G. KUNDU, T. H. LAMBERT* (CORNELL UNIVERSITY, ITHACA, USA)

Electrochemical Vicinal C–H Difunctionalization of Saturated Azaheterocycles
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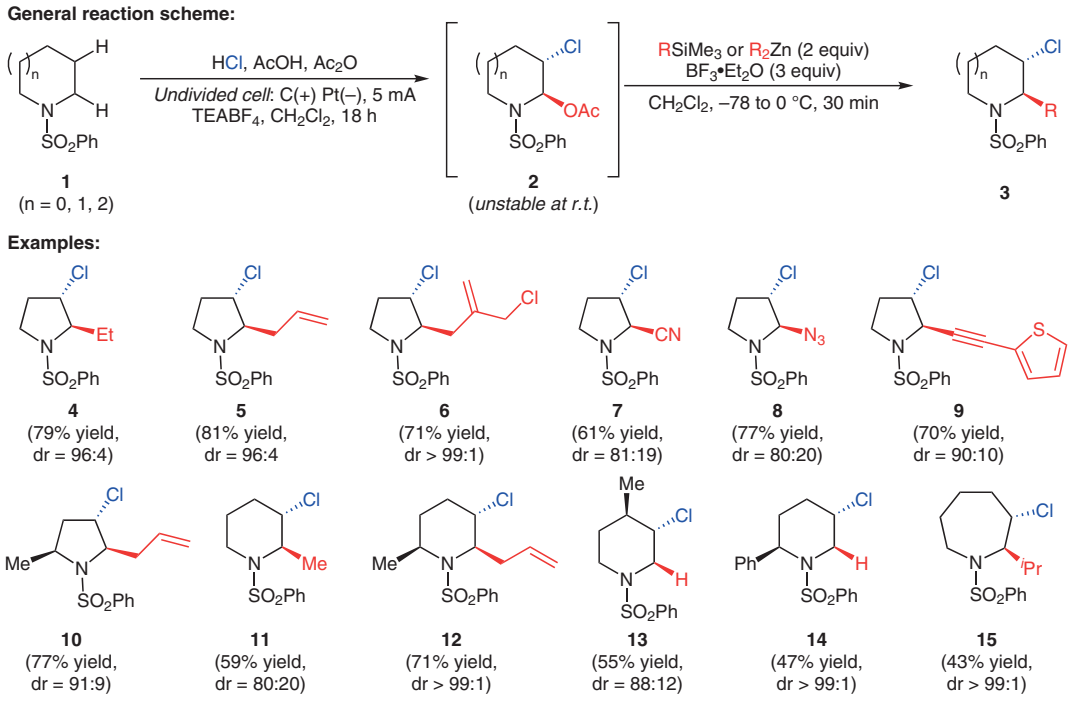
Efficient Chloroacetoxylation of Pyrrolidines and Piperidines



Significance: Numerous protocols exist to achieve the selective α-C–H bond functionalization of saturated cyclic amines through several reaction paradigms, while in addition photoredox protocols have been developed to allow the introduction of a variety of functional groups to the β-position of saturated azacycles. However, methods to achieve difunctionalization are significantly less explored, and while electrochemical approaches have been known for almost 40 years, these are inefficient owing to large amounts of side products being formed. The current report describes a facile electrochemical method for the high-yielding stereoselective synthesis of α-acetoxy-β-chloro-derived azaheterocycles with in situ replacement of the labile α-OAc moiety using a range of silyl or diorganozinc reagents allowing access to carbon, heteroatom, or hydrogen-containing derivatives.

Comment: Crucial to the success of the reaction is use of the *N*-phenylsulfonyl derivatives of the azaheterocycles with a single difunctionalized product being obtained upon subjecting a suspension of **1** in a mixture of commercially available acids to a constant current at room temperature with the yield being determined by NMR owing to the instability of the α-substituent. Protected pyrrolidines, piperidines and azepanes could all be successfully derivatized to provide β-chloro-azaheterocycles with the β-substituent further functionalized through C–C bond formation in Ni-mediated Suzuki couplings. A mechanistic hypothesis is provided with anodic oxidation of chloride leading to a radical capable of H-atom abstraction to initiate the reaction while the stereochemical outcome is rationalized through the conformational bias of the cyclic sulfonamide leading to abstraction of the hydrogen from the less-substituted carbon.

SYNFACTS Contributors: Paul Richardson (Pfizer)
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Category
Synthesis of Heterocycles

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