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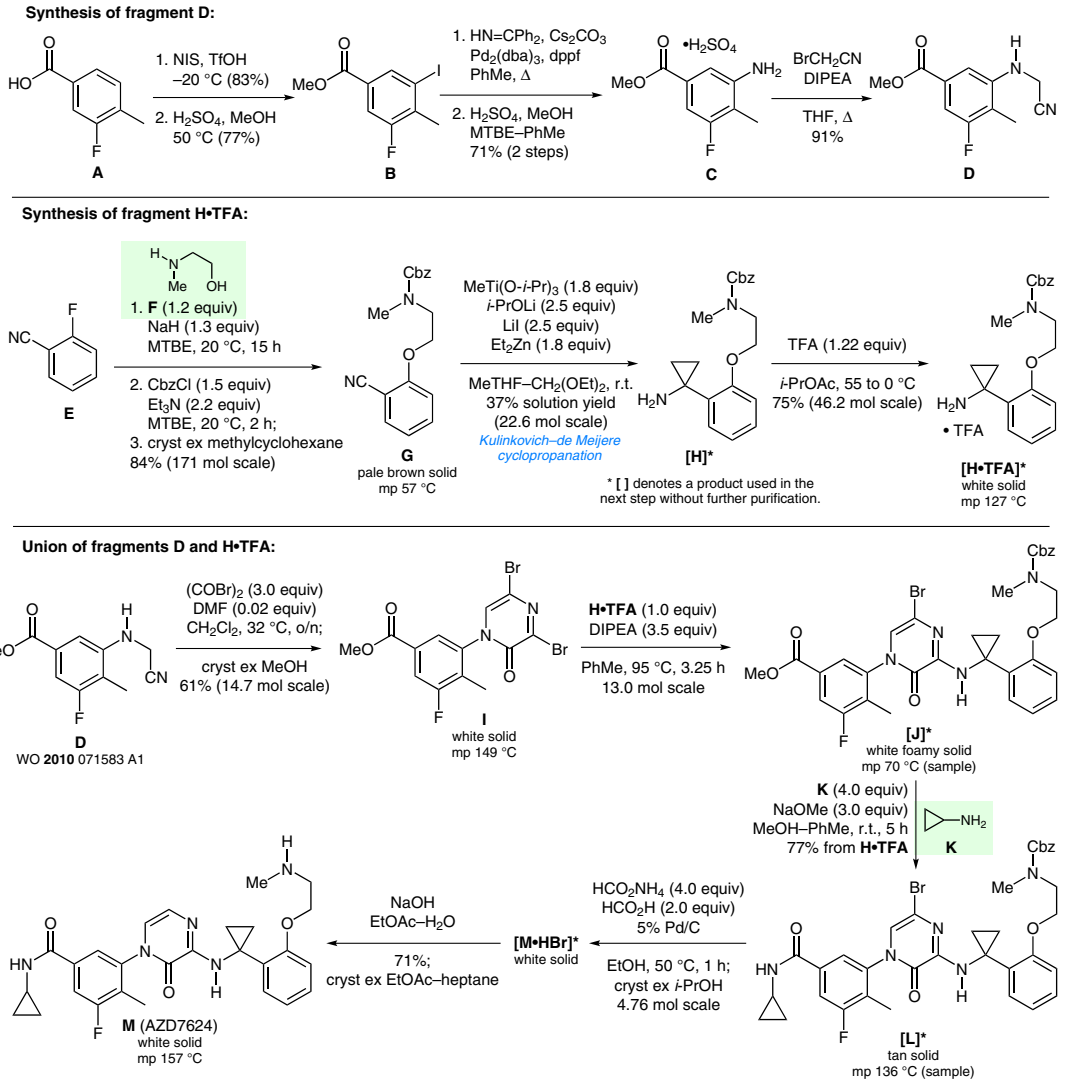
Expedited Kilolab Development of AZD7624 Using Kulinkovich–de Meijere Cyclopropanation
Org. Process Res. Dev. **2021**, *25*, 2351–2366, DOI: 10.1021/acs.oprd.1c00283.

Synthesis of AZD7624



Significance: The p38α mitogen-activated protein kinase is expressed and activated in several cell types associated with chronic obstructive pulmonary disease (COPD). AZD7624 inhibits p38a but its development was halted after phase 2a trials failed to show any benefit over placebo. The synthesis depicted delivered 5.3 kg of API.

Comment: A noteworthy feature of the synthesis is the implementation of the de Meijere modification of the Kulinkovich cyclopropanation that converts the benzonitrile **G** to the cyclopropylamine **H** in 37% yield on a 22.6 mol scale. On a laboratory scale the yield was 57%. For an alternative synthesis of AZD7624, see: WO **2017** 162304 A1.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

AZD7624

cyclopropanation

Buchwald–Hartwig reaction

de Meijere reaction

Kulinkovich reaction