Asymmetric Synthesis of (S)-Ketoprofen

Significance: A synthesis of the non-steroidal anti-inflammatory drug (S)-ketoprofen exemplifies a new general tandem catalysis approach to the enantioselective organocatalytic α-arylation of aldehydes. The scope of the reaction is illustrated by 22 examples (67–95% yield, 91–94% ee) involving ten different aldehydes and 13 different diaryliodonium salts. A five-step synthesis of catalyst C (17% overall) from L-phenylglycine N-methylamide is provided.

Comment: A mechanism is proposed involving reaction of the aryl copper(III) species G (derived from oxidative addition of CuBr to the diaryliodonium salt A) with the enamine H (derived from condensation of the organocatalyst C with propanal) to give the η1-iminium copper(III) species I. Reductive elimination with retention of configuration then gives the α-aryl iminium salt J, which hydrolyzes to the product with regeneration of the organocatalyst C.