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 \( \alpha \)-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 \( \text{CuBr} \) to the diaryliodonium salt \( A \)) with the enamine \( H \) (derived from condensation of the organocatalyst \( C \) with propanal) to give the \( \eta^1 \)-iminium copper(III) species \( I \). Reductive elimination with retention of configuration then gives the \( \alpha \)-aryl iminium salt \( J \), which hydrolyzes to the product with regeneration of the organocatalyst \( C \).