Supporting Information

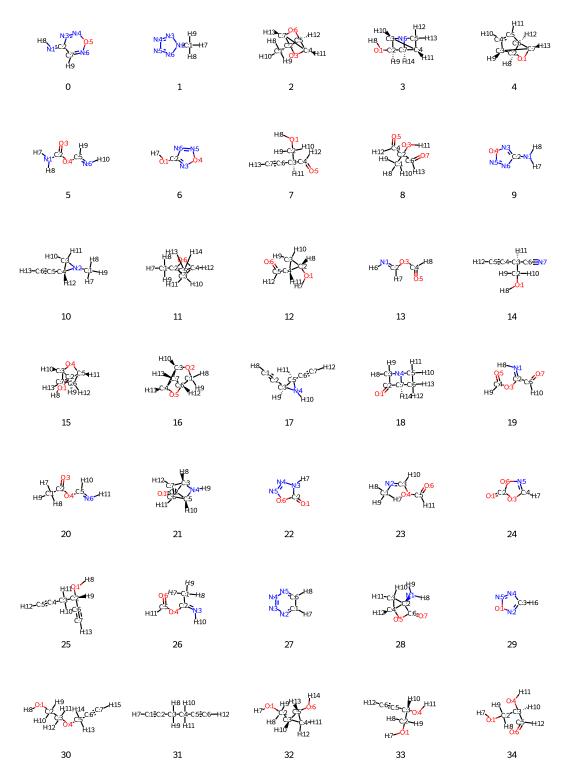


Figure S1: 163 reactants tested - part 1

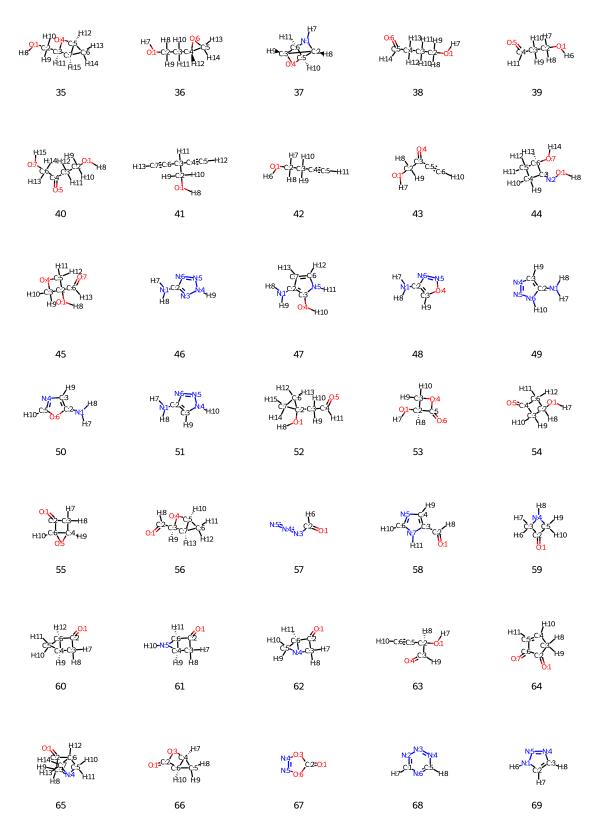


Figure S1: 163 reactants tested - part 2

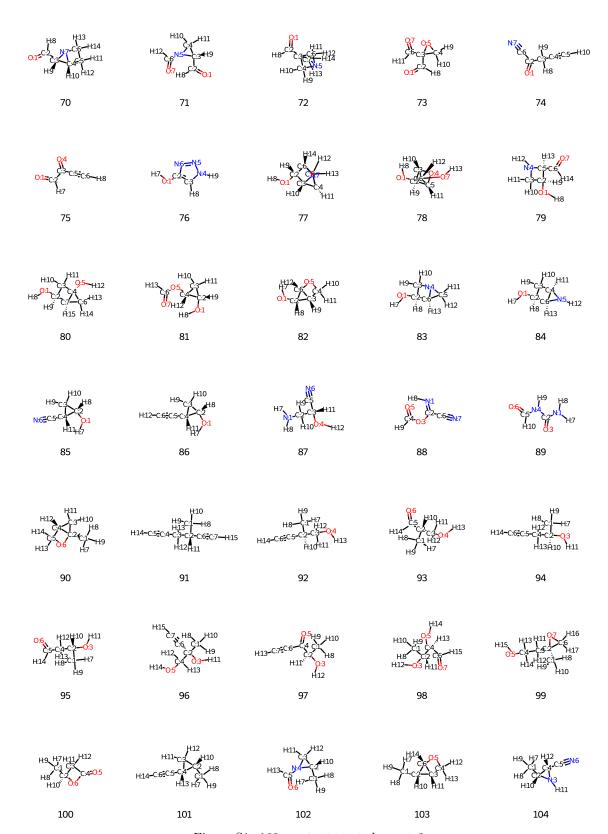


Figure S1: 163 reactants tested - part 3

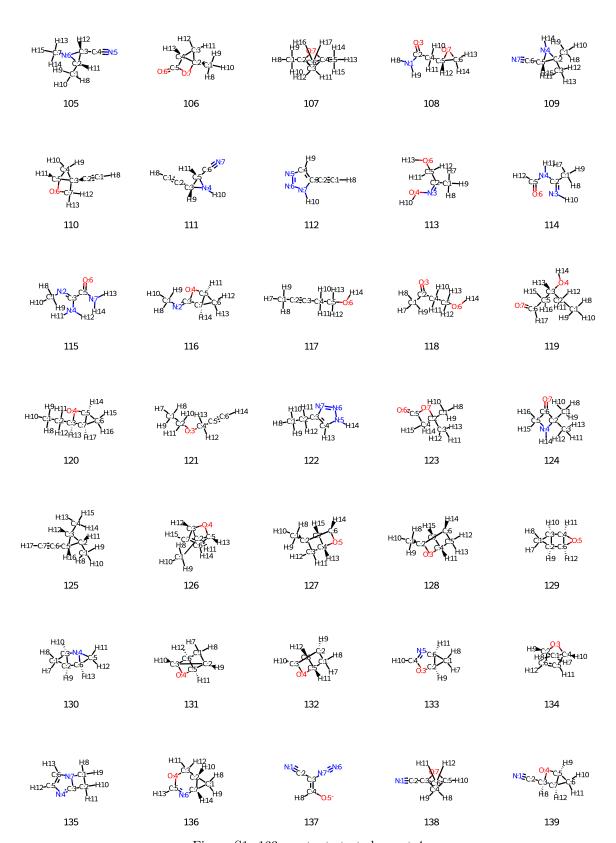


Figure S1: 163 reactants tested - part $4\,$

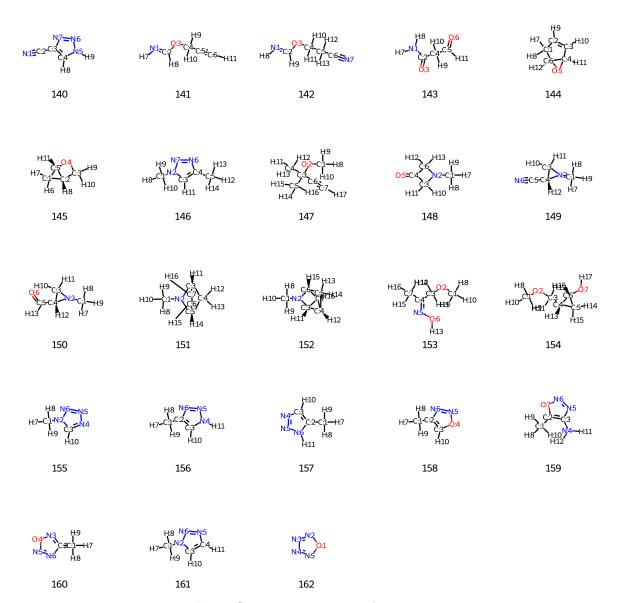


Figure S1: 163 reactants tested - part 5

$ m R_{ID}$	Reactant	Energetics	Reaction
R1084	89	ΔE^{\dagger} = 28 kcal/mol ΔE = 8 kcal/mol	0.6 H9 H8 O.5 N4 C.2 N1 H7 H10 C.5 N4 C.2 N1
R1108	26	ΔE^{\dagger} = 21 kcal/mol ΔE = -13 kcal/mol	H11 63 H8 H8 H10 H10 H9 H10 H8 H11 H8 H11 H8
R1110	26	ΔE^{\dagger} = 20 kcal/mol ΔE = -8 kcal/mol	H ₁₀
R1334	20	ΔE^{\dagger} = 26 kcal/mol ΔE = -16 kcal/mol	H_{7} H_{9} C_{1} C_{1} C_{1} C_{1} C_{1} C_{1} C_{1} C_{2} C_{1} C_{1} C_{2} C_{3} C_{4} C_{1} C_{1} C_{2} C_{3} C_{4} C_{5} C_{1} C_{2} C_{1} C_{2} C_{3} C_{4} C_{5} C_{5} C_{6} C_{7} C_{1} C_{1} C_{2} C_{3} C_{4} C_{5} C_{5} C_{6} C_{1} C_{1} C_{2} C_{1} C_{2} C_{3} C_{4} C_{5} C_{1} C_{2} C_{3} C_{4} C_{5} C_{5} C_{6} C_{7} C_{1} C_{1} C_{2} C_{1} C_{2} C_{3} C_{4} C_{5} C_{5} C_{5} C_{6} C_{7} C_{7
R1689	5	ΔE^{\dagger} = 15 kcal/mol ΔE = -5 kcal/mol	H7 N5 H10 H10 H10 H10 H17
R1957	13	ΔE^{\dagger} = 29 kcal/mol ΔE = -13 kcal/mol	H6 N3 03 04 H8 05 €04 + H7 H6
R1958	13	ΔE^{\dagger} = 25 kcal/mol ΔE = -18 kcal/mol	H ₁₆ N ₁ C ₂ O ₃ C ₄ H ₁₈ O ₅
R2399	23	ΔE^{\dagger} = 21 kcal/mol ΔE = -19 kcal/mol	$\begin{array}{c} & & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ &$

R2514	6	$\Delta E^{\dagger} = 23 \text{ kcal/mol}$ $\Delta E = -3 \text{ kcal/mol}$	N6=N5 + H7 01-C2=N3L-O4
R2523	114	ΔE^{\dagger} = 30 kcal/mol ΔE = -2 kcal/mol	H:12 H:10 H:10 H:10 H:10 H:10 H:10 H:10 H:10
R2552	67	ΔE^{\dagger} = 16 kcal/mol ΔE = -49 kcal/mol	N4=03 N5=06 + 03=C2=01
R3096	22	ΔE^{\dagger} = 19 kcal/mol ΔE = -24 kcal/mol	N5 N4 N3 H7 + 06 C2 C2 C2 C1
R3504	27	ΔE^{\dagger} = 25 kcal/mol ΔE = 8 kcal/mol	N:4 N:5 C:6 H:8 N:4 N:5 C:6 C:1 N:3 N:3 N:3 N:3 N:3 N:3 N:5 C:6 N:2 N:3 N:3 N:5 C:6 N:2 N:3 N:5 C:6 N:2 N:3 N:5 C:6 N:2 N:3 N:5 C:6 N:2 N:5 C:6 N:5 C:
R3648	61	ΔE^{\dagger} = 29 kcal/mol ΔE = -3 kcal/mol	H:10 $H:10$
R3725	29	ΔE^{\dagger} = 17 kcal/mol ΔE = -21 kcal/mol	H:9 H:8 N5 N4 + H6 C3 N2 → N5 N4 + H6 C3 N2 → O1
R4612	49	ΔE^{\dagger} = 26 kcal/mol ΔE = 13 kcal/mol	H9 N4 C3 H10 N6 C2 N1 N5 N6 N5 N6 N5 N6 N5 N6
R4808	66	ΔE^{\dagger} = 26 kcal/mol ΔE = -10 kcal/mol	H10 H10 H10 H10 H10 H10 H10 H10

R5847	86	ΔE^{\dagger} = 25 kcal/mol ΔE = -20 kcal/mol	H12— $C6$ = $C5$ — $C4$ $H11$ $H10$ H
R6490	159	ΔE^{\dagger} = 11 kcal/mol ΔE = -14 kcal/mol	H9 H12 H11 H10 H8 + N6 N5
R7201	19	ΔE^{\dagger} = 28 kcal/mol ΔE = -8 kcal/mol	H8 H10 O.5 C.6 O.7 H.9 H.9 O.3 C.6 O.7
R7207	19	ΔE^{\dagger} = 27 kcal/mol ΔE = 0 kcal/mol	H ₈ H ₉ H ₁₀ H
R7885	21	ΔE^{\dagger} = 13 kcal/mol ΔE = -47 kcal/mol	H12 01 = 02 + H10 H10 H10 H10
R7931	135	ΔE^{\dagger} = 28 kcal/mol ΔE = -2 kcal/mol	$\begin{array}{cccccccccccccccccccccccccccccccccccc$
R8367	79	ΔE^{\dagger} = 24 kcal/mol ΔE = -2 kcal/mol	H11 H13 H13 H13 H14
R8701	58	ΔE^{\dagger} = 27 kcal/mol ΔE = 19 kcal/mol	H_{10} C_{10} C

R8816 47
$$\Delta E^{\dagger} = 20 \text{ kcal/mol}$$

$$\Delta E = 17 \text{ kcal/mol}$$

$$\Delta E = 18 \text{ kcal/mol}$$

$$\Delta E = -2 \text{ kcal/mol}$$

$$\Delta E = 21 \text{ kcal/mol}$$

$$\Delta E = -3 \text{ kcal/mol}$$

$$\Delta E = -10 \text{ kcal/mol}$$

Table S1: 30 target reactions with one-fragment reactants and barriers below 30 kcal/mol Reactions colored in red: IRC following re-optimization of the TS led to different reactant/product pair than the one stated.

Reactions colored in blue: IRC following re-optimization of the TS led to a different stereoisomer of the reactant (rotation around C=N bond).

R_{ID} refers to the reaction labelling in 19 while the Reactant index refers to the indexing in Figure 51

$ m r_{ID}$	Reactant	Energetics	Reaction
N11	14	ΔE^{\dagger} = 37 kcal/mol	H11 H12—C5=C4—C3—C6=N7 H12 C4 C3 H9 01
		ΔE = 4 kcal/mol	H: C5 H10 H8 C6 N7 H10
N12	37	ΔE^{\dagger} = 43 kcal/mol	H:11 H:8 O:4
		ΔE = -44 kcal/mol	H9 $C:3$ $C:2$ $C:2$ $C:3$ $C:2$ $C:3$
			H:10 H:11
N13	45	ΔE^{\dagger} = 35 kcal/mol	H110 C3 C5 H111 H112 C5 C4 H19
		ΔE = -18 kcal/mol	H9 $C2$ $H12$ $H8$ $C2$ $H13$ $H8$ $C2$ $H10$
			H8—O:1
N14	52	ΔE^{\dagger} = 39 kcal/mol	H15 C6 H9 O5 C6 H11
		$\Delta E = -21 \text{ kcal/mol}$	C2-C3-C4 H14 C2-C3-C4 H14 C2-C3-H9 H10 H10 H11
NI1F	F.C.	Λ E [†] - 27 l1/1	H:10 H:10 O:1.
N15	56	ΔE^{\dagger} = 37 kcal/mol ΔE = -34 kcal/mol	C2 C3 C6 H11 0.4 C.5 H12 C2
		AL - Of Real mor	O.1 H.12 H.11 H.13 H.13
N16	73	ΔE^{\dagger} = 42 kcal/mol	H:11 0.5
		$\Delta E = 32 \text{ kcal/mol}$	H:9 C:3 C:2 H:8
		,	H:10 H:10 C:6 O:7
N17	73	ΔE^{\dagger} = 42 kcal/mol	H:11 05 H:9
		$\Delta E = -7 \text{ kcal/mol}$	0.7 C3 C4 C3
			H:8 C2 O:5 H:8 H:8
N18	141	ΔE^{\dagger} = 33 kcal/mol	H10 H10 H8
		ΔE = -22 kcal/mol	H_7 C_5 C_6 C_7 C_8

N19 | 141 |
$$\Delta E^{\dagger} = 43 \text{ kcal/mol}$$
 | $\Delta E = -31 \text{ kcal/mol}$ | $\Delta E = -31 \text{ kcal/mol}$ | $\Delta E = 38 \text{ kcal/mol}$ | $\Delta E = 33 \text{ kcal/mol}$ | $\Delta E = 33 \text{ kcal/mol}$ | $\Delta E = 34 \text{ kcal/mol}$ | $\Delta E = -3 \text{ kcal/mol}$ |

Table S2: 11 new reactions found with barriers above 30 kcal/mol - lower than existing reactions.

 $r_{\rm ID}$ refers to the reaction labelling used for new reactions while the Reactant index refers to the indexing of reactants in Figure $\boxed{\rm S1}$

$ m r_{ID}$	Reactant	Energetics	Reaction
N22	5	ΔE^{\dagger} = 32 kcal/mol ΔE = -21 kcal/mol	H7 N1 C2 A C5 N6 H10 H8 H9 O3 H7 H7
N23	8	ΔE^{\dagger} = 46 kcal/mol ΔE = -7 kcal/mol	H11 Q3 H9 05 C4 C2 H8 H12 C6 H13 H12 H8 H12 H8 H13 H9 H10
N24	8	ΔE^{\dagger} = 48 kcal/mol ΔE = -4 kcal/mol	H11 03 H9 H10 H10 H11 03 H112 H11 03 H113 H113 H111 03 H112 H111 03 H1
N25	8	ΔE^{\dagger} = 47 kcal/mol ΔE = 1 kcal/mol	H11
N26	8	ΔE^{\dagger} = 49 kcal/mol ΔE = 43 kcal/mol	H11 03 H9 H10 05 H8 07 C6 C2 C1 H10 H12 H13 H11 03 H9
N27	12	ΔE^{\dagger} = 42 kcal/mol ΔE = -5 kcal/mol	H10 H2 H30 H30 H41
N28	19	ΔE^{\dagger} = 66 kcal/mol ΔE = -1 kcal/mol	H8 H10
N29	21	ΔE^{\dagger} = 39 kcal/mol ΔE = -65 kcal/mol	$\begin{array}{cccccccccccccccccccccccccccccccccccc$

N30 23
$$\Delta E^{\dagger} = 58 \text{ kcal/mol}$$
 $\Delta E = 30 \text{ kcal/mol}$ $\Delta E = 30 \text{ kcal/mol}$ $\Delta E = 14 \text{ kcal/mol}$ $\Delta E = 14 \text{ kcal/mol}$ $\Delta E = 0 \text{ kcal/mol}$ $\Delta E = 0 \text{ kcal/mol}$ $\Delta E = -21 \text{ kcal/mol}$ $\Delta E = -21 \text{ kcal/mol}$ $\Delta E = -3 \text{ kcal/$

Table S3: 15 new reactions found with barriers over 30 kcal/mol. Note that Grambow et al reported a reaction to another diastereomer of the product of N32. We include it here because we saw a significantly lower barrier than the reported (55 kcal/mol). $r_{\rm ID}$ refers to the reaction labelling used for new reactions while the Reactant index refers to the indexing of reactants in Figure $\boxed{\$1}$

$ m R_{ID}$	Reactant	Energetics	Reaction
R129	1	ΔE^{\dagger} = 8 kcal/mol ΔE = -34 kcal/mol	04 C3 C5 N6 H7 + 01 = C7 N6 C5 C3 101
R5946	2	ΔE^{\dagger} = 14 kcal/mol ΔE = -44 kcal/mol	NS=CS=CS + H9 CS + H8 H2 OA H12 H10 H8 H20 OA H12
R2793	3	ΔE^{\dagger} = 10 kcal/mol ΔE = -24 kcal/mol	H7 C3 N4 C5 06 H8 H9 C5 H8 H9 C5 06 C2 O1
R1689	4	ΔE^{\dagger} = 20 kcal/mol ΔE = 5 kcal/mol	H8 + H9 H7 H10 H7 H8
R4870	5	ΔE^{\dagger} = 15 kcal/mol ΔE = -19 kcal/mol	H3 H3 H3 H312 H32 H33 H34 H33 H35 H36 H37
R2042	6	ΔE^{\dagger} = 19 kcal/mol ΔE = -62 kcal/mol	H11—H7 + H13 H10
R2191	7	ΔE^{\dagger} = 19 kcal/mol ΔE = -46 kcal/mol	$H_{12} \xrightarrow{H_8} H_{7} + H_{13} \xrightarrow{H_{10}} H_{10} \xrightarrow{H_{10}} H_{10} \xrightarrow{H_{11}} H_{11} \xrightarrow{H_{11}} H_{11} \xrightarrow{H_{12}} H_{13} \xrightarrow{H_{13}} H_{11} \xrightarrow{H_{12}} H_{13} \xrightarrow{H_{13}} H_{13} \xrightarrow{H_{14}} H_{14} \xrightarrow{H_{14}}$
R2353	8	ΔE^{\dagger} = 20 kcal/mol ΔE = -39 kcal/mol	H9 C3 04 + H10 H2 C3 04 H10

R2858	9	$\Delta E^{\dagger} = 19 \text{ kcal/mol}$ $\Delta E = -52 \text{ kcal/mol}$	H8 H11 H2 H12 H2 H3
R6677	10	$\Delta E^{\dagger} = 20 \text{ kcal/mol}$ $\Delta E = -34 \text{ kcal/mol}$	03—H11 H12 H10 H13 H14 H15 H16 H10 H19
R1110	11	ΔE^{\dagger} = 28 kcal/mol ΔE = 8 kcal/mol	H9 N3 €C2 −C1 −H7 + H10 C5 C5 C4 H3 H11 H11 H11 H11 H11 H10
R7854	12	ΔE^{\dagger} = 21 kcal/mol ΔE = -58 kcal/mol	H10. C3. C5H11 + H13H12 H13H12 H13
R73	13	ΔE^{\dagger} = 28 kcal/mol ΔE = -33 kcal/mol	H6 H11 H11 H2 H13
R11240	14	ΔE^{\dagger} = 26 kcal/mol ΔE = -38 kcal/mol	H11 H13 H13 H15 H16 H16 H16 H16 H16 H17 H18
R11355	15	ΔE^{\dagger} = 25 kcal/mol ΔE = -48 kcal/mol	H15-C6 H12 H13-H9 H15-C6 H12 H9 H16 H16 H18
R11396	16	ΔE^{\dagger} = 28 kcal/mol ΔE = -56 kcal/mol	06 ■C5 + 04 N3 C2 N10 H8
R11478	17	ΔE^{\dagger} = 25 kcal/mol ΔE = -44 kcal/mol	H11

R10077	18	ΔE^{\dagger} = 10 kcal/mol ΔE = -39 kcal/mol	H11 C2 H12 H12 H12 H11 H11 H11 H11 H11 H11 H1
R10514	19	ΔE^{\dagger} = 25 kcal/mol ΔE = -33 kcal/mol	H9 1=C H12 H13 O5 H8 H15 H14 H12 H10 H15 H14 H12 H10 H15 H14 H15 H15 H14 H12 H10 H15 H15 H14 H12 H10 H15
R8426	20	ΔE^{\dagger} = 26 kcal/mol ΔE = -39 kcal/mol	H10 H13 H16 H16 H17 H16 H17 H16 H17 H16 H17 H16 H17 H16 H17 H16

Table S4: 20 target reactions with two-fragment reactants and barriers below 30 kcal/mol. $R_{\rm ID}$ refers to the reaction labelling in 19 while the Reactant index will be used to refer to the reactant of the reaction

Figure S2

Figure S2: (continued)

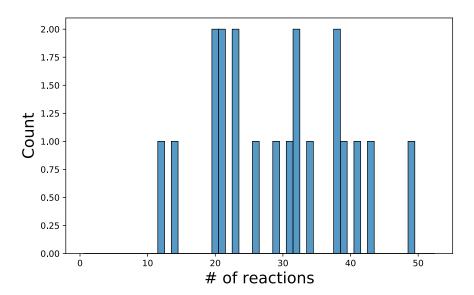


Figure S3: Distribution of the number of different reactions found during the 100 meta-MD runs (with default hyperparameter set) for the 20 bimolecular reactants. The average is 29.3 reactions/reactant.