Supplementary Information for

Prediction of Transition State Structures of General Chemical Reactions via Machine Learning

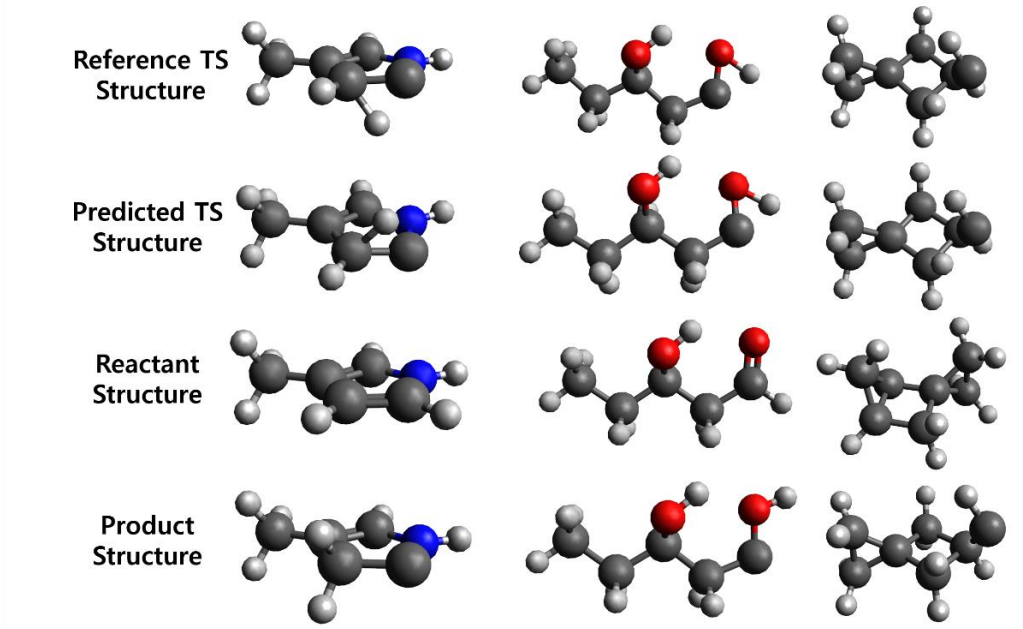
Sunghwan Choi

Division of National Supercomputing,
Korea Institute of Science and Technology Information,
245 Daehak-ro, Yuseong-gu, Daejeon 34141, Republic of Korea

*E-mail: sunghwanchoi@kisti.re.kr

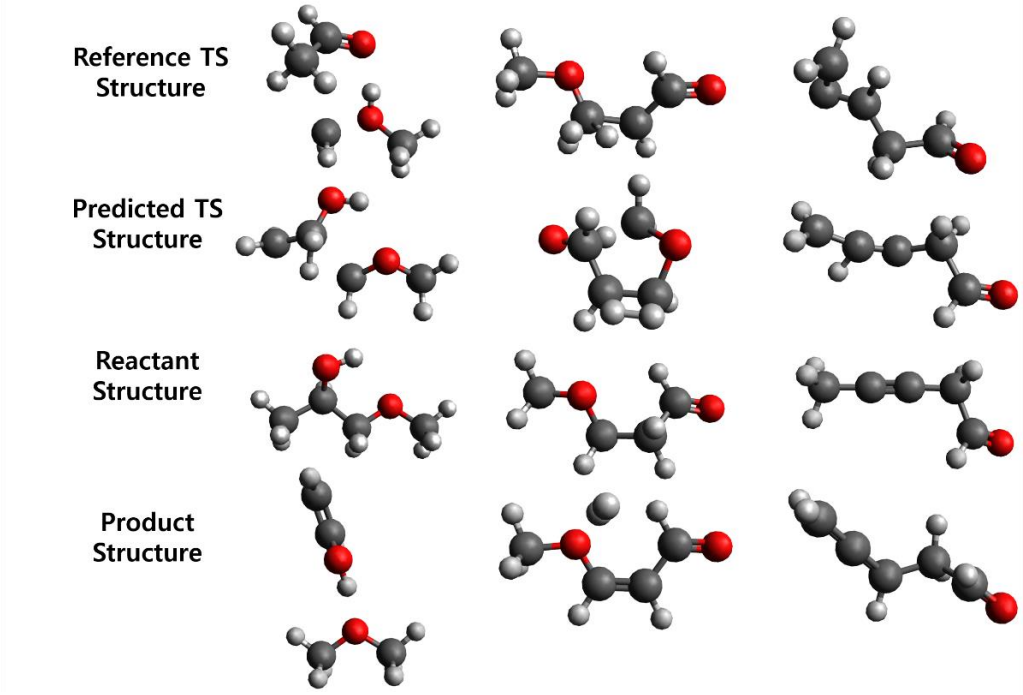
(a)

Reaction Index	700	7842	9558
Molecular MAPE(%)	0.88	0. 89	0.95
Molecular MAE (pm)	2.28	2.48	2.51

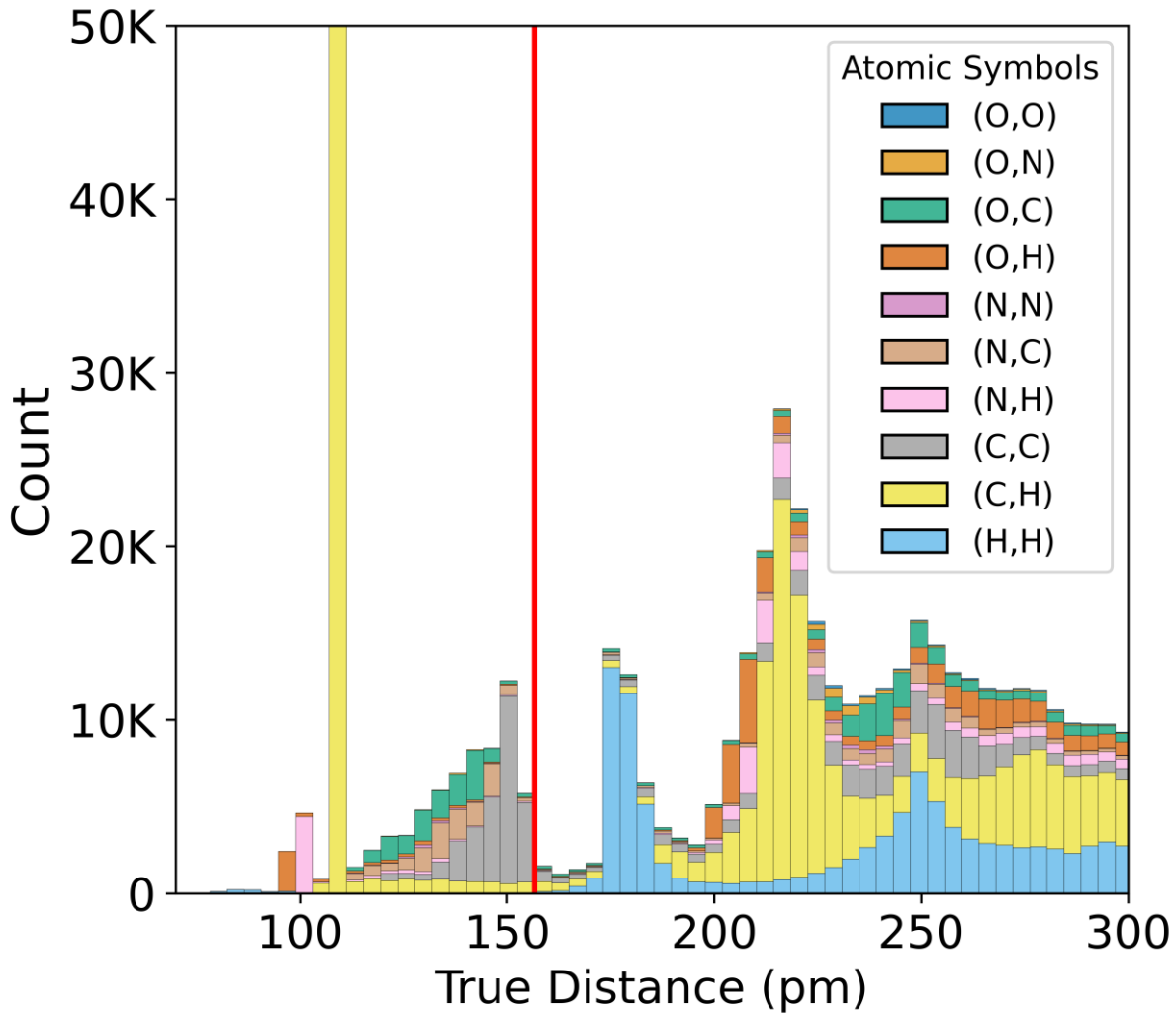


(b)

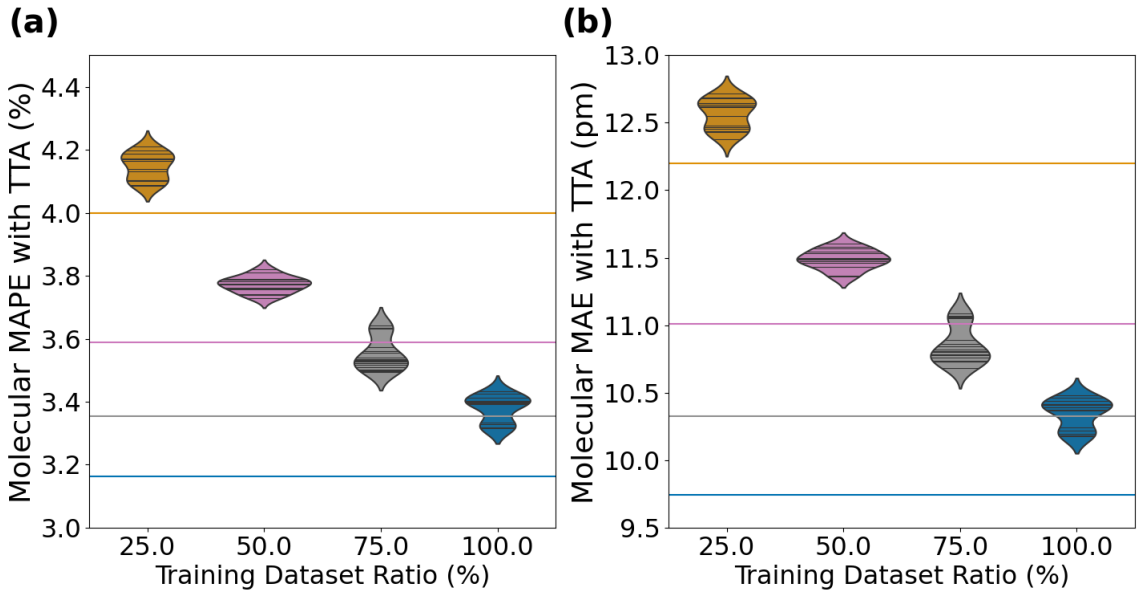
Reaction Index	5028	3985	2011
Molecular MAPE(%)	16.8	16.7	15.3
Molecular MAE (pm)	52.3	61.2	41.9



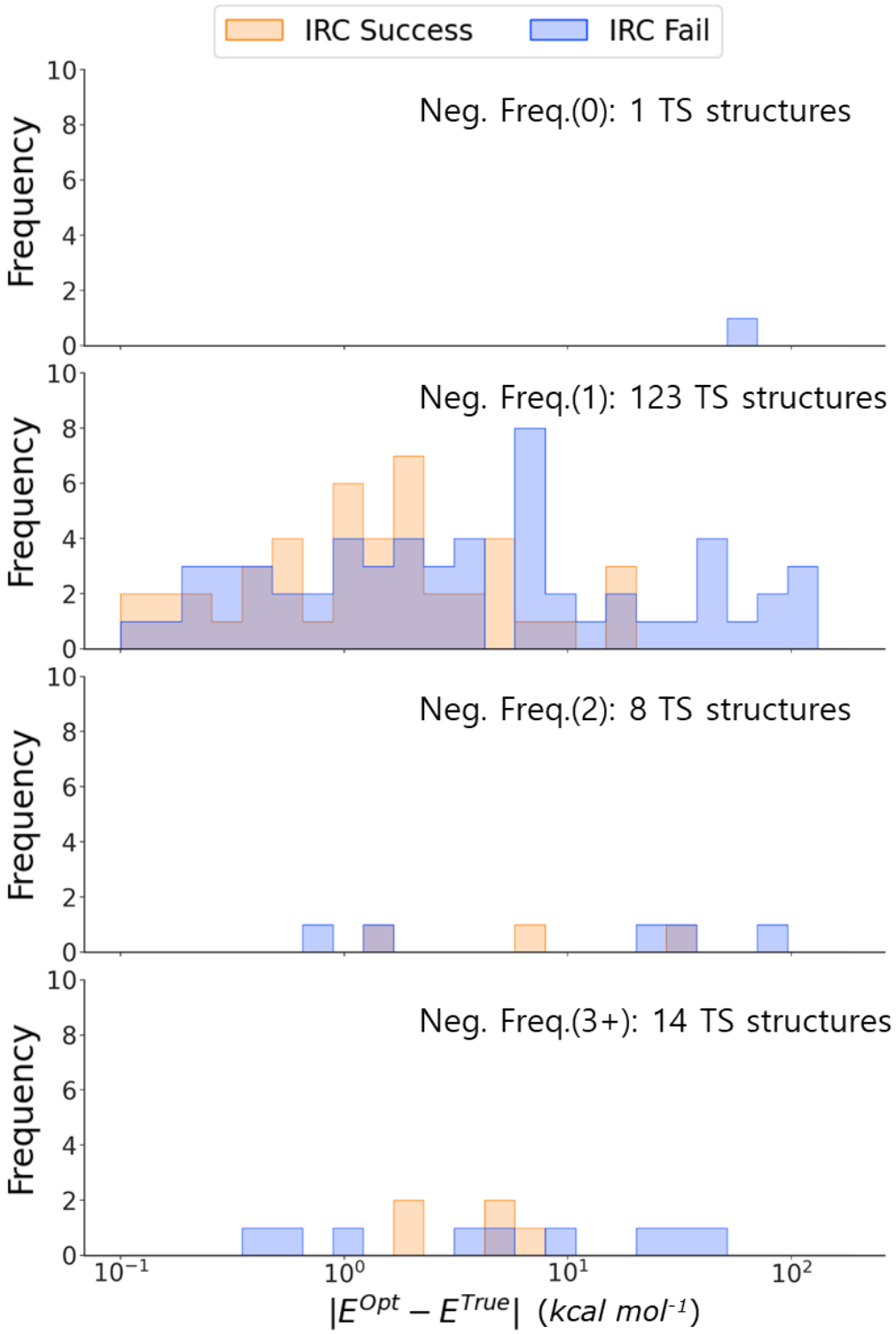
Supplementary Figure 1. Three (a) best and (b) worst inferences for test reactions in terms of molecular mean absolute percentage error (MAPE). The train and test are performed with random spitted subsets of Grambow's reaction database.



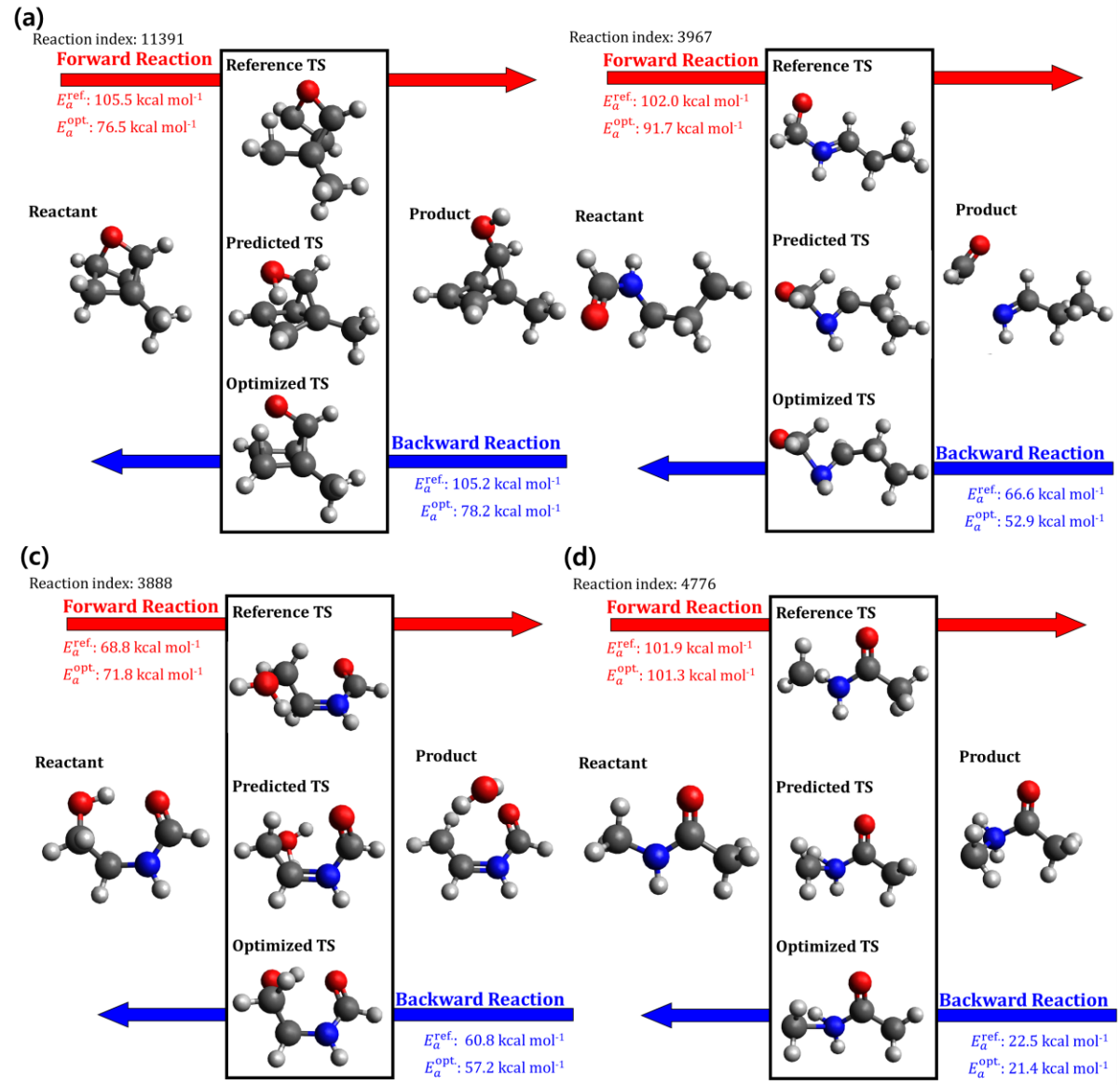
Supplementary Figure 2. Stacked bar chart to represent distribution of all combinations of atomic numbers in Grambow's reaction database. The red vertical line indicate a value of 156.6 pm, which is the criterion for the presence of a chemical bond.



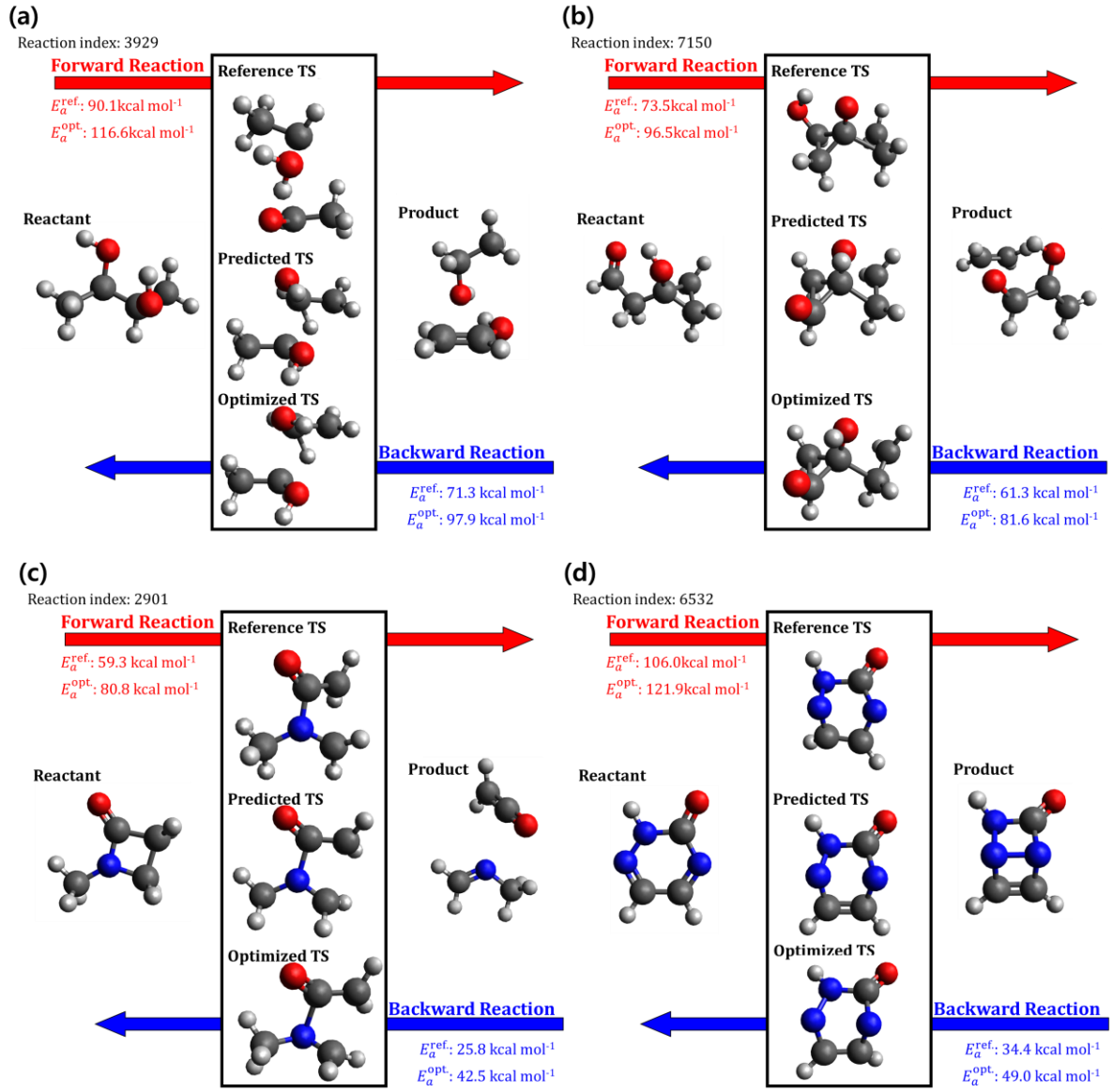
Supplementary Figure 3. Model accuracy in (a) Molecular mean absolute percentage error (MAPE) and (b) Molecular mean absolute error (MAE) according to training dataset size. The solid lines represents the accuracy of ensemble predictions from 15 models (5 epoch ensemble and 3 seed ensemble) The violin plot represents the performance of the single models used in the ensemble. Yellow, pink, grey, blue colors represent the cases trained with 25%, 50%, 75%, and 100% of training dataset, respectively. 500.0, and 0.0 are used for c and c' in Eq. 5 in the main manuscript.



Supplementary Figure 4. Distribution of energy deviations of quantum chemically optimized transition state from machine learning prediction to reference according to number of negative frequencies (Neg. Freq.). Among 126 TS structure that have larger than 0.1kcal/mol energy error, 123 TS structures have one negative frequency which imply the proper saddle point at the potential energy surface. Some cases that have unwanted numbers of negative frequencies are observed. Red and blue bars represents the number of predictions whose geometry yield target reactant and product structures.



Supplementary Figure 5. Molecular structures and activation barriers of four largest positive error cases among the inferred structures that yielded correct reactant and product structures through intrinsic reaction coordinate calculations. A positive error indicates that the obtained transition state structure is energetically less favorable than the corresponding reference transition state.



Supplementary Figure 6. Molecular structures and activation barriers of four largest negative error cases among the inferred structures that yielded correct reactant and product structures through intrinsic reaction coordinate calculations. A negative error indicates that the obtained transition state structure is energetically more favorable than the corresponding reference transition state.

Supplementary Table 1. Accuracy of ensemble predictions according to splitting methods.

TTA	MAPE(%)		MAE(pm)	
	Random splitting	Scaffold splitting	Random splitting	Scaffold splitting
Yes	3.162	3.031	9.214	9.742
No	3.164	3.037	9.244	9.758

Supplementary Table 2. Hyperparameters for model training.

Batch size	80
Learning rate	0.0002
Gradient clipping value	1
Precision	64
Number of GRU Layers	2
Number of PSI Layers	2
Dropout for GRU Layer	0.4
Feature size for atomic numbers	32
Feature size for interatomic distance	64
Exponent (α) for Gaussian kernel (Å^{-2})†	10
Grid spacing for centers of Gaussian function (Å) †	0.1

†Embedding of interatomic distances are performed with Gaussian kernel, $f_{ijk} = e^{-\alpha(d_{ij}-g_k)^2}$, where d_{ij}, g_k, and α are interatomic distance, center of Gaussian, and exponent, respectively. g_k is sampled on equidistant grid on the range of [0, 30.0].

Supplementary Table 3. Molecular mean absolute percentage error (MAPE) and molecular mean absolute error (MAE) of reconstructed TS structures according to ensemble sizes. The lowest error values are bolded. c and c′ are weight factors for total loss which are defined in Equation 5 in the main manuscript. When c′ is non zero, multi-label learning is performed.

TTA	hyperparameters		Molecular MAPE (%)			Molecular MAE (pm)		
	c′	c	Ensemble Size (5)[1)]	Ensemble Size (15)[2)]	Ensemble Size (90)[3)]	Ensemble Size (5)[1)]	Ensemble Size (15)[2)]	Ensemble Size (90)[3)]
Yes	Yes (1.0)	2000	3.263	3.168	3.162	9.999	9.749	9.742
		1000	3.266	3.169		10.010	9.773	
		500	3.411	3.306		10.433	10.153	
	No (0.0)	2000	3.233	**3.112**		9.971	**9.610**	
		1000	3.282	3.118		10.064	9.632	
		500	3.348	3.162		10.270	9.742	
No	Yes (1.0)	2000	3.292	3.171	3.164	10.095	9.764	9.758
		1000	3.301	3.187		10.120	9.839	
		500	3.466	3.316		10.616	10.198	
	No (0.0)	2000	3.246	3.115		10.018	9.627	
		1000	3.317	3.119		10.187	9.642	
		500	3.367	3.164		10.333	9.758	

[1)] Averaging results from 5 best epochs from a single training

[2)] Averaging results from 5 best epochs from 3 independent trainings (3 seeds)

[3)] Averaging results from 5 best epochs from 18 independent trainings (3 seeds and 6 hyperparameters)