Responses concerning edits:

1. Charge evolution was examined over the course of the reaction coordinate for three representative compounds (ethylene, vinyl chloride, and nitroethylene) were perfomed at B3LYP/LACVP\*\* complete with Hirshfeld population analysis was at each stationary point to examine the charge separation between the substrate and heme fragments. This served to rationalize the correlation between barriers and Fukui indices, showing that charge delocalizes toward electron withdrawing substituents in the substrate, resulting in more negative substrate fragment total charge. The need to delocalize this charge is consistent with the definition of the *f+* Fukui index.
2. The reviewer commented that we only considered 2 descriptors. The total number of descriptors examined was 9 at each level of theory. The reviewer suggests employed a feature selection algorithm, which was performed. As pointed out in the manuscript, a Lasso regression was used for feature selection. The reviewer also points out that only descriptors that make physical/chemical sense should be selected. As pointed out in a previous response, we suggested FOD and Fukui indices were physically relevant on the basis of a radical mechanism for epoxidation (FOD) and electron density delocalization (Fukui indices).
3. Reviewer 3 had suggested expanding the data set generated by Zhang and Liu. To this end, we have computed the zero-point potential energy barriers at the same level of theory employed by Zhang and Liu (B3LYP/Wachters+f (Fe)/TZVP//B3LYP/LACVP\*\*). This included 3 known substrates for P450cam and several more electron rich compounds. This validated the scope of our models, specifically that electron rich compounds are out of scope for the model, while the P450cam substrates were predicted in accordance with the performance of the hold out validation strategy. All structures have been added to the SI.
4. The reviewer had suggested employing DFT to compute the necessary descriptors. While the reviewer rightly notes that many of the compounds presented in our manuscript are small, larger systems of interest are not. We envision our model being applied along side docking where thousands to tens of thousands of poses would be generated. If we consider something like a steroid which has on the order of 50 atoms with multiple heteroatoms, thousands of docking poses would require significant computational resources to treat just the substrate with respectable DFT. This is excessively expensive in our view. Additionally, docking typically requires conformer ensemble generation. Given Grimme’s CREST utility generates ensembles with his GFN family of methods and pairs well with docking, it is sensible in our view to build our models using descriptors derived from the same, affordable levels of theory. We’ve added comments to this end in the conclusion.
5. Other minor edits have been made, as well as cleaning up the supporting information files.