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Convergent Synthesis of PI3K Inhibitor GDC-0908 Featuring Palladium-Catalyzed Direct C–H Arylation toward Dihydrobenzothienooxepines

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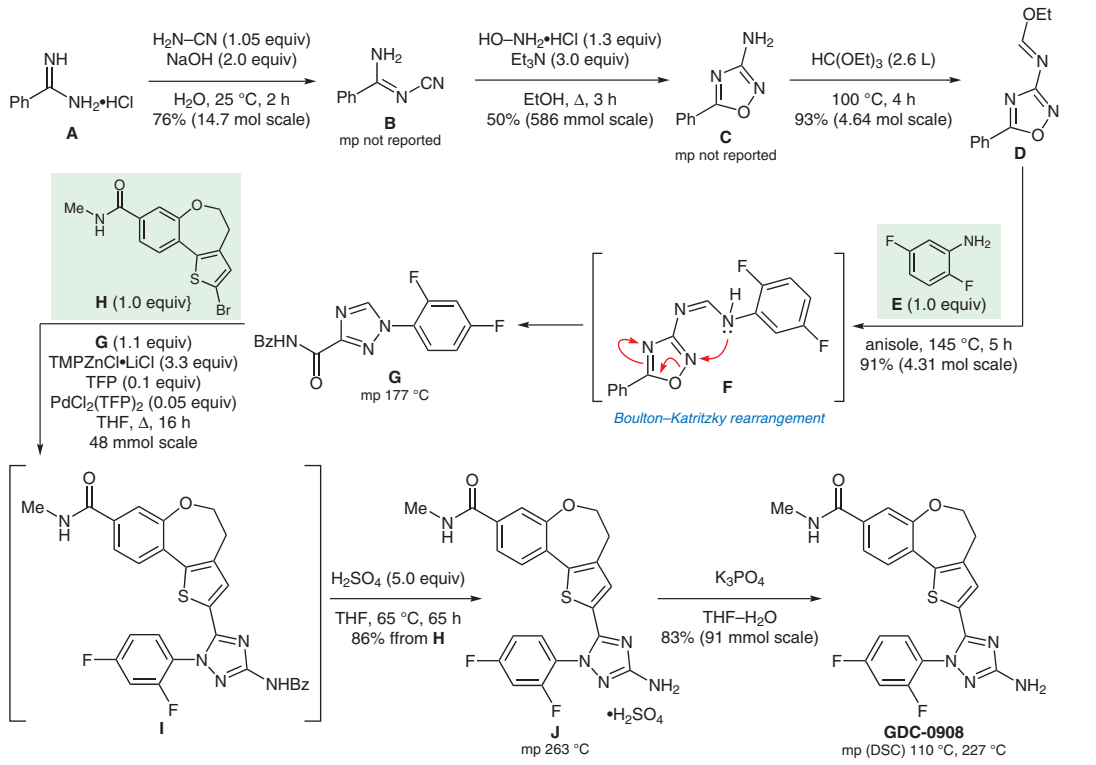
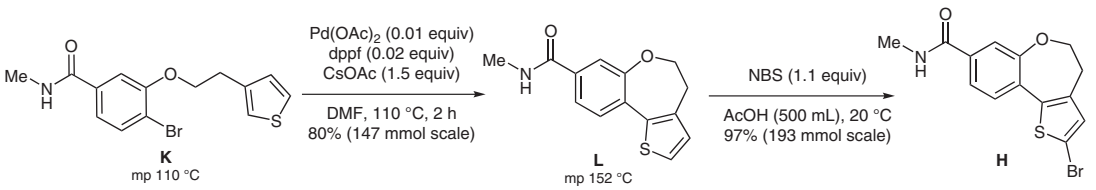
Synthesis of GDC-0908



Synthesis of fragment H:



Significance: GDC-0908 is a phosphoinositide 3-kinase (PI_3K) inhibitor that is of interest for the treatment of cancer. The convergent synthesis depicted features (1) a palladium-catalyzed direct C–H arylation to construct 4,5-dihydrobenzo[*b*]-thieno[2,3-*d*]oxepine **L**, (2) a Boulton–Katritzky rearrangement of 1,2,4-oxadiazole **F** to the 1,2,4-triazole **G**, and (3) a palladium-catalyzed Negishi reaction to forge the heterobiaryl linkage.

Comment: In order to deploy the Negishi coupling to forge heterobiaryl **I**, chemoselective metalation of the C3–H in triazole **G** was accomplished using the hindered Knochel base TMPZnCl • LiCl (see Review below). An excess of the base (3.3 equiv) was required because of competing metallation of amide functionalities in **G** and **H**.

Review: B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel *Angew. Chem. Int. Ed.* **2011**, *50*, 9794–9824.

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