Synthesis of GDC-0908

Significance: GDC-0908 is a phosphoinositide 3-kinase (PI3K) 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 metatation 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 metatation of amide functionalities in G and H.