Catalytic Processes

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Towards Direct Mukaiyama-Type Reactions Catalytic in Silicon**

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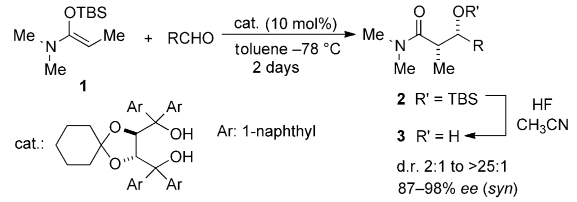
amides · asymmetric catalysis · direct addition · Mannich reaction · silicon

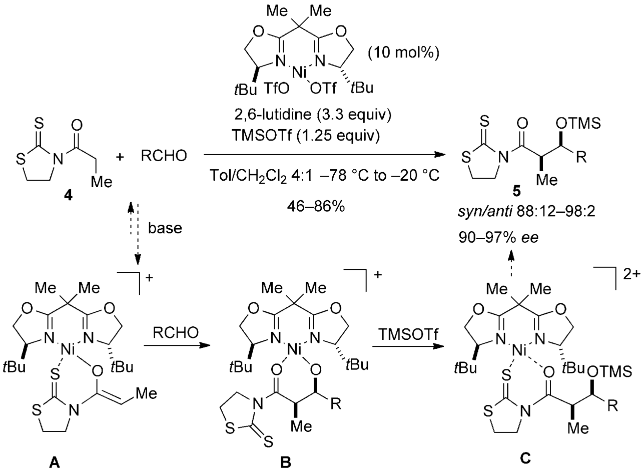
In memory of Rafael Suau

Silicon is one of the most abundant elements on Earth, and silicon-containing reagents are useful tools in organic chemistry, not only as widely applicable protecting groups, but also as reaction components capable of controlling and directing the reaction outcome. Thus, one of the most venerable C–C bond-forming reactions, the aldol addition reaction, has a silicon-mediated version named the Mukaiyama aldol reaction[1] after its discoverer. In this process a silyl enolate (either silyl enol ether or the corresponding *O*-, *N*-, or *S*-silyl ketene acetal) is prepared in the first step and then reacts with an aldehyde or related electrophile. In contrast to most other metal enolates, silyl enolates are usually isolable species that react smoothly with the corresponding electrophile with the assistance of a Lewis acid,[2] Brønsted acid,[3] or Lewis base[4] catalyst. Among the silyl enolates used for Mukaiyama-type reactions, those derived from amides are of particular relevance since the presence of the enamine unit makes these substrates highly nucleophilic. An illustrative example has been reported by Rawal and co-workers[3c] (Scheme 1), who have demonstrated that *O*-silyl-*N*,*O*-ketene acetals **1** are capable of reacting with aldehydes at low temperature in the presence of a tetraaryl-1,3-dioxolane-4,5-dimethanol (taddol) as the chiral hydrogen-bond donor, and after desilylation of **2**, afford the expected aldol adduct **3** with good yield and very high enantioselectivity.



Scheme 1. Enantioselective Mukaiyama reaction of silicon enolates of amides. TBS = *tert*-butyldimethylsilyl.

A common limitation of the classic Mukaiyama aldol and related (Mannich, Michael, and so on) reactions is the need for the generation of the silyl enolate species in a separate prior step with the consumption of at least stoichiometric amounts of the silylating reagent and base. However, recent works from the laboratories of Evans,[5] and Downey,[6] independently, have skipped such additional step, thus demonstrating that silicon-mediated aldol reactions can occur in a direct fashion with intervention of stoichiometric amounts of the silylating reagent. Downey and Johnson, for example, have shown that a slight excess of silyl triflate mediates a tandem enol silane formation/Mukaiyama aldol reaction of aryl methyl ketones and acetate esters with aromatic, heteroaromatic, and α,β-unsaturated aldehydes in the presence of Hünig's base.[6] Most significantly, in an earlier work by Evans it has been shown that a nickel(II) bis(oxazoline) complex (Scheme 2) is capable of promoting a highly enantioselective reaction of *N*-propionyl thiazolidin-2-thione (**4**) with a range of both enolizable and nonenolizable aldehydes in the presence of base and silyl triflates. In this instance, no silicon enolate was observed and the authors



Scheme 2. Catalytic enantioselective direct aldol addition reactions of *N*-propionyl thiazolidin-2-thione and proposed intermediates. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

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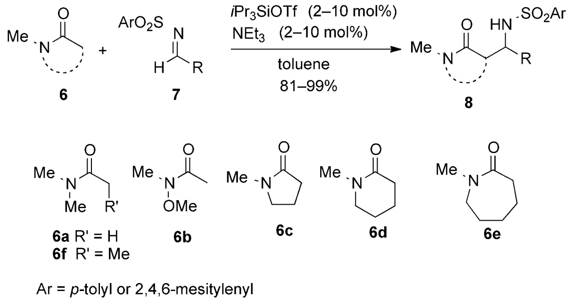
proposed the catalytic cycle shown in Scheme 2, wherein aldolate **B**, which is formed from the reaction of enolate **A** with the aldehyde, is silylated by the silyl triflate to give **C**; an event that facilitates decomplexation of the aldol product and catalyst turnover.[5,7]

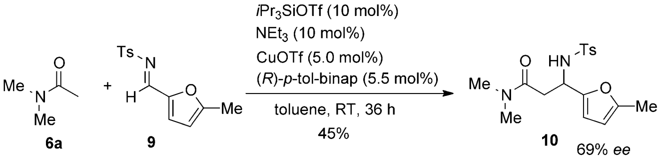
More strikingly, Kobayashi et al.[8] have very recently reported a direct Mannich reaction of amides that requires no more than 10 mol % of base and silylating reagent. The initial study from a survey of carboxylic acid derivatives, such as esters, thioesters, and amides, as pronucleophiles, revealed that only the less-acidic amides are productive in the catalytic system. This finding constitutes a rare case of amides efficiently participating in an addition reaction that proceeds through a soft enolization process.[9] For example, *N*,*N*-dimethylacetamide **6a** and Weinreb acetamide **6b** react with a wide range of N-sulfonyl imines **7**, including aromatic, α,β-unsaturated, and α-branched aliphatic *N*-sulfonyl imines, in presence of a 5 mol % of both the *i*Pr_3SiOTf and NEt_3, to provide the addition adducts **8** in yields within the range 81–99 % (Scheme 3).



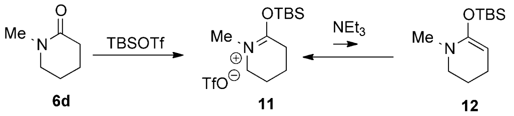
Scheme 3. Direct addition reaction of amides to imines catalytic in silicon.

Cyclic amides appear to be less-reactive substrates, only producing the expected adducts when more active imine counterparts, such as the *N*-tosyl imino esters, are used. Further exploration revealed that this catalytic system is tolerant to Lewis acids and that the Lewis acids are capable of activating less-reactive imines, with CuOTf being the most active cocatalyst for this reaction. Thus, *N*-benzylidene-*N*-tosylamine reacts with either cyclic (**6c–e**) or acyclic (**6f**) amides in the presence of CuOTf (5 mol %), *i*Pr_3SiOTf (10 mol %), and NEt_3 (10 mol %) to afford the Mannich products in essentially quantitative yields and with good diastereoselectivities (from 4.2:1 to 27:1). Importantly, using just 10 mol % of the cooperative catalytic system *i*Pr_3SiOTf/NEt_3, together with a 5 mol % of a chiral complex formed between CuOTf and *p*-tol-binap it was possible to accomplish the catalytic Mannich reaction between acetamide **6a** and N-tosyl imine **9** enantioselectively (Scheme 4). Although a moderate *ee* value was obtained (69 %), this reaction represents the first example of an asymmetric enolate addition reaction catalytic in silicon.

In several experiments designed to clarify the mechanism, Kobayashi and co-workers proved the formation of the amide/R_3SiOTf complexes in the catalytic cycle and proposed that, although silicon enolates were not observed, they would be generated in a very small amount from these complexes. Therefore, this process appears to be different from the mechanistic pathway that is involved in the Evans direct aldol reaction. In support of this assumption, complex **11** was prepared from amide **6d** and *tert*-butyldimethylsilyl triflate (Scheme 5). No Mannich reaction between complex **11** and *N*-benzylidene-*N*-2,4,6-mesitylenesulfonylamine was observed in the presence of CuOTf (5 mol %) if Brønsted base was not added, but when triethylamine (100 mol %) was also employed in this reaction, the corresponding Mannich adduct was obtained in 38 % yield. These observations suggest the participation of the silicon enolate **12**, which once generated would react with the imine in a probable acyclic transition state[10] to provide the product with high diastereoselectivity (*anti*/*syn* 23:1). Nevertheless, owing to the presence of CuOTf, another reaction pathway through a more reactive copper enolate cannot be ruled out.[11]



Scheme 4. Enantioselective direct Mannich addition reaction of *N*,*N*-dimethylacetamide catalytic using silicon. Configuration not assigned. *p*-tol-binap = 2,2′-bis(di-*p*-tolylphosphanyl)-1,1′-binaphthyl, Ts = toluene-*p*-sulfonyl.



Scheme 5. Formation of amide/TBSOTf complex.

While all these direct processes might not follow a uniform mechanism and the precise role played by the likely generated silyl enolates remains not fully deciphered yet, these results constitute a real breakthrough in the area of catalytic functionalization of C−H systems adjacent to a carbonyl group.[12] Whilst soft deprotonation of carboxylic acid derivatives provides a mild and operationally simple method for enolate generation, the development of an efficient and general asymmetric catalytic system for simple unactivated substrates remains undiscovered and the catalytic silicon cycle described by Kobayashi can help to achieve this synthetic challenge.

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