A. E. ALLEN, D. W. C. MACMILLAN* (MERCK CENTER FOR CATALYSIS AT PRINCETON UNIVERSITY, USA)

Enantioselective α-Arylation of Aldehydes via the Productive Merger of Iodonium Salts and Organocatalysis
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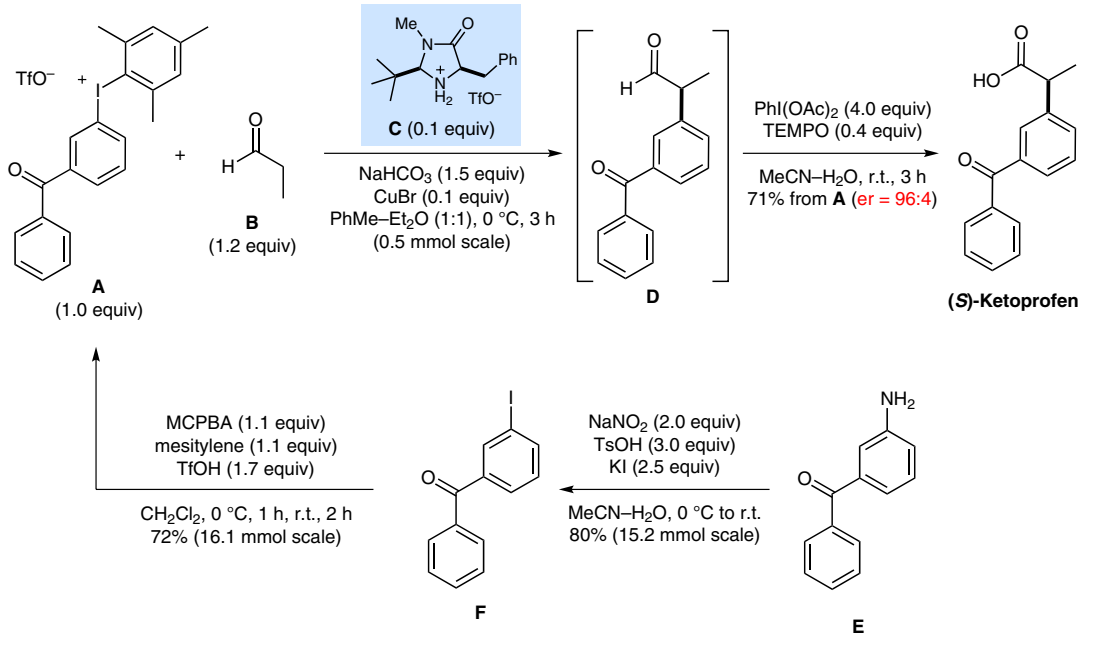
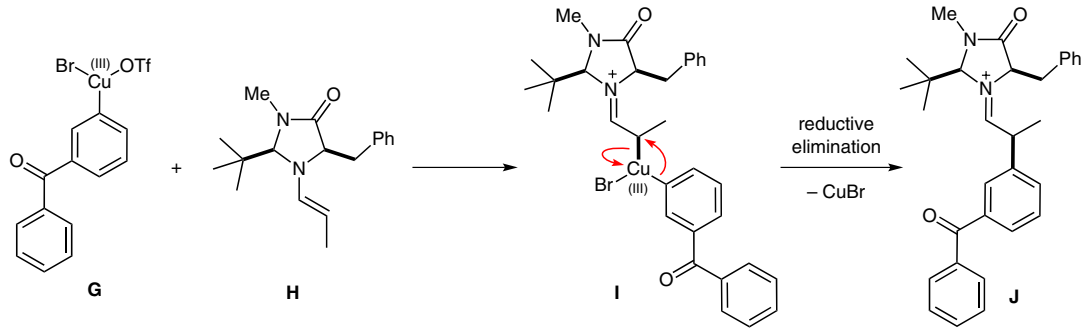
Asymmetric Synthesis of (*S*)-Ketoprofen



Proposed mechanism for the aldehyde α-arylation:



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 η^1-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**.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

ketoprofen
organocatalysis
iodonium salts
iminium ions
α-arylation

SYNFACT of the month