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Adventures in Atropisomerism: Total Synthesis of a Complex Active Pharmaceutical Ingredient with Two Chirality Axes

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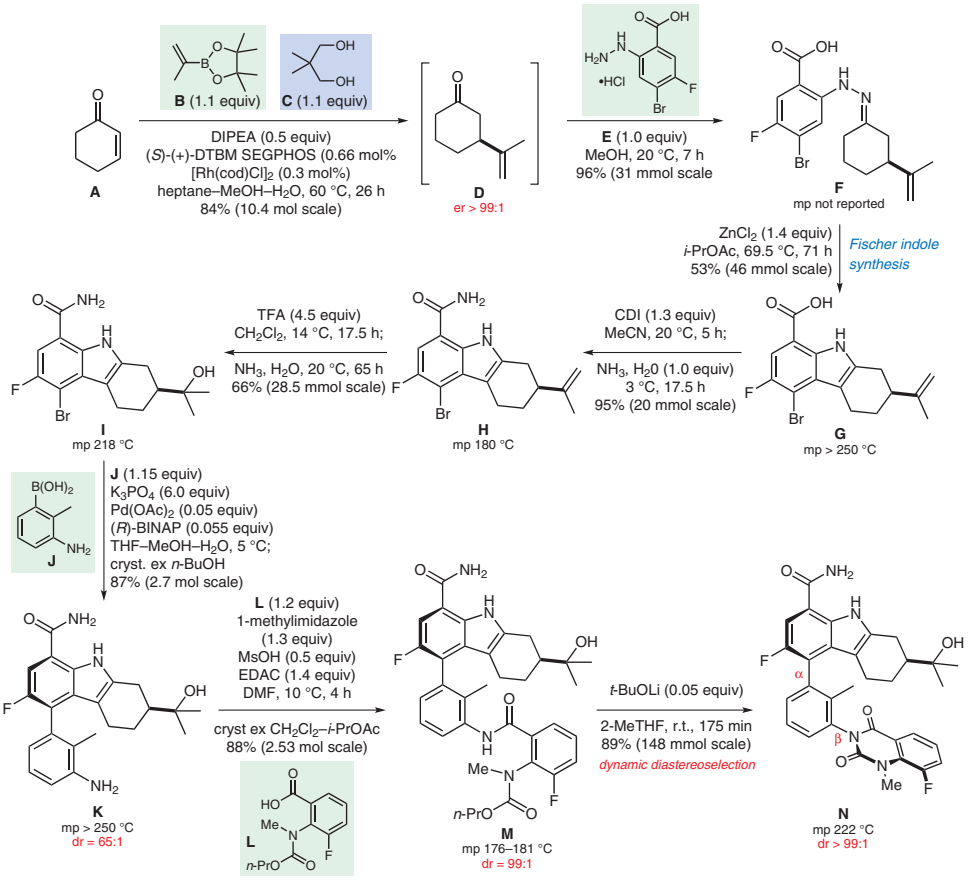
# Synthesis of a Bruton's Tyrosine Kinase Inhibitor




**Significance:** The target molecule **N** is a Bruton's tyrosine kinase (BTK) inhibitor that is of interest for the treatment of rheumatoid arthritis. A major challenge in the synthesis depicted is the construction of the two axes of chirality marked α and β. Rotation about these chiral axes gives four possible atropisomeric diastereoisomers. While the higher-energy C–C chirality axis α is relatively stable (rotational barrier 28 kcal/mol), the lower-energy C–N bond β (rotational barrier 26 kcal/mol) has a rotational half-life of hours to days, with a risk of epimerization.

**Comment:** The chiral axis α was constructed using an asymmetric Suzuki–Miyaura reaction at 5 °C to afford biaryl **K** (dr = 16:1). After crystallization from *n*-BuOH, **K** was obtained with dr = 65:1. The chiral axis β was created by crystallization-induced diastereoselection at 25 °C. Compound **N** was obtained in 90% yield and dr > 99:1. Thus the higher barrier diastereoisomer **K** acted as a chiral template to construct the stereochemical configuration of lower barrier bond β. This route delivered >200 kg of the target compound **N** in 28.3% overall yield.

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