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Atroposelective Negishi Coupling Optimization Guided by Multivariate Linear Regression Analysis: Asymmetric Synthesis of KRAS G12C Covalent Inhibitor GDC-6036

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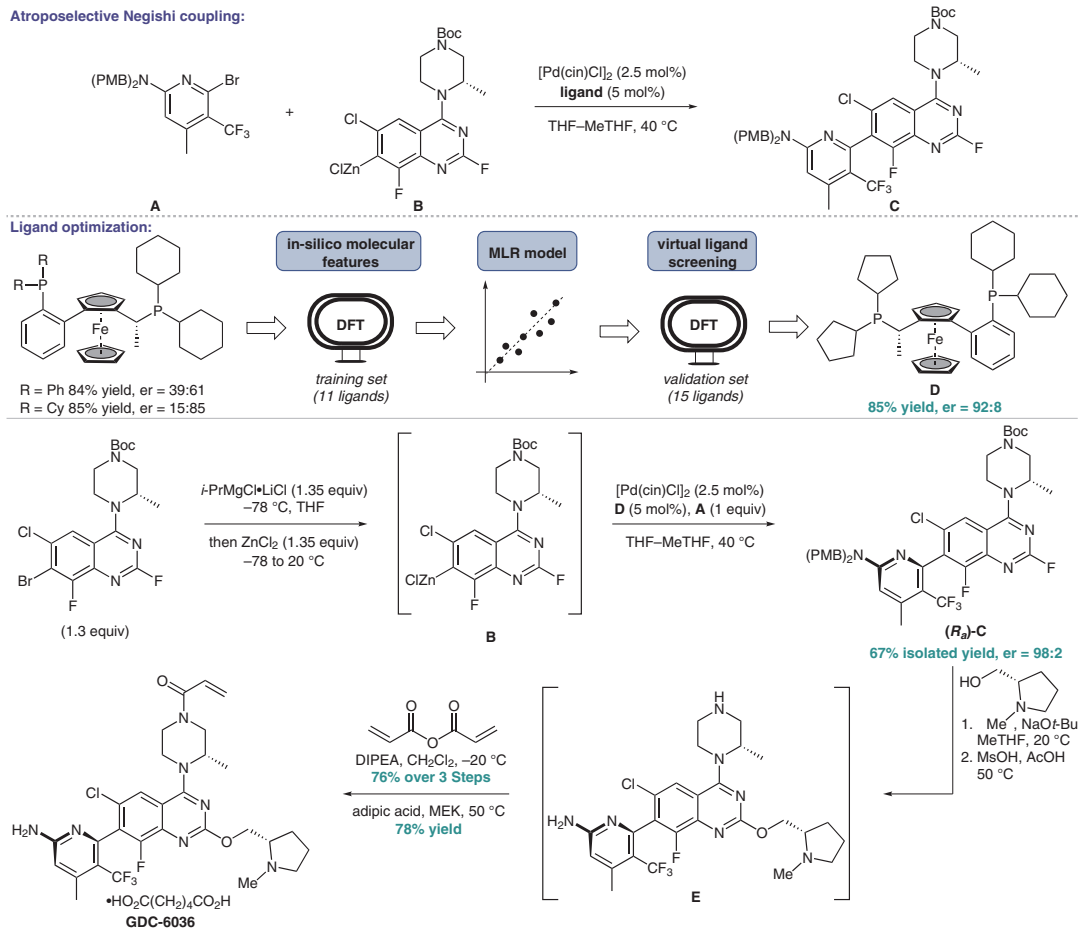
Multivariate Linear Regression Informs Ligand Design to Improve the Synthesis of a KRAS Inhibitor



Significance: KRAS, a frequently mutated oncogene, has been linked to the progression of various cancers and is therefore pursued as an anticancer target. Genentech has recently developed **GDC-6036**, an irreversible covalent inhibitor of the KRAS G12C mutation which features an axial chiral pyridine–quinazoline biaryl moiety that poses a significant synthetic challenge.

Comment: Utilizing high-throughput experimentation, the Walphos ligand class was found to yield biaryl intermediate **C** via a Negishi coupling as either (*R*)- or (*S*)-atropisomer with moderate er values. However, no intuitive structure–selectivity trends of the ligands tested could be identified. Therefore, multivariate linear regression (MLR) analysis was employed which successfully predicted ligand **D** to be more selective. Using **D**, desired **(R_a)-C** was obtained with er = 98:2 and could be further elaborated to **GDC-6036**.

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Category

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