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Learning Structure-Activity Relationship (GE-SAR) of the Wittig Reaction from Genetically-Encoded substrates

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Abstract: The Wittig reaction can be used for late stage functionalization of proteins and peptides to ligate glycans, pharmacophores, and other natural or unnatural functionalities do not present in polypeptides made of 20 natural amino acids. It is not obvious how peptide sequence influences the rate and outcome of Wittig ligation. Our group has previously employed the Wittig reaction to modify N-terminal aldehydes in Genetically-Encoded (GE) peptide libraries. It was found that the reaction rate strongly depends on the nature of the two N-terminal amino acids: specifically peptides with penultimate Pro-Pro exhibit a significantly decreased reaction rate. A plausible mechanistic hypothesis is that the hydrogen bonds inside the peptide backbone stabilize the transition state (TS) of the Wittig reaction and accelerate this reaction. I synthesized two model isoteric peptide substrates—CHO-Ala-Ala and CHO-Sarcosine-Sarcosine—with and without primary amides. The DFT calculation of the geometry of transition states in model peptide CHO-Ala-Ala indeed detected a contribution of hydrogen bond between backbone N-H and the betaine in the late TS while CHO-Sarcosine-Sarcosine does not have this characteristic. I measured reaction rates with model ylide and compare the observed results to the energy and geometry of the Wittig reaction TSs for CHO-Ala-Ala and CHO-Sarcosine-Sarcosine obtained in DFT calculation.