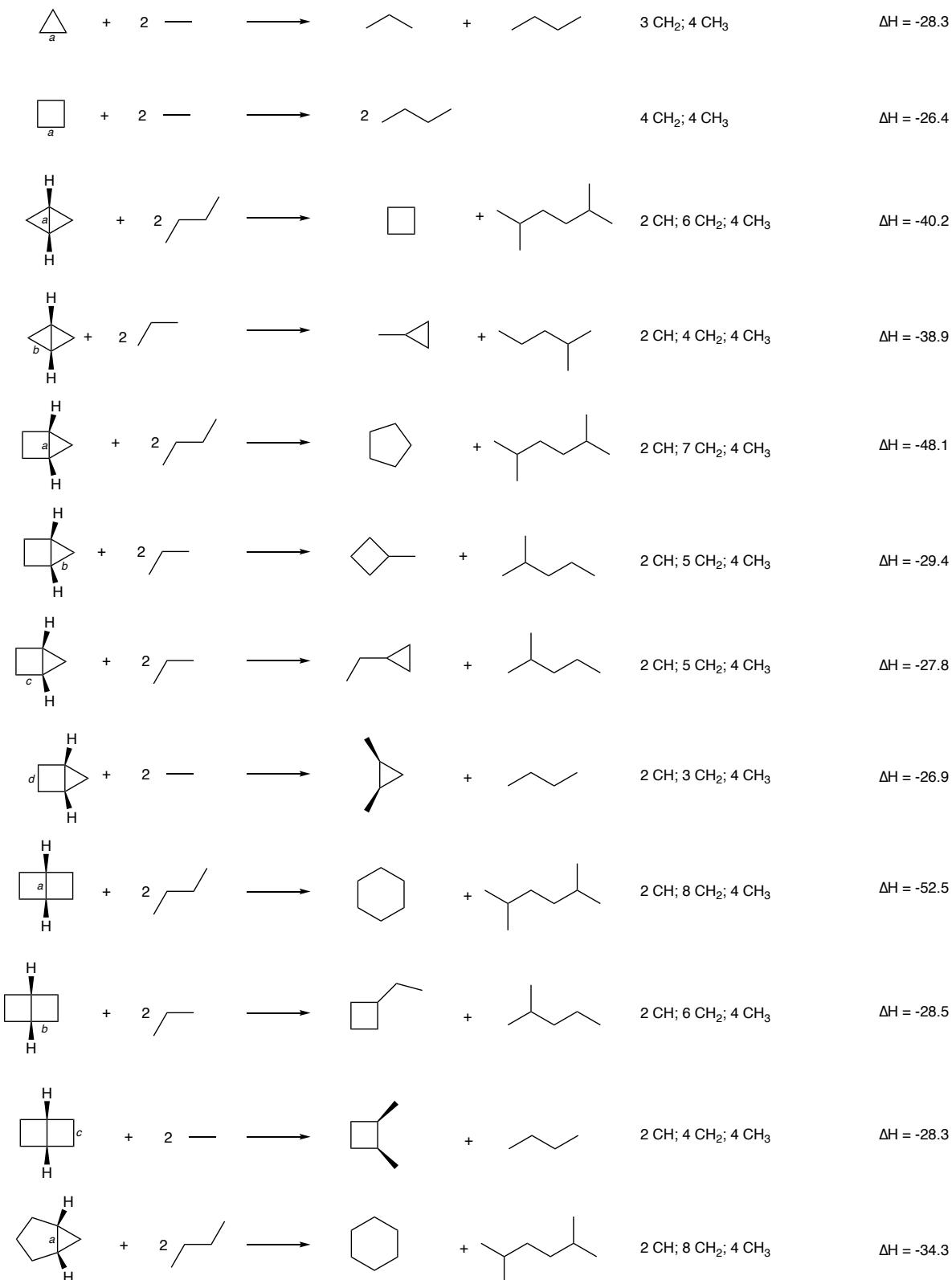


Figure S7: Balanced hydrogen transfer reactions by bond type, group classifications and reaction enthalpies (kcal mol^{-1}) calculated at the DLPNO-CCSD(T)/def2-QZVPP (TightPNO)//B2PLYP-D3BJ/def2-TZVP level.

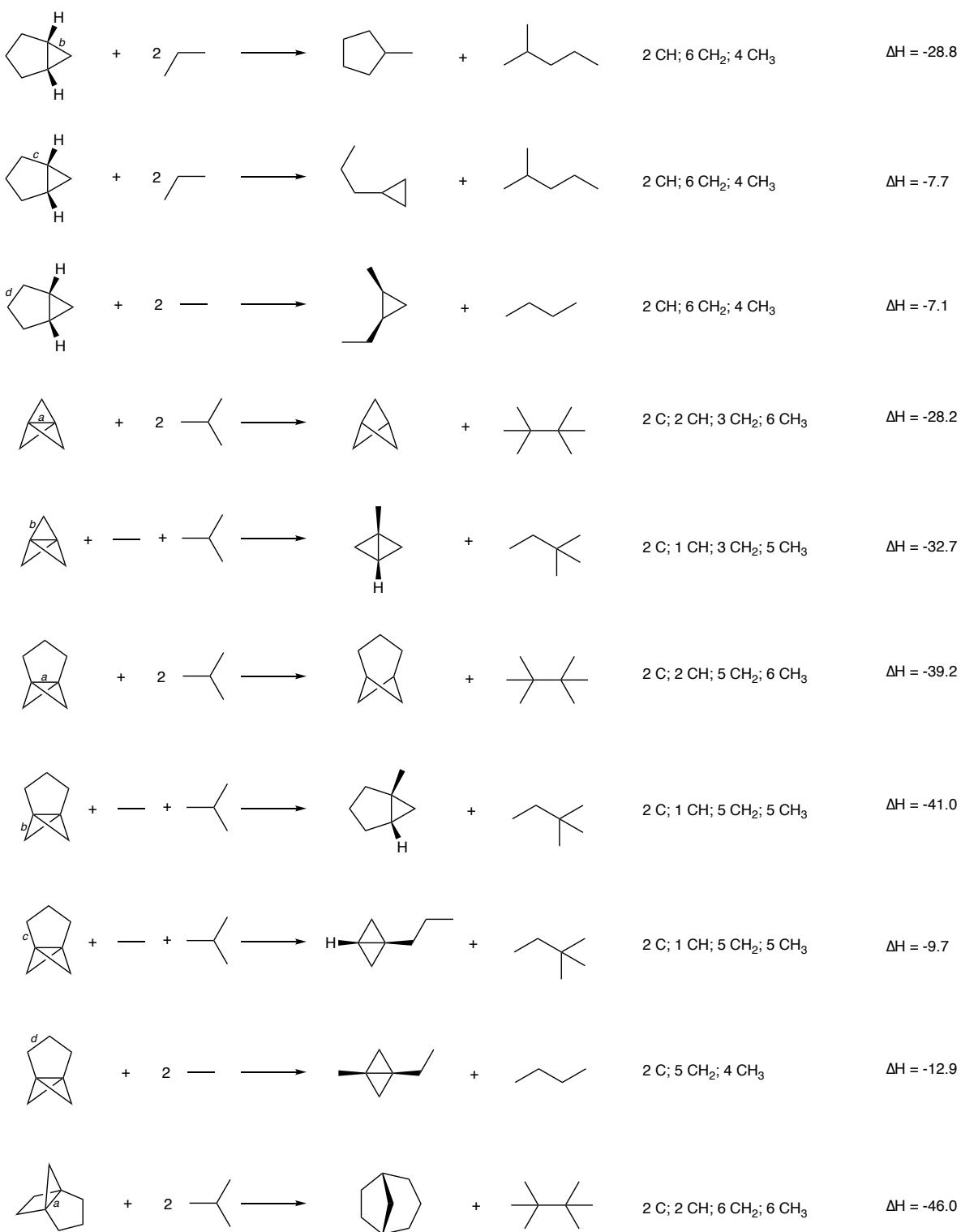


Figure S8: Balanced hydrogen transfer reactions by bond type, group classifications and reaction enthalpies (kcal mol^{-1}) calculated at the DLPNO-CCSD(T)/def2-QZVPP (TightPNO)//B2PLYP-D3BJ/def2-TZVP level.

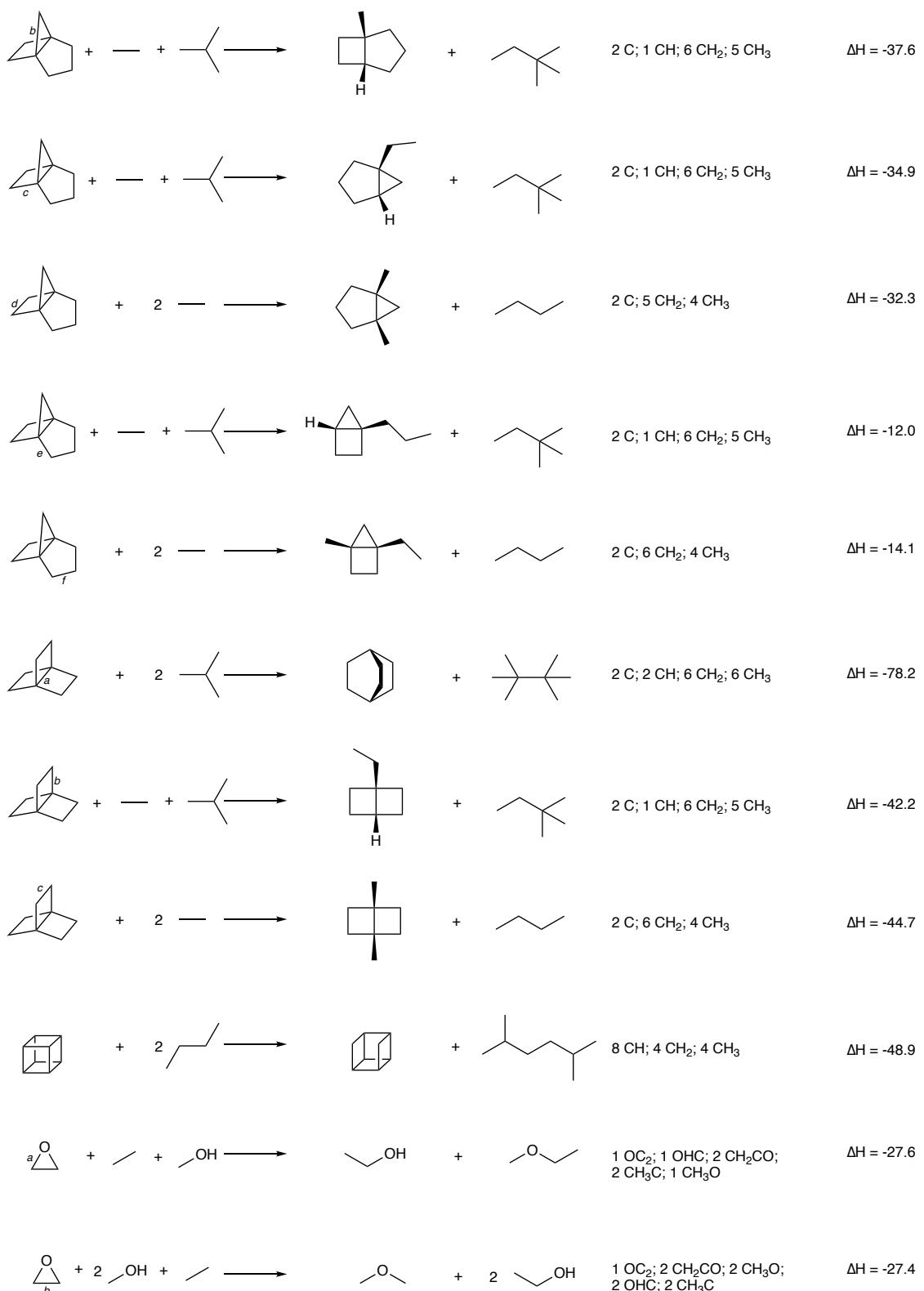


Figure S9: Balanced hydrogen transfer reactions by bond type, group classifications and reaction enthalpies (kcal mol^{-1}) calculated at the DLPNO-CCSD(T)/def2-QZVPP (TightPNO)//B2PLYP-D3BJ/def2-TZVP level.

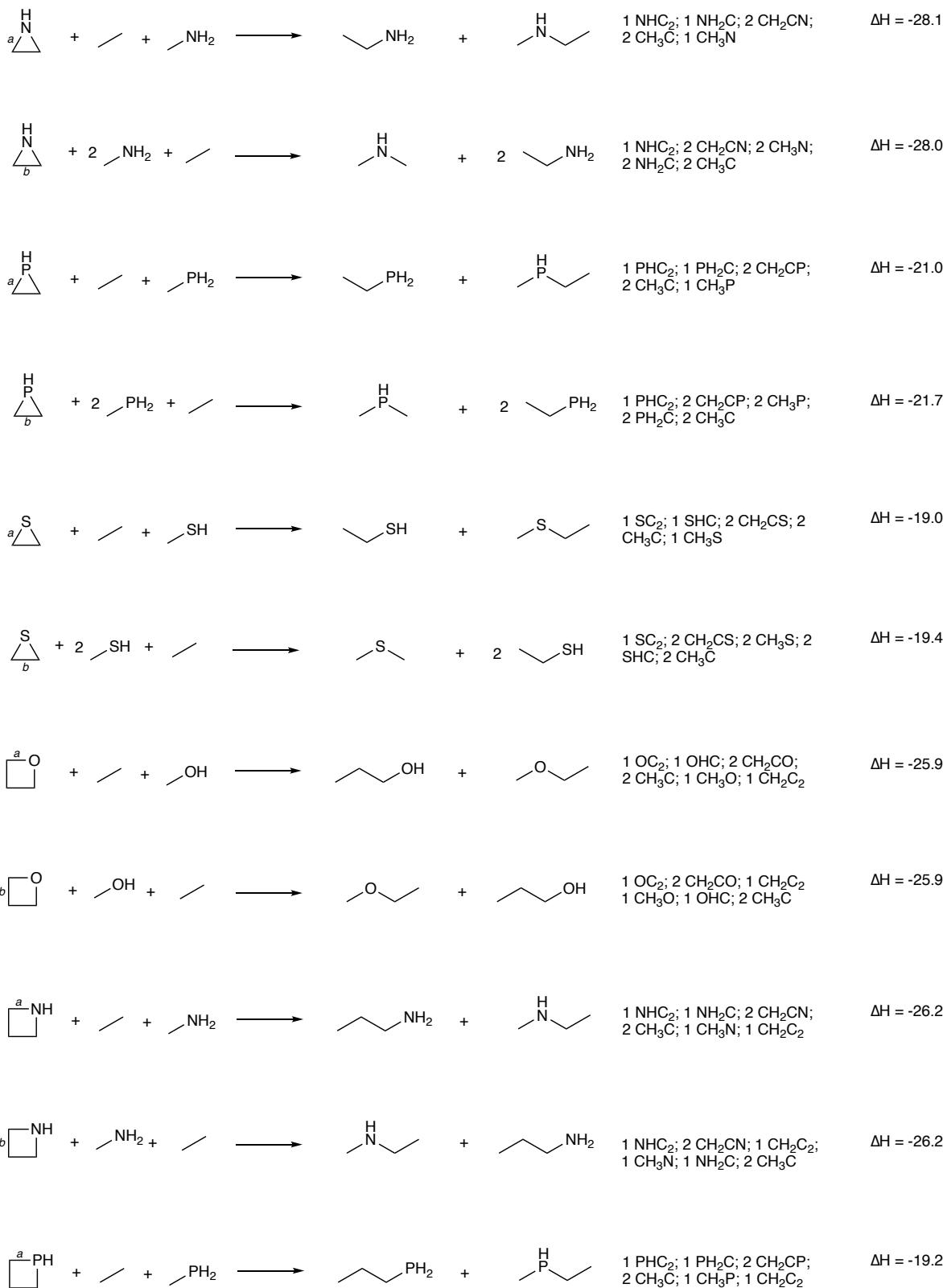


Figure S10: Balanced hydrogen transfer reactions by bond type, group classifications and reaction enthalpies (kcal mol^{-1}) calculated at the DLPNO-CCSD(T)/def2-QZVPP (TightPNO)//B2PLYP-D3BJ/def2-TZVP level.

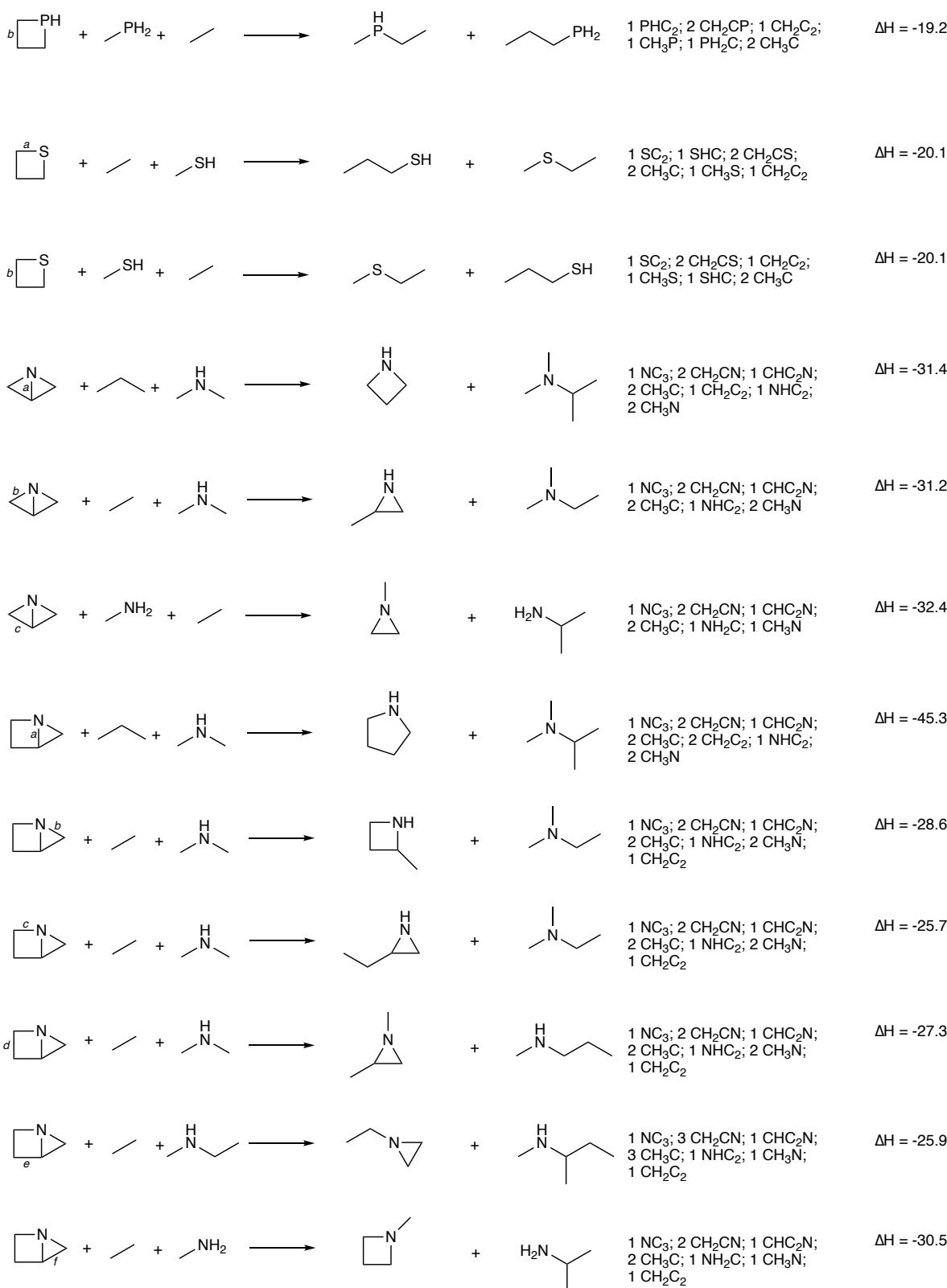


Figure S11: Balanced hydrogen transfer reactions by bond type, group classifications and reaction enthalpies (kcal mol^{-1}) calculated at the DLPNO-CCSD(T)/def2-QZVPP (TightPNO)//B2PLYP-D3BJ/def2-TZVP level.

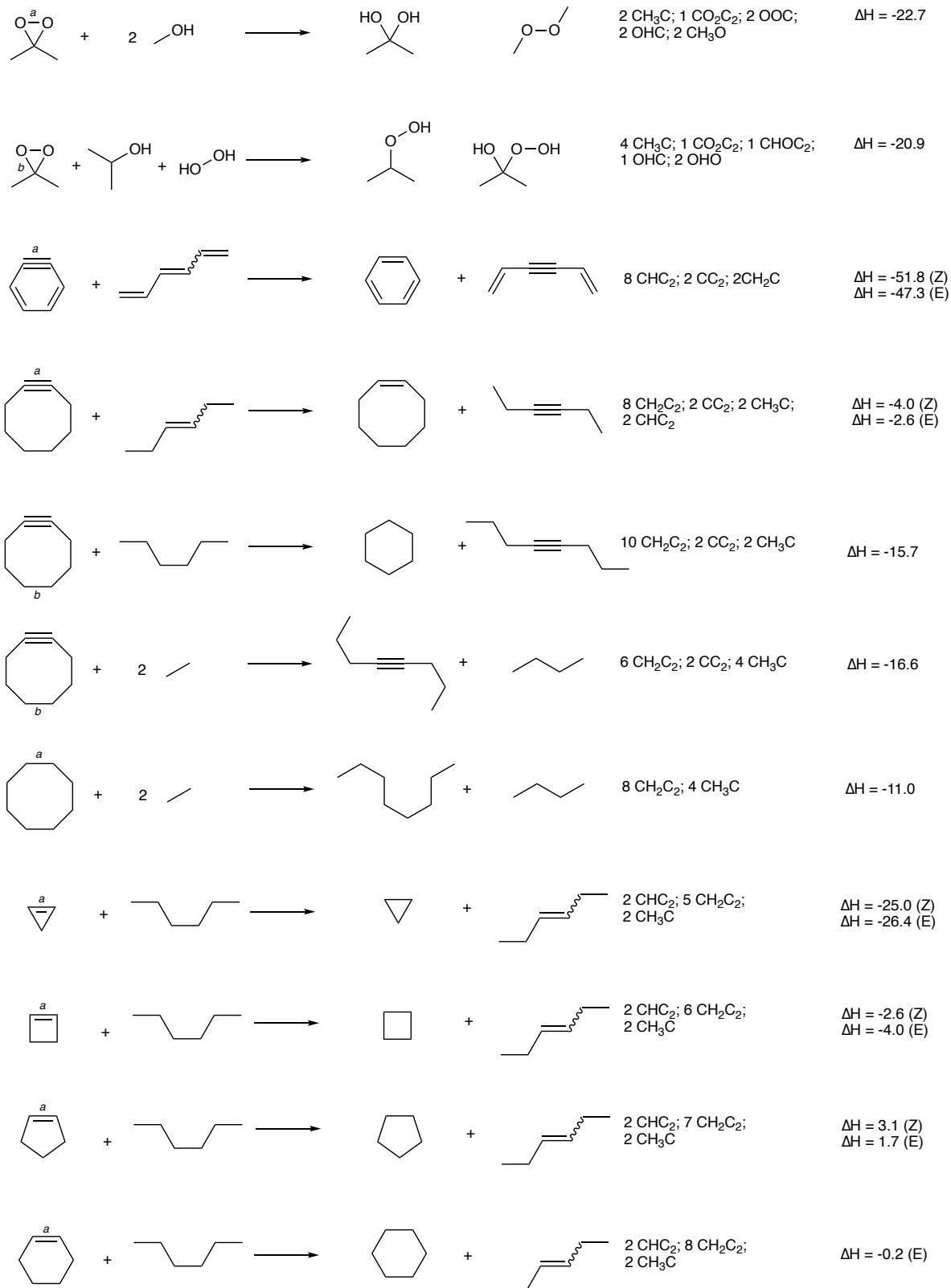


Figure S12: Balanced hydrogen transfer reactions by bond type, group classifications and reaction enthalpies (kcal mol^{-1}) calculated at the DLPNO-CCSD(T)/def2-QZVPP (TightPNO)//B2PLYP-D3BJ/def2-TZVP level.

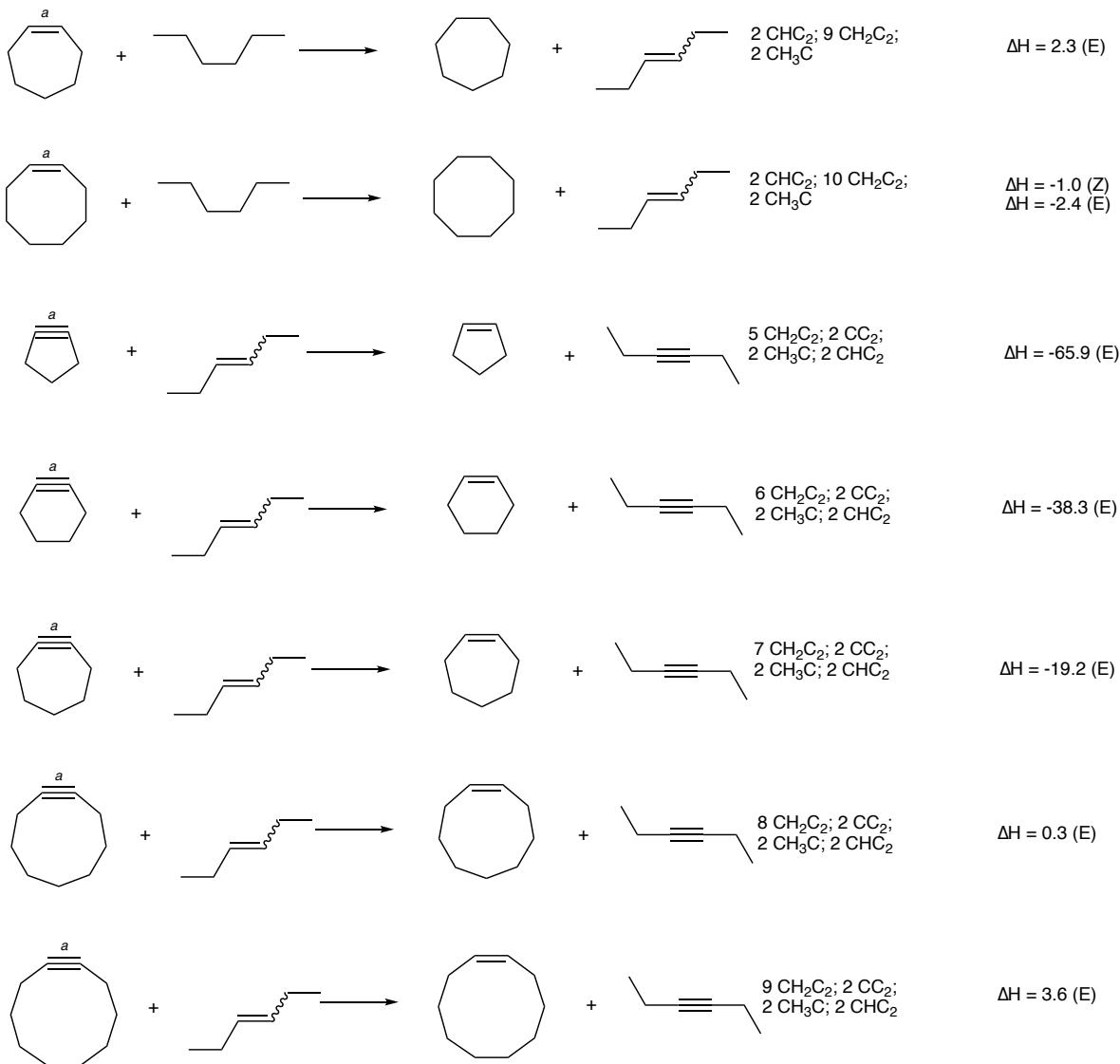


Figure S13: Balanced hydrogen transfer reactions by bond type, group classifications and reaction enthalpies (kcal mol^{-1}) calculated at the DLPNO-CCSD(T)/def2-QZVPP (TightPNO)//B2PLYP-D3BJ/def2-TZVP level.

Molecule	Strain release energy (bond ‘a’) / kcal mol⁻¹			
	This work	Rablen 2020²¹	Wiberg 1986²²	L&G 1976²³
<i>ortho</i> -Benzyne	-51.8	—	—	-44
Cyclopentyne	-65.9	—	—	—
Cyclohexyne	-38.3	—	—	—
Cycloheptyne	-19.2	—	—	—
Cyclooctyne	-2.6	—	—	—
Cyclononyne	0.3	—	—	—
Cyclodecyne	3.6	—	—	—
Cyclopropene	-26.4	-26.3	-27.7	—
Cyclobutene	-4.0	-3.5	-1.9	—
Cyclopentene	1.7	2.1	2.1	—
Cyclohexene	-0.2	-1.5	0.3	—
Cycloheptene	2.3	—	2.7	—
Cyclooctene	-2.4	—	5.5	—

Table S4: Strain release energies (kcal mol⁻¹ for the type ‘a’ bonds (π) shown in Figures S5–S11, calculated at the DLPNO-CCSD(T)/def2-QZVPP (TightPNO)//B2PLYP-D3bJ/def2-TZVP level (this work). Comparison is made with a variety of values from other sources using different computational methods.^{21–23}

Molecule	Strain release energy (bond ‘a’) / kcal mol ⁻¹				
	This work	Rablen 2020 ²¹	Wiberg 1986 ²²	Morgan 2013 ²⁴	Expt
Cyclopropane	-28.3	-27.9	-27.5	—	-27.5 ^a / -27.6 ^b
Cyclobutane	-26.4	-26.8	-26.5	—	-26.5 ^a / -26.2 ^b
Bicyclo[1.1.0]butane	-40.2	-39.7	-37.4	—	-40.3 ^b
Bicyclo[2.1.0]pentane	-48.1	-48.1	-48.5	—	-50.8 ^b
Bicyclo[2.2.0]hexane	-52.5	-52.3	-51.8	—	-50.7 ^b
Bicyclo[3.1.0]hexane	-34.3	-30.6	-31.0	—	-33.9 ^b
[1.1.1]Propellane	-28.2	-32.3	-30.0	—	—
[3.1.1]Propellane	-39.2	—	—	—	—
[3.2.1]Propellane	-46.0	-46.0	—	—	—
[2.2.2]Propellane	-78.2	-82.3	-81.6	—	—
Cubane	-48.9	—	—	—	—
Oxirane	-27.6	—	—	-27.1	-27.4 ^a
Aziridine	-28.1	—	—	-27.5	-27.1 ^a
Epiphosphine	-21.0	—	—	-19.4	—
Episulfide	-19.0	—	—	-17.6	—
Oxetane	-25.9	—	—	—	—
Azetidine	-26.2	—	—	—	—
Phosphetane	-19.2	—	—	—	—
Thietane	-20.1	—	—	—	—
1-Azabicyclo[1.1.0]butane	-31.4	—	—	—	—
1-Azabicyclo[2.1.0]pentane	-45.3	—	—	—	—
Dimethyldioxirane	-22.7	—	—	—	—

^aTaken from ref. [24]. ^bTaken from ref. [23].

Table S5: Strain release energies (kcal mol⁻¹ for the type ‘a’ bonds (σ) shown in Figures S5–S11, calculated at the DLPNO-CCSD(T)/def2-QZVPP (TightPNO)//B2PLYP-D3BJ/def2-TZVP level (this work). Comparison is made with a variety of values from other sources using different computational or experimental methods.^{21–24}

S4 Azide-alkyne (3+2) cycloaddition reactivity

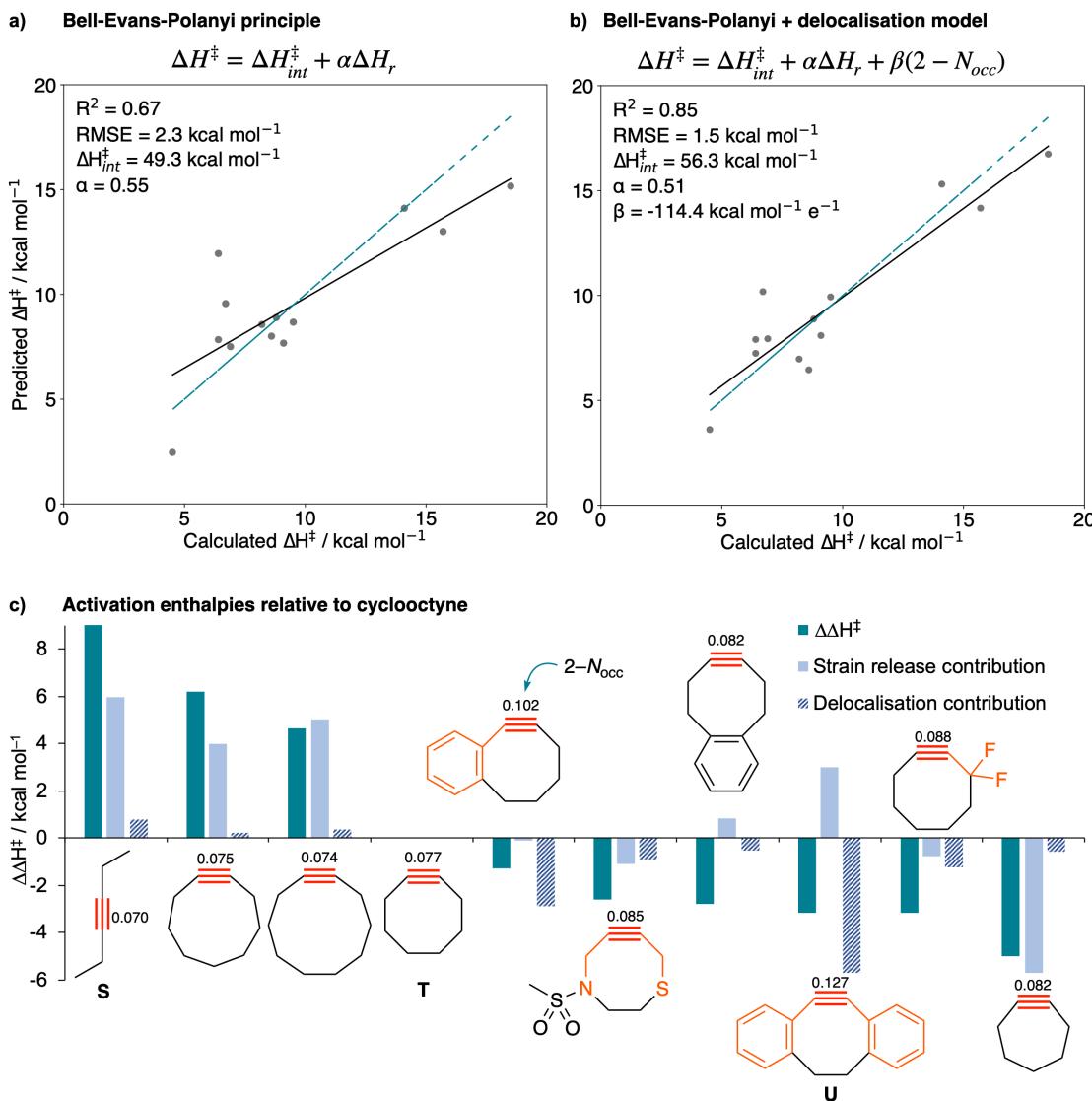


Figure S14: Bell-Evans-Polanyi (**a**) and Bell-Evans-Polanyi + delocalisation (**b**) plots for (3+2) cycloaddition reactions between methyl azide and a selection of alkynes, with data listed in Table S7. Each alkyne $2 - N_{occ}$ value is the mean value obtained for the two π NBOs of the alkyne (Table S6. The blue dashed line denotes perfect correlation. **c**) Delocalisation, not strain release, explains the enhanced reactivity of mono- and dibenzo (**U**) annulated cyclooctynes over unsubstituted cyclooctyne in (3+2) cycloadditions with methyl azide due to enhanced π -conjugation. Difluoro- and heterosubstituted cyclooctynes enjoy cumulative barrier-lowering effects from strain release and enhanced delocalisation through hyperconjugation. Strain release dominates the barrier-lowering effect through decreasing the size of the cycloalkyne ring from $n = \infty$ (**S**) to $n = 7$. Substrates are arranged by decreasing activation enthalpy relative to cyclooctyne (**T**). All enthalpies in kcal mol^{-1} , and $2 - N_{occ}$ values are in e .

Alkyne	π NBO 1	π NBO 2	Mean π 2 – N_{occ}
Hex-3-yne	0.070	0.070	0.070
Cyclooctyne	0.076	0.078	0.077
F ₂ -Cyclooctyne	0.085	0.091	0.088
Dibenzocyclooctyne	0.088	0.166	0.127
Cycloheptyne	0.078	0.086	0.082
Cylononyne	0.075	0.075	0.075
Cyclodecyne	0.073	0.075	0.074
Monobenzocyclooctyne	0.080	0.124	0.102
Distal monobenzocyclooctyne	0.078	0.085	0.082
N,S-Cyclooctyne	0.077	0.093	0.085

Table S6: Delocalisation values (2 – N_{occ} , in e) for the triple bonds of a selection of alkynes.

Alkyne		ΔE	ΔZPE	ΔH	$T\Delta S$	ΔG
Hex-3-yne	TS	18.3	0.7	18.5	-13.5	32.0
	rxn	-64.7	4.6	-61.5	-15.1	-46.4
Cyclooctyne	TS	9.2	0.6	9.5	-12.8	22.3
	rxn	-76.8	4.9	-73.2	-15.4	-57.8
F_2 -Cyclooctyne, syn	TS	5.9	0.8	6.4	-12.9	19.3
	rxn	-78.5	5.2	-74.7	-15.6	-59.1
F_2 -Cyclooctyne, anti	TS	8.4	0.7	8.8	-12.7	21.5
	rxn	-76.5	5.0	-72.8	-15.6	-57.2
Dibenzocyclooctyne	TS	5.8	0.9	6.4	-13.4	19.8
	rxn	-70.7	4.5	-67.3	-14.8	-52.5
Cycloheptyne	TS	4.1	0.7	4.5	-12.1	16.6
	rxn	-88.1	5.1	-84.4	-14.9	-69.5
Cyclononyne	TS	15.5	0.5	15.7	-12.5	28.3
	rxn	-68.8	4.7	-65.4	-14.9	-50.5
Cyclodecyne	TS	13.7	0.9	14.1	-13.3	27.4
	rxn	-66.9	5.0	-63.4	-15.7	-47.7
Monobenzocyclooctyne, syn	TS	8.2	0.7	8.6	-12.9	21.4
	rxn	-78.0	5.0	-74.4	-15.5	-58.9
Monobenzocyclooctyne, anti	TS	7.8	0.8	8.2	-13.0	21.2
	rxn	-76.9	4.7	-73.4	-15.1	-58.3
Distal monobenzocyclooctyne	TS	6.4	0.6	6.7	-12.5	19.2
	rxn	-75.2	4.9	-71.6	-14.8	-56.7
N,S-Cyclooctyne, anti	TS	8.8	0.5	9.1	-12.7	21.8
	rxn	-78.6	5.1	-75.0	-15.9	-59.1
N,S-Cyclooctyne, syn	TS	6.5	0.8	6.9	-13.5	20.4
	rxn	-78.8	5.1	-75.3	-16.4	-58.9

Table S7: Differences in thermodynamic quantities (kcal mol^{-1}) for the cycloaddition between methyl azide and a range of alkynes, at the B2PLYP-D3BJ/def2-TZVP level.

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