P. E. BRENNAN*, M. D. SMITH* ET AL. (UNIVERSITY OF OXFORD, UK AND UNIVERSITY OF TORONTO, CANADA)

Discovery of a Highly Selective Cell-Active Inhibitor of the Histone Lysine Demethylases KDM2/7
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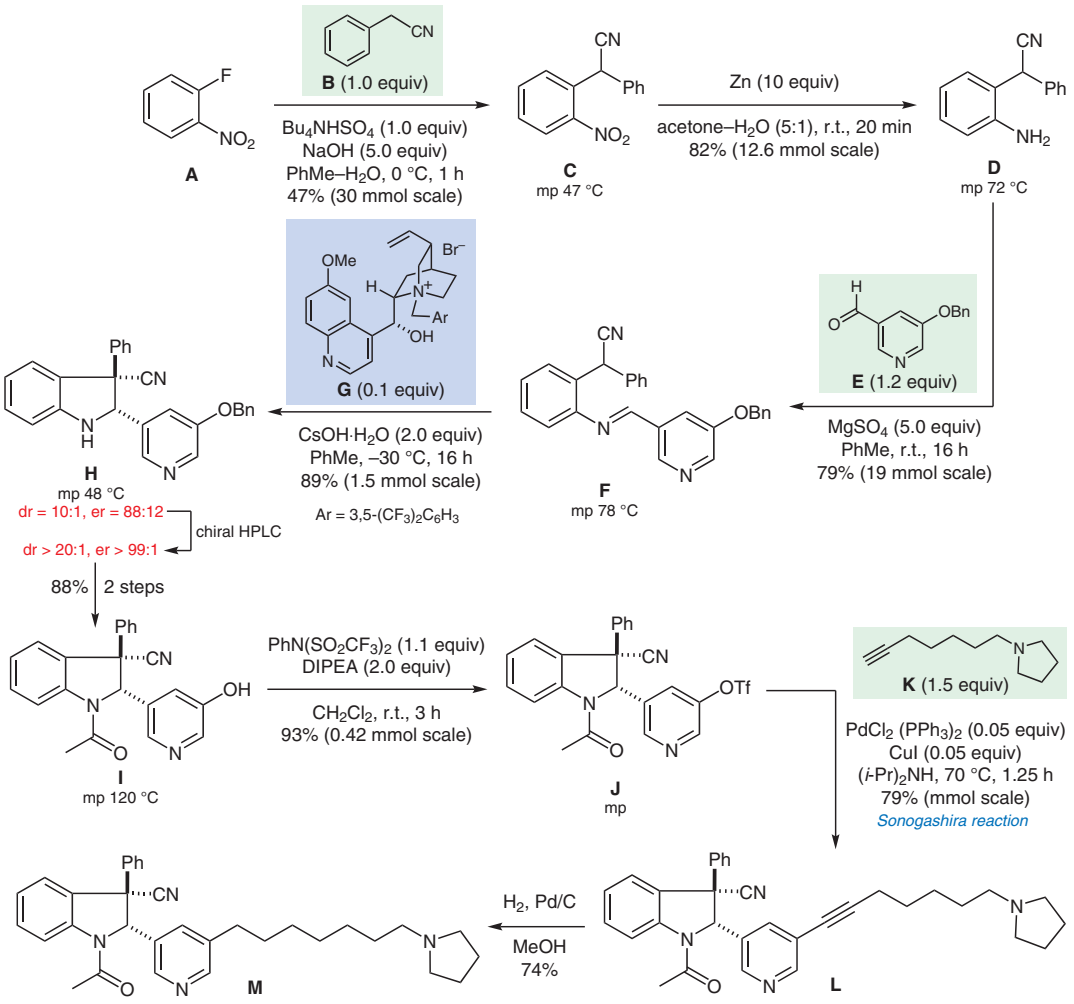
Synthesis of an Inhibitor of Histone Lysine Demethylases KDM2/7



Significance: The target molecule **M** is a first-in-class highly selective cell-active inhibitor of the histone lysine demethylases KDM2/7 that are involved in epigenetic gene expression. In total 45 racemic *N*-acyl indoline derivatives were prepared, from which the enantiomers of **M** were selected for further evaluation.

Comment: Synthesis of the indoline (*S*,*S*)-**H** entails treatment of the *N*-aryl imine **F** with cesium hydroxide under phase-transfer conditions in the presence of the quinine-derived salt **G** (0.1 equiv). A delocalized 2-aza-pentadienyl anion is generated that undergoes 6π electrocyclization in 89% yield (dr = 10:1, er = 88:12). Preparative chiral HPLC then delivered **H** with dr > 20:1 and er > 99:1. For details on the asymmetric electrocyclization, see: E. E. Maciver, S. Thompson, M. D. Smith *Angew. Chem. Int. Ed.* **2009**, *48*, 9979).

SYNFACTS Contributors: Philip Kocienski
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