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

**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]thienooxepine \( L \), (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 metalla- tion 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 metalla- tion of amide functionalities in \( G \) and \( H \).


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**Synfacts of the Month**

**Category**

- **Synthesis of Natural Products and Potential Drugs**

**Key words**

- GDC-0908
- phosphoinositide 3-kinase inhibitor
- C–H arylation
- Negishi reaction
- Boulton–Katritzky rearrangement
- 1,2,4-triazoles
- 1,2,4-oxadiazoles

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