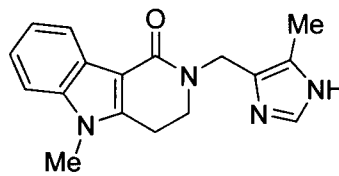


ondansetron (Zofran)
GlaxoSmithKline

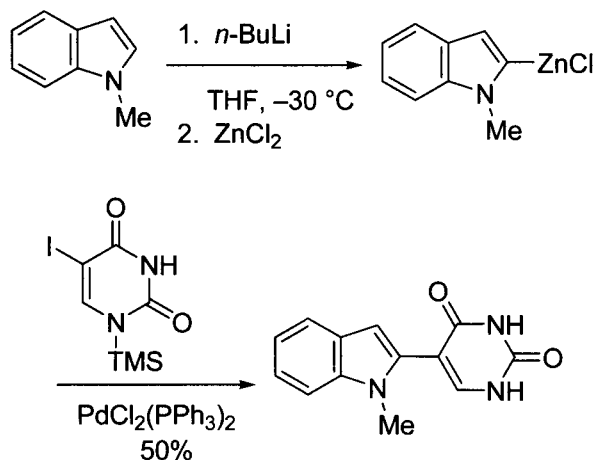


alosectron (Lotronex)
GlaxoSmithKline/Prometheus Lab

3.5.2 Negishi Coupling

The Negishi reaction is the palladium-catalyzed cross-coupling of organozinc reagents with organohalides or triflates. It is compatible with many functional groups including ketones, esters, amines and nitriles. The organozinc reagents are usually generated and used *in situ* by transmetalation of Grignard or organolithium reagents with $ZnCl_2$. In addition, some halides may oxidatively add to $Zn(0)$ to give the corresponding organozinc reagents.

Although the Negishi coupling has been less frequently used in indole synthetic manipulations than either Suzuki or Stille couplings, we will see in this chapter that Negishi chemistry is often far superior to other Pd-catalyzed cross-coupling reactions involving indoles. One of the first such examples is the coupling of 1-methyl-2-indolylzinc chloride with iodopyrimidine to give the indolyl-pyrimidine-dione.⁶⁸



Since direct alkylation of a 2-lithioindole failed, a Negishi protocol was utilized to synthesize a 2-benzylindole, an intermediate for the novel CNS agent.⁶⁹