Carbene catalysis: An internal affair

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News and Views

NHC Catalysis

An Internal Affair

Forming powerful reactive intermediates for C–C bond formation such as enolates and homoenolates used to require strong bases and harsh conditions. Using NHC-catalysis, they can be now be generated from alpha-functionalized aldehydes or even saturated esters under mild conditions.

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Students of organic chemistry are encouraged to studiously master “functional group transformations”, the inter-conversion of each carbon-based functional group to the others, taking careful account of the oxidant state and choosing, as necessary, the appropriate oxidant or reducing agent. More recently, chemists have taken a more holistic view of functional groups and oxidation states within an organic molecule and recognized that isohypsic or “redox neutral” transformations can be achieved by concomitant transformation of functional group arrays. This sophisticated approach to rearrangements and the generation of uniquely reactive intermediates is most evident in the field of N-heterocyclic carbene (NHC) catalysis, which has quickly risen from near obscurity to one of the most active and powerful classes of catalysis.

The new era of NHC-catalyzed reactions began in 2004 with the recognition that NHCs can catalytic convert alpha-functionalized aldehydes into activated carboxylic acids, allowing ester and amide formation without the need for coupling reagents or the production of byproducts.[1],[2] Alpha,beta-unsaturated aldehydes could be converted not only to the saturated esters by simultaneous reduction of the olefin and oxidation of the aldehyde, but could also be used to catalytically generate species that react as homoenolates,[3,4] and enolates,[5] depending on the choice of reaction conditions and catalysts. The generation and bond-forming reactions of each of these intermediates could even be sequenced together in a single catalytic cycle, leading to the formation of complex, multicyclic products under simple reaction conditions.[6,7] These powerful, often highly enantioselective processes were long thought to be a one-way street, with the enolates and homoenolates being generated by the downhill reaction of the more complex enal or enone starting materials. Recent reports by Chi et al, however, demonstrates that the indentical enolates[8] and homoenolates[9] can be generated from the *saturated* esters, thereby allowing formal activation of saturated C–H bonds.

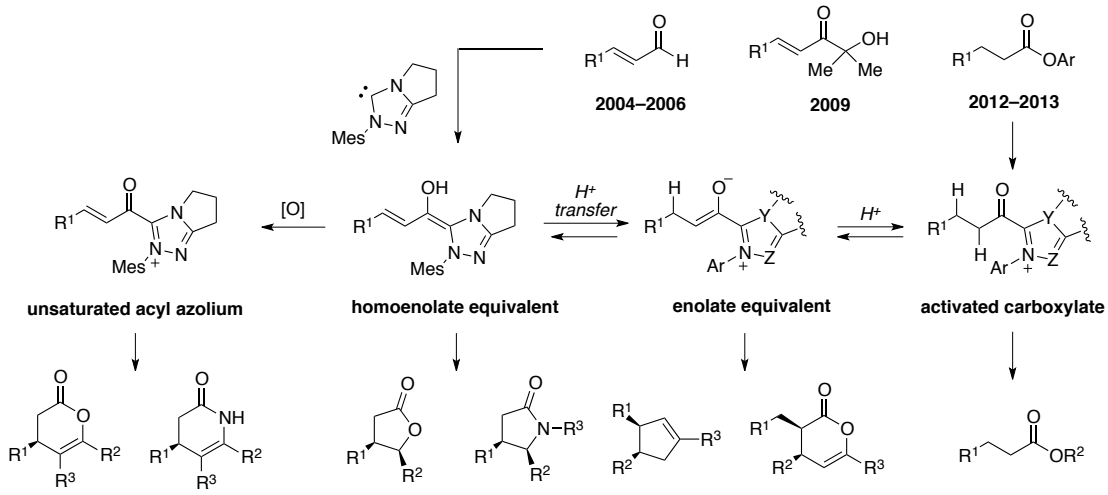

Figure 1. Catalytic generation of reactive intermediates from functionalized aldehydes or saturated esters. Selected products that can be prepared from each activation mode are shown, usually in excellent yields and nearly perfect enantioselectivities.

Using *para*-nitrobenzoate esters as starting materials and a chiral NHC, Chi et al can form many of the enantiomerically enriched products that typically begin by generation of the homoenolate equivalent, including gamma-lactones, gamma-lactams, and cyclopentenes. As the enal starting materials often require several steps for their preparation, the saturated aryl esters serve as an attractive starting point. Alpha-hydroxyenones, which have also been advanced as convenient, easily prepared starting materials for NHC-catalysis,[10] are limited to the formation of racemic products using less sterically hindered achiral NHCs.

More importantly, the activation of the beta-position of a saturated ester under mild conditions with an organic catalyst is an outstanding demonstration of the power of catalysis to functionalize remote C–H bonds. Similar activation of saturated esters can be achieved with palladium or rhodium catalysis, but often require high reaction temperatures or special directing groups.[11] This work also compliments the photocatalytic oxidation of saturated aldehydes and ketones to electrophilic enones or enals reported by MacMillan et al.[12] The transformation described by Chi are all the more impressive given that no added oxidant is necessary and the saturated esters are being transformed, at least in a transient, formal sense, to alpha,beta-unsaturated aldehydes!

Chi presents some data to suggesting that the homoenolate intermediates generated from the saturated esters are somehow superior to those prepared from enals. This is a bit disingenuous, as this effect is mostly likely due to differences in the formation of geometric isomers of the homoenolate equivalent and a change in the rate-determining step of the catalytic cycle. This may be useful in certain cases, but for most of the transformation reported superior results starting from enals can be obtained simply by using the commercially available N-mesityl substituted, chiral aminoindanol derived triazolium salt.[13]

With so many unique reaction modes from a diverse panel of starting materials available with NHC catalysis, one may wonder what remains to be done? Despite the elegance of Chi's work, the products provided are identical to those already reported – often with higher yield and better enantioselectivity – from the enal starting materials. All of these processes suffer from inherent limitations in substrate scope, often requiring aryl substituents on either or both of the reaction partners. Even aromatic N-heterocycles, which are tolerated when enals or alpha-hydroxyenones are used as the homoenolate precursors, are omitted from the substrate scope when saturated esters are used. Given that such specialized products will be needed only rarely, it not clear that starting from saturated compounds offers a significant advantage. The catalyst loading and reaction rates, currently at 20 mol % and 24–48 hours, leave room for improvement. Chi's method also requires *para*-nitrophenyl esters which must be prepared from the corresponding acids; the far less expensive methyl or ethyl esters – or the carboxylic acids themselves – are currently not suitable starting materials.

The emphasis here is on *currently*, as Chi's work conclusively demonstrates that the mechanistic basis for room temperature activation of simple, inexpensive feedstock materials exists, opening the door to potentially transformative new processes in the chemical industry. These later challenges will be solved only by the design and development of new NHC catalysts that prove to be more reactive both as nucleophiles and generate more reactive homoenolates or through the combination of catalysts to achieve the same goals. But given the remarkable progress in the field over the past decade, there is every reason to believe that NHC catalysis will soon be able to transform feedstock materials such as simple acetate or propionate esters into valuable chemicals under simple, inexpensive conditions.

The catalytic generation enolates from esters stood for years as one of the Holy Grails of asymmetric catalysis. It is remarkable that activation modes buried within the mechanism of the benzoin reaction and the chemistry of vitamin B1 provide a route for catalytic generation of not only enolates but of homoenolates as well, all under mild reaction condition and with exceptional enantioselectities. With each passing year, NHCs continue to emerge as the superheros of organic chemistry – it truly seems that there is nothing they cannot do.

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