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Supporting Information

for

Enhancing chemical synthesis planning: automated quantum mechanics-based regioselectivity prediction for C–H activation with directing groups

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Additional computational data

Reaxys query for C–H activation

The query on Reaxys consists of the following steps:

1. Search for “C–H activation”, which yields 553472 reactions.
2. Filter by catalyst “$Pd(OAc)_2$”, which yields 705 reactions.
3. Filter by reaction class “C–C bond formation”, which yields 17 reactions.
4. Selecting the one reaction that is actually a Pd-catalyzed C–H activation with a directing group and search for similar reactions with criterion “wide”, which yields 37105 reactions.
5. Filter by catalyst “$Pd(OAc)_2$” which yields 1955 reactions.
6. Filter by reaction class “C–C bond formation” and the subcategories “Ar-H to Ar-CH2-”, “ArH to Ar-C(=)-”, “ArH + -C(=)-X to Ar-C(=)-”, “ArH + -C(=)-O- to Ar-C(=)-”, and “ArH + -CH2-O- to Ar-CH2-”, which yields 330 reactions.
7. Out of the 330 reactions, we chose all examples that had several potential reaction sites and/or directing groups, which yields 10 reactions.

Evaluation threshold

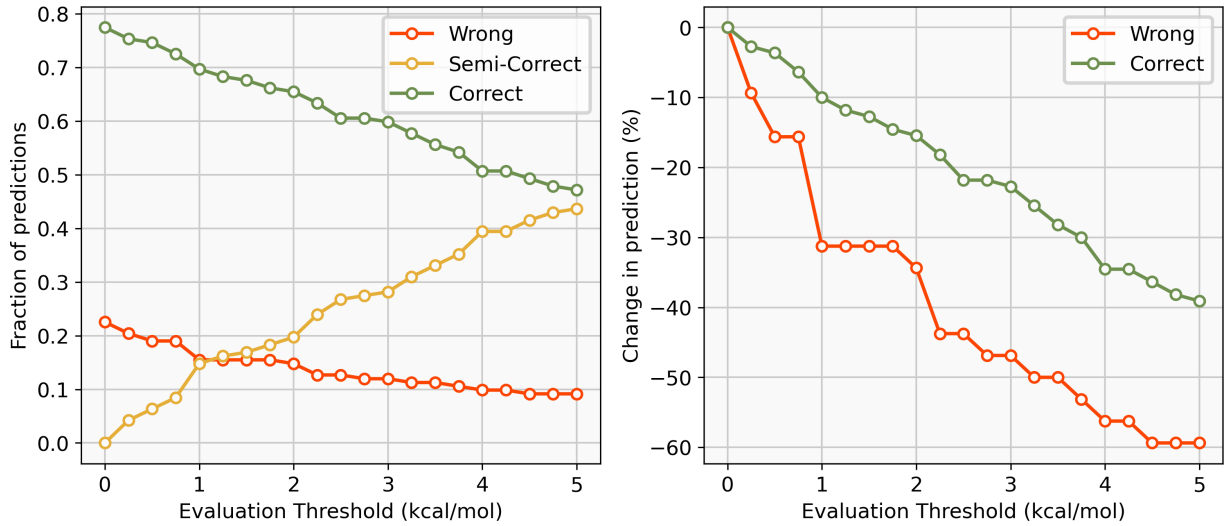

Figure S1: Left: Fraction of each prediction class as a function of evaluation threshold. Right: Change of fraction of correct and wrong predictions as a function of evaluation threshold.

Potential complexes for C–H activation of a specific substrate

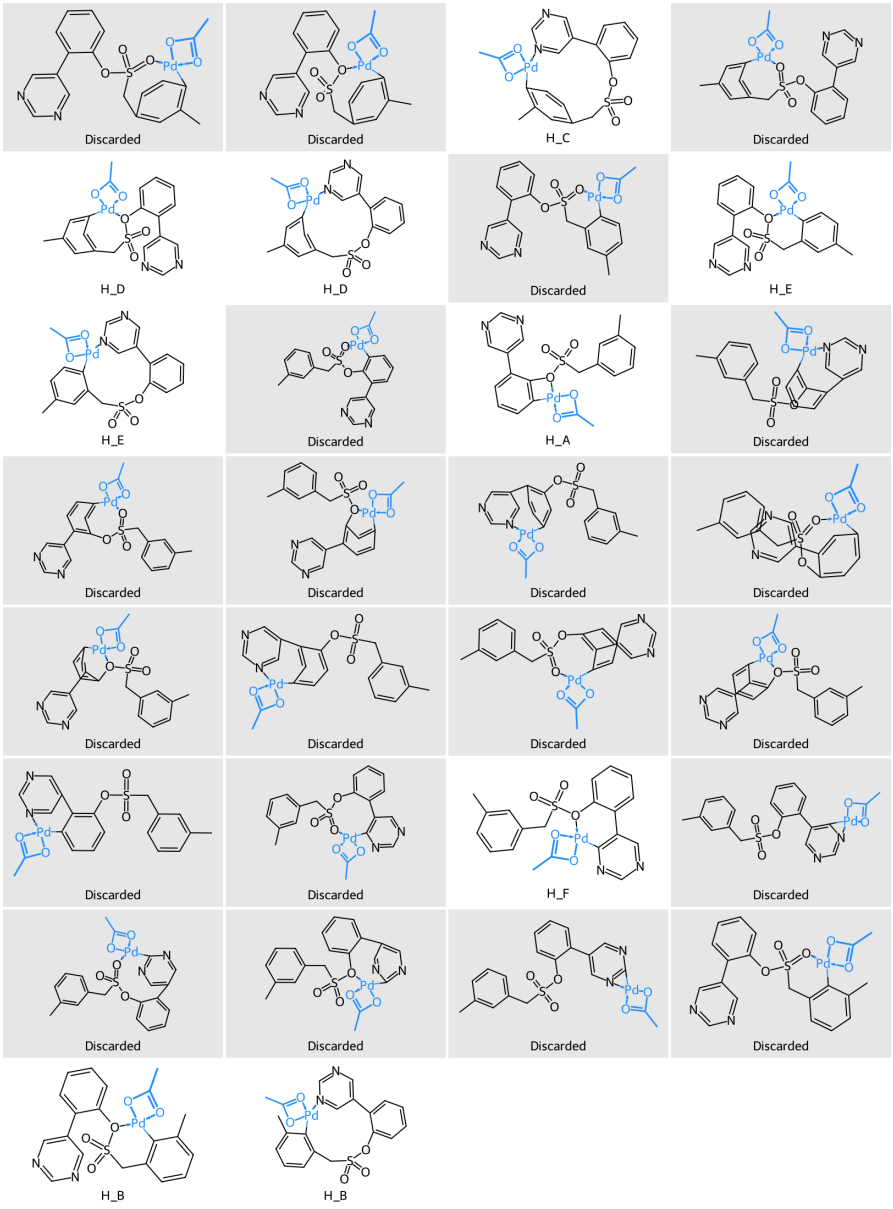

Figure S2: All potential palladacylce intermediates for a substrate from Achar et al. [1]. Via screening of the MMFFs energy contribution from the angle-related terms, unreasonable combinations of C–H site and directing groups are discarded.

Correct regioselectivity prediction for the dataset from Tomberg et al. [2]/Chen et al. [3]

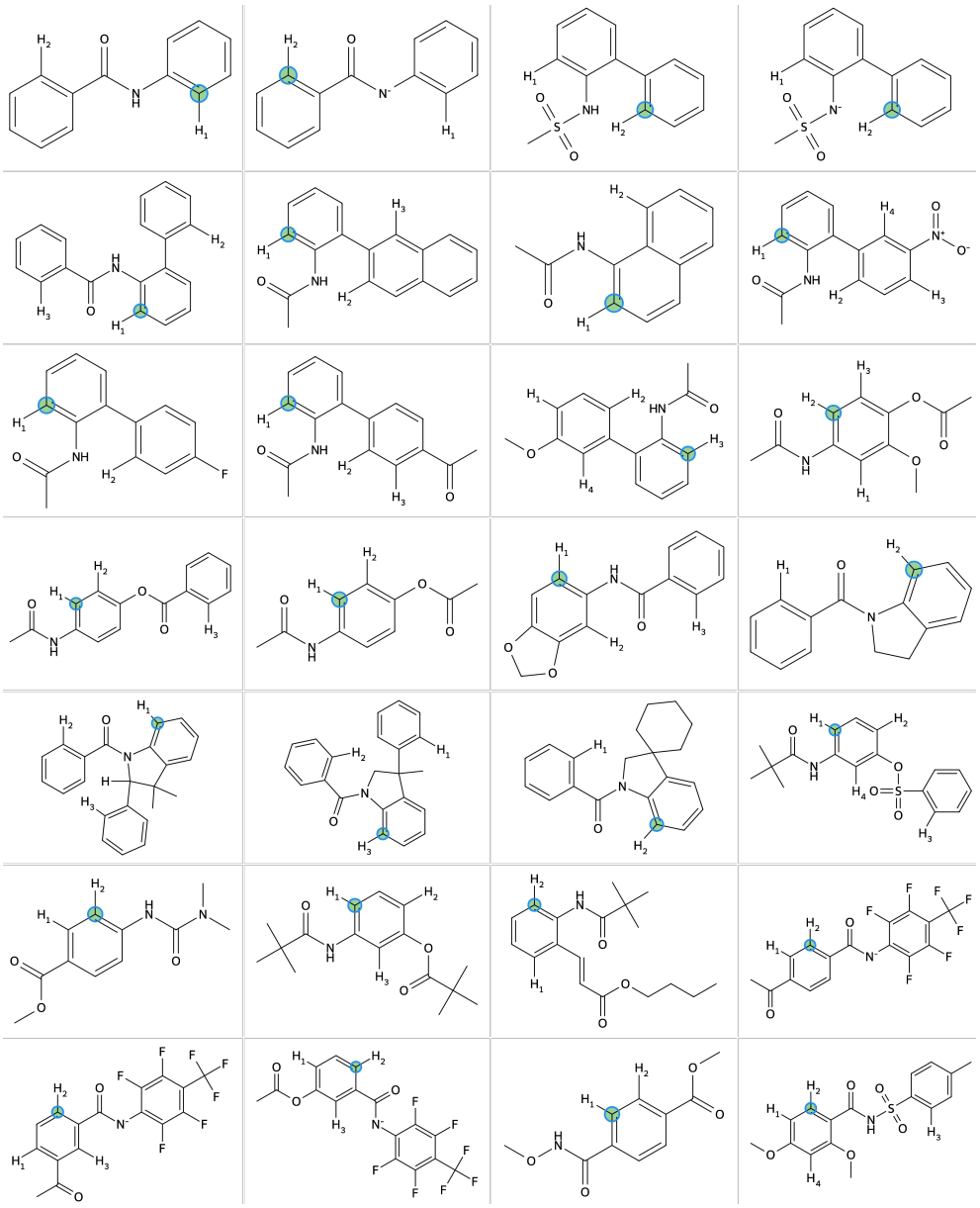

Figure S3: (*1/4*) Correct regioselectivity predictions for molecules from Tomberg et al. [2]/Chen et al. [3]. The predicted reaction site is marked by a blue circle, the experimentally observed reaction site is highlighted with a green circle.

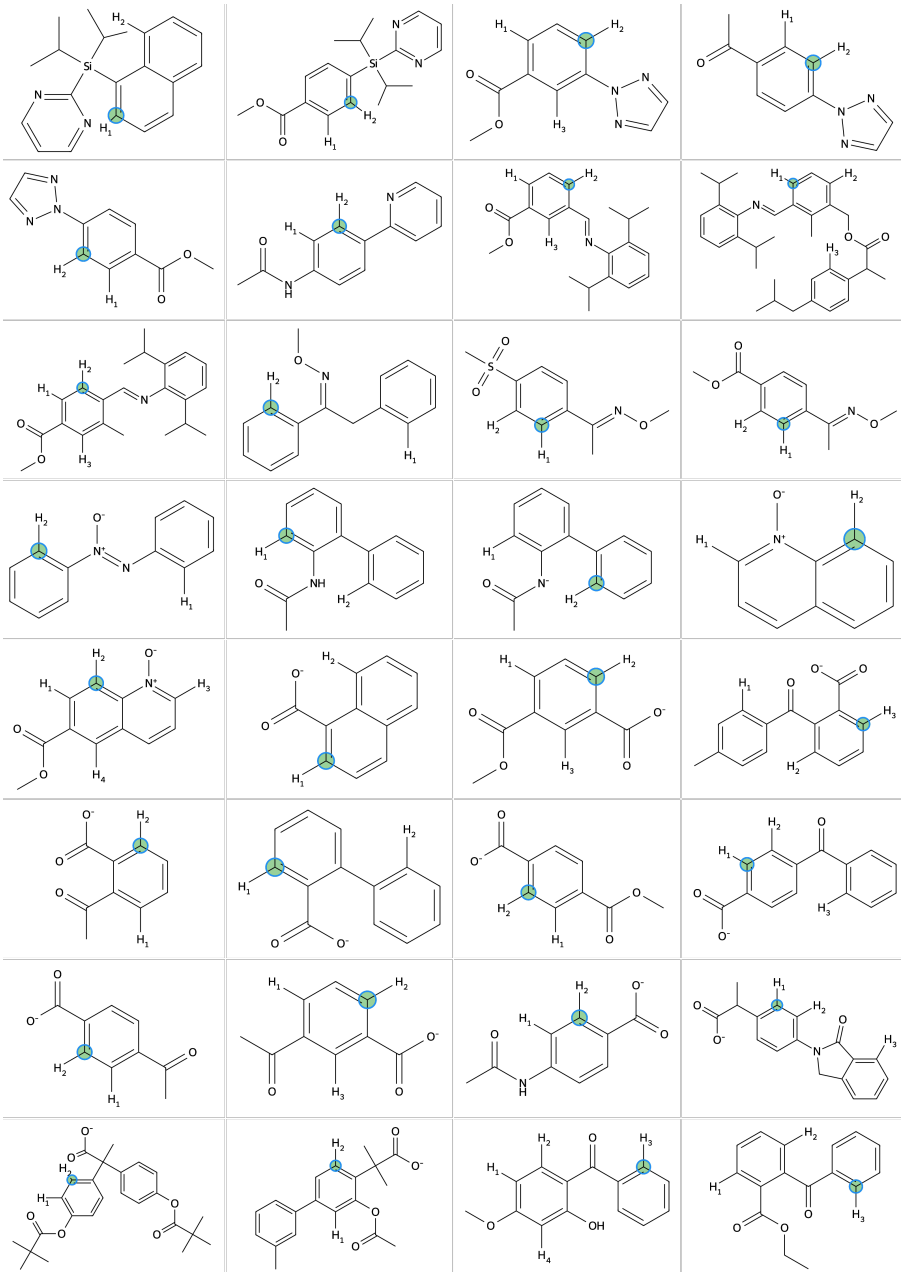

Figure S4: (*2/4*) Correct regioselectivity predictions for molecules from Tomberg et al. [2]/Chen et al. [3]. The predicted reaction site is marked by a blue circle, the experimentally observed reaction site is highlighted with a green circle.

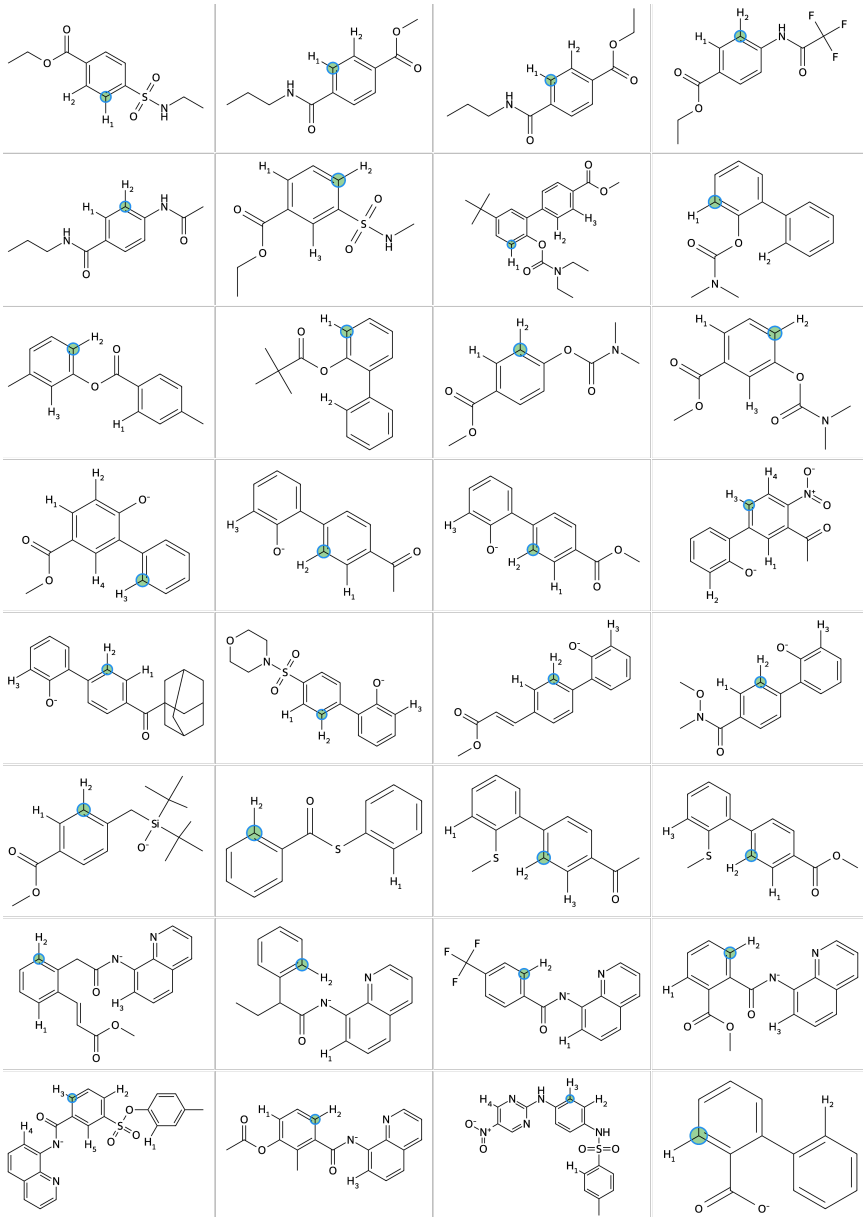

Figure S5: (*3/4*) Correct regioselectivity predictions for molecules from Tomberg et al. [2]/Chen et al. [3]. The predicted reaction site is marked by a blue circle, the experimentally observed reaction site is highlighted with a green circle.

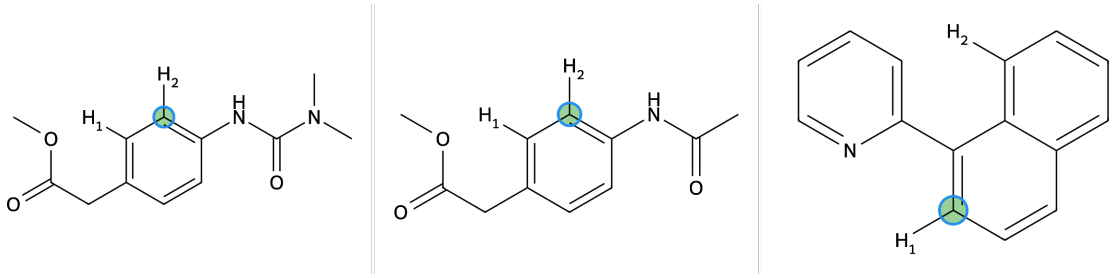

Figure S6: (*4/4*) Correct regioselectivity predictions for molecules from Tomberg et al. [2]/Chen et al. [3]. The predicted reaction site is marked by a blue circle, the experimentally observed reaction site is highlighted with a green circle.

Semi-correct regioselectivity prediction for the dataset from Tomberg et al. [2]/Chen et al. [3]

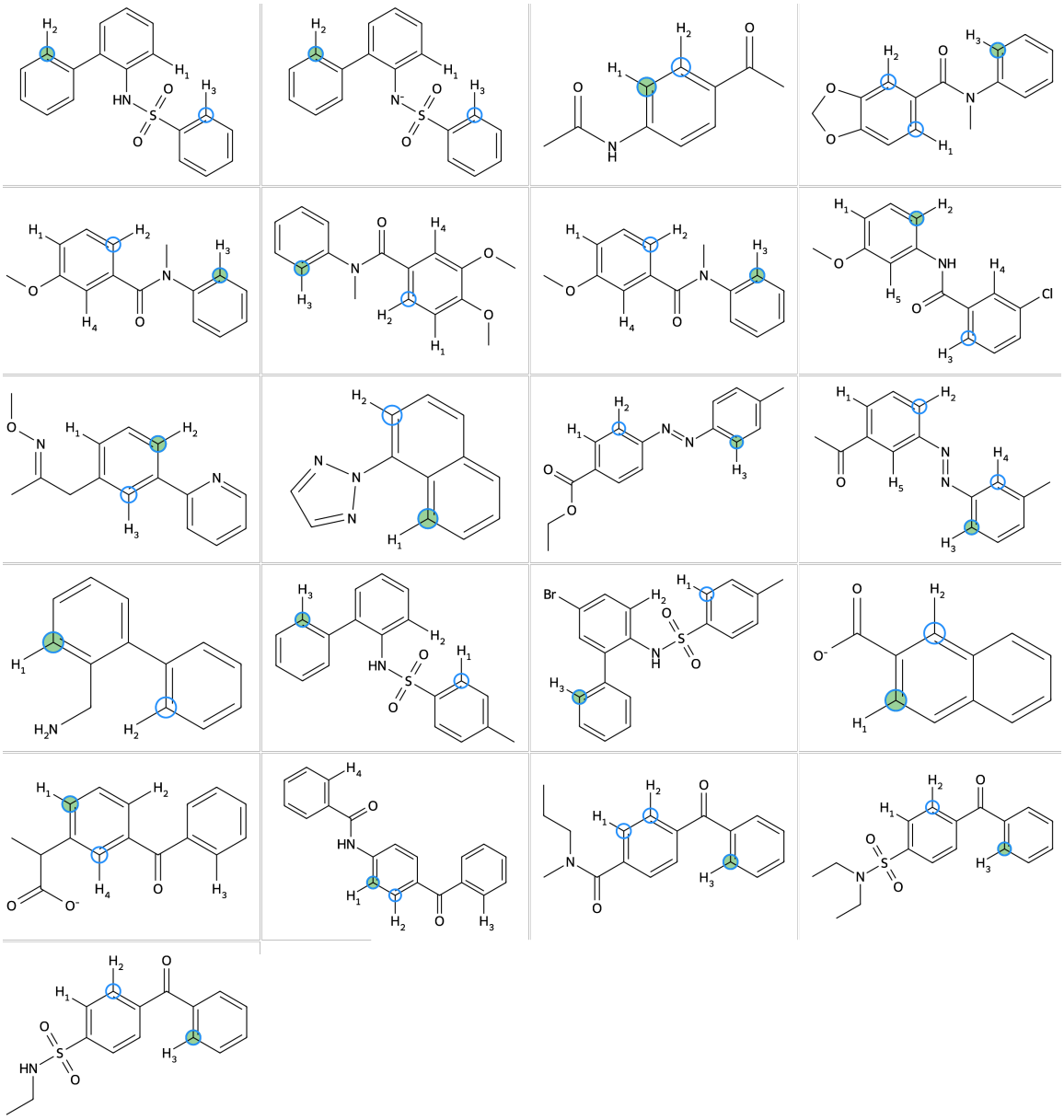

Figure S7: Semi-correct regioselectivity predictions for molecules from Tomberg et al. [2]/Chen et al. [3]. Predicted reaction sites are marked by a blue circle, the experimentally observed reaction site is highlighted with a green circle.

Wrong regioselectivity prediction for the dataset from Tomberg et al. [2]/Chen et al. [3]

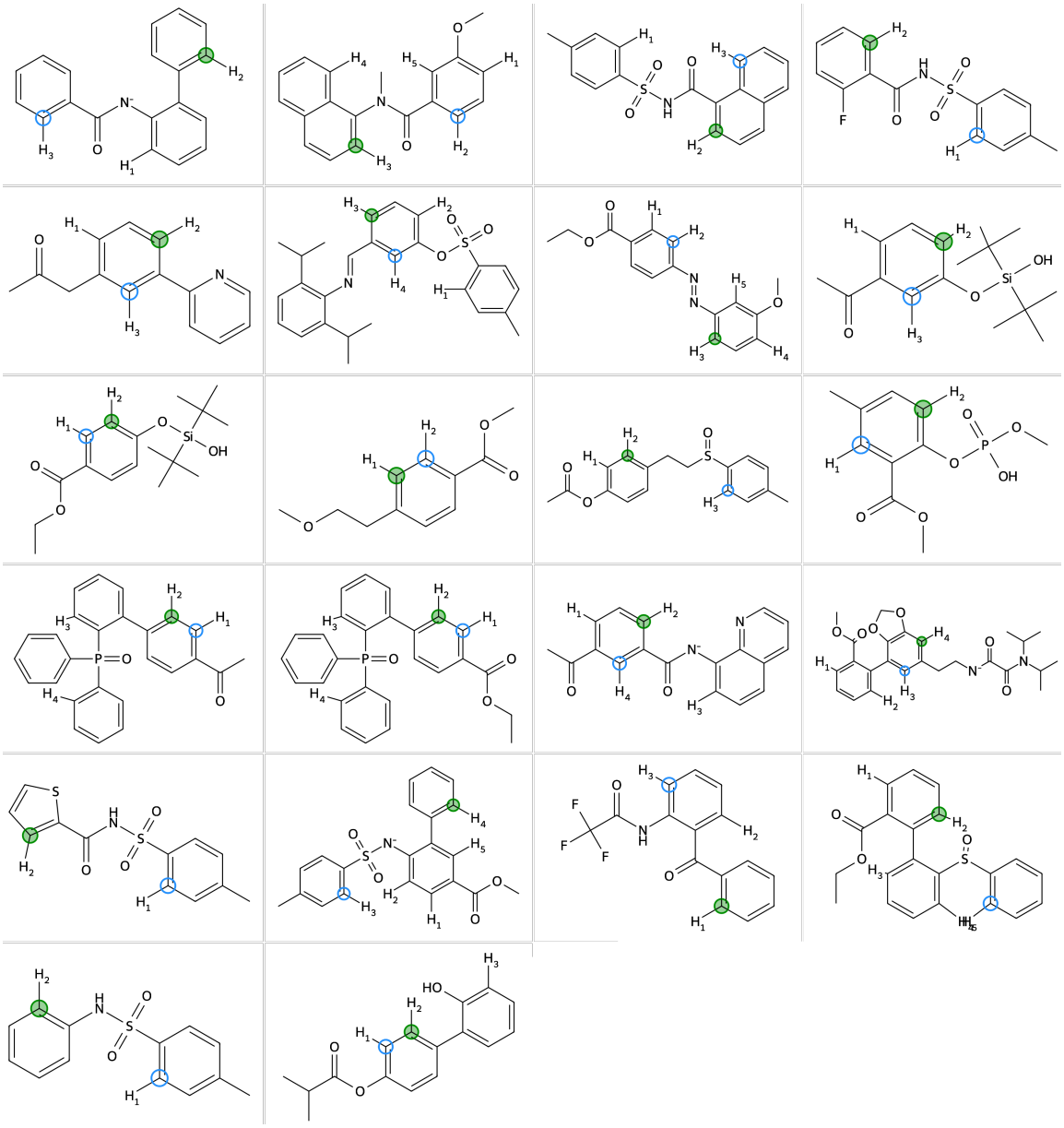

Figure S8: Wrong regioselectivity predictions for molecules from Tomberg et al. [2]/Chen et al. [3]. The predicted reaction site is marked by a blue circle, the experimentally observed reaction site is highlighted with a green circle.

References

1. Achar, T. K.; Zhang, X.; Mondal, R.; Shanavas, M. S.; Maiti, S.; Maity, S.; Pal, N.; Paton, R. S.; Maiti, D. *Angew. Chem., Int. Ed.* **2019**, *58*, 10353–10360. doi:10.1002/anie.201904608.

2. Tomberg, A.; Muratore, M. É.; Johansson, M. J.; Terstiege, I.; Sköld, C.; Norrby, P.-O. *iScience* **2019**, *20*, 373–391. doi:10.1016/j.isci.2019.09.035.

3. Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107–1295. doi:10.1039/c5qo00004a.