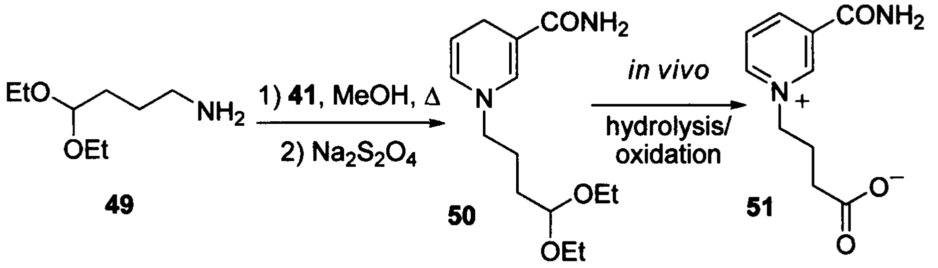
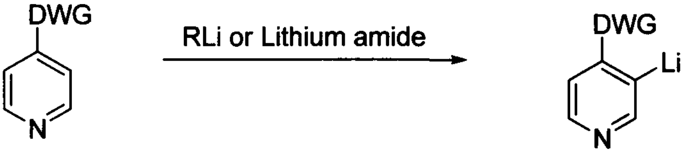


10.2.2 C–C/C–N Cross-Coupling Reactions with Organometallic Reagents[43]

Among all the methods of introducing a pyridine moiety into a drug-like molecule, metal-catalyzed carbon–carbon or carbon–nitrogen bond formation reactions of *C*-metallated pyridines or pyridine halides are the most important and widely used.

Synthesis of C-metallated pyridines via directed lithiation

Direct lithiation of pyridine is a common method of generating the precursors required for palladium-catalyzed cross-coupling reactions. Most methods employ the concept of directed *ortho*-metallation (DoM).[44] A directing metallation group (DMG) enables the precomplexation with the metal, resulting in metallation at adjacent to (*ortho* to) the substituent for deprotonation. Once deprotonation has been completed, the DMG assists in the stabilization of the metallated species. Known DMGs are halogens, CF_3, OH, OR, $OCONR_2$, $OSONR_2$, SO_2NR_2, SOR, NHCOR, $NHCO_2R$, CO_2H, 2-oxazolino, CONHR, $CONR_2$, COR, N–O, *etc.*



R = *n*Bu, *s*Bu, Ph, etc
lithium amide = LDA, LiTMP, etc
DMG = halogens, CF_3, OH, OR, $OCONR_2$, $OSONR_2$, SO_2NR_2, SOR, NHCOR, $NHCO_2R$, CO_2H, 2-oxazolino, CONHR, $CONR_2$, COR, etc

Regioselectivity of the reaction is affected by coordination and induction