

Silicon-Catalyzed Mannich Reaction of Unactivated Amides

Category

Organo- and Biocatalysis

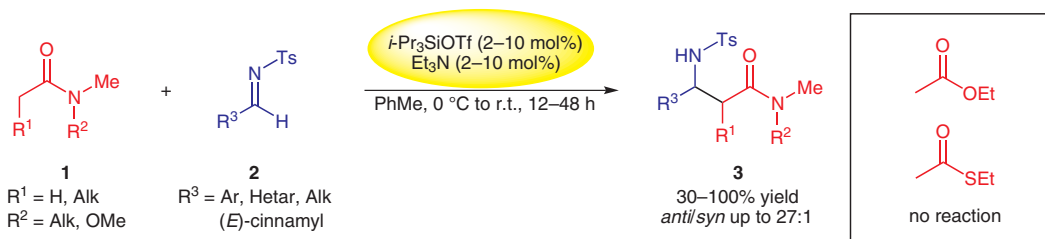
Key words

Mannich reaction

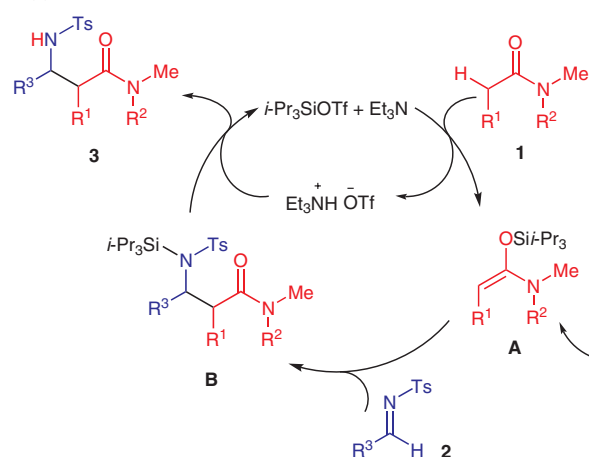
catalytic silicon enolates

unactivated amides

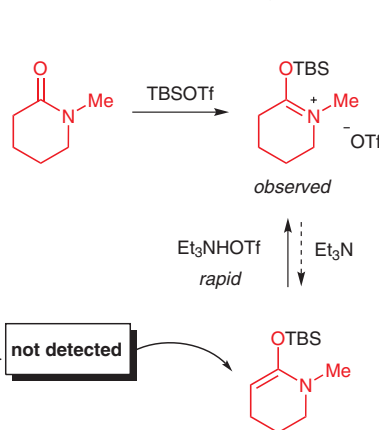
SYNFACT
of the month



Suggested catalytic cycle:



Selected mechanistic investigations:



Significance: Kobayashi and colleagues report an unusual Mannich reaction between unactivated amides **1** and tosylimines **2**, catalyzed by triisopropylsilyl triflate and triethylamine. The authors propose that the reaction proceeds via a catalytic formation of a silyl enol ether **A** from amide **1**, which reacts with imine **2** to form intermediate **B**. The ammonium triflate salt then regenerates the silicon catalyst, affording product **3** and completing the cycle. Although the proposed silyl intermediate **A** was elusive by NMR spectroscopy, several indirect experiments provide support for the suggested catalytic cycle. For less reactive substrates, a metal co-catalyst (CuOTf) was found necessary, which presumably provides Lewis acid activation of imines **2** rather than forming a copper enolate from **1**.

Comment: Given the usefulness and versatility of silicon enolates in C–C bond-forming reactions, the lack of methods with silicon catalysts is notable. The major challenge to achieve turnover is likely the regeneration of the catalyst from the product, which covalently incorporates silicon. Kobayashi and colleagues developed a Mannich reaction, where the catalytic formation of silicon enolate intermediates seems plausible. The relative weakness of the N–Si bond and the specificity of the nitrogen protecting group appear to be prerequisites for the observed turnover. It is intriguing why amides proved to be productive substrates in contrast with esters, and whether a parallel Lewis acid activation involving the silicon catalyst or another species is operative in the reaction. Further mechanistic insight into this reaction is expected.

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