Synthesis of Highly Functionalized Oxetanes

Significance: In 2014, the Bull group reported a two-step approach for preparing substituted oxetanes through a reaction sequence involving rhodium-catalyzed O–H insertion of diazomalonates into substituted bromohydrins and subsequent base-mediated cyclization to form the oxetane (O. A. Davis, J. A. Bull Angew. Chem. Int. Ed. 2014, 53, 14230). In the present report, the scope of this chemistry is expanded to include other malonate derivatives, including phosphonate, sulfone, nitrile, aryl, and amide functionalities. The resulting products and their related derivatives constitute interesting fragments for drug discovery research, and many would be difficult to prepare by using more conventional approaches, such as Williamson etherification, epoxide ring expansion, the use of sulfoxonium ylides, or photochemical methods.

Comment: Oxetanes are valuable bioisosteres for gem-dimethyl and carbonyl functionalities and they have been shown to improve aqueous solubility markedly when applied in these and other contexts (K. Muller et al. J. Med. Chem. 2010, 53, 3227). Starting from either 3-iodooxetane or oxetane-3-one, methods for preparing 3-substituted or 3,3-disubstituted oxetanes have been well developed over the past decade. However, available methods for preparing 2-substituted oxetanes are less well explored. The use of dichloromethane as solvent in the O–H insertion step is important for obtaining good yield when nitrile-containing starting materials are employed. For aryl-substituted oxetanes, the use of LiHMDS as solvent in the cyclization step rather than sodium hydride afforded superior yields.