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Organocatalytic Hydroacylation of Unactivated Alkenes **

Daniel A. DiRocco and Tomislav Rovis*

Department of Chemistry, Colorado State University, Fort Collins, CO 80526

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Aldehyde umpolung, the inversion of the electrophilicity of the carbonyl group into a nucleophile, has its origins in Wohler and Liebig's 1832 paper describing the cyanide catalyzed benzoin reaction.¹ One hundred years later, Ukai demonstrated the same transformation using thiazolium precatalysts in the presence of base.² In 1958, Breslow first proposed the currently accepted mechanism of this transformation, building on Lapworth's mechanism for the cyanide catalyzed benzoin.³ In 1974, Stetter showed that Michael acceptors may also be used as electrophiles for the acyl anion equivalent.⁴ With the advent of *N*-heterocyclic carbenes, there has been a huge upsurge in reactivity associated with these systems, with chiral catalysts, novel reactions, new modes of reactivity and their applications to synthesis all making an appearance.⁵

Nevertheless, the limitations initially demonstrated by Wohler and Liebig had remained: namely, the requirement for an electrophilic partner for the acyl anion equivalent to couple. Recent work, however, has suggested that this limitation will no longer apply. A serendipitous discovery by She has culminated in a recent paper by Glorius documenting an asymmetric version that suggests *these acyl anion equivalents, thought to be modest nucleophiles at best, may yet be reactive enough to add to unfunctionalized alkenes.*

In 2006, She and coworkers reported that aldehydes bearing tethered alkyl tosylates result in cyclization to the ketone, an example of carbene-catalyzed alkylation of aldehydes.⁶ As with every transformation, the reaction scope was limited but it was a side reaction that was particularly puzzling. Tosylate **1** did not result in cyclization to the six-membered ketone **4** but rather to the five-membered ring **3**. The authors proposed that the reaction proceeds via a rather unlikely primary cation followed by hydride shift and alkylation. However, it seems more reasonable that the tosylate undergoes elimination to the alkene **5** and the acyl anion equivalent adds to it to form the ring. This hypothesis was confirmed by the She group which published the cyclization of aldehydes onto tethered alkenes.⁷

Glorius and coworkers also identified the same reactivity.⁸ These workers found that even simple terminal alkenes participate and introduced a bicyclic thiazolium catalyst for the transformation, which delivers optimal yields.

Most impressively, Glorius has now demonstrated that the reaction may be rendered asymmetric. The cyclization of aldehydes onto tethered 1,1-disubstituted alkenes proceeds in excellent enantioselectivity to afford cyclic ketones with quaternary stereocenters in very good yield.⁹ The scope of the reaction is currently limited to aryl substituted alkenes, but

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* rovis@lamar.colostate.edu, http://www.chem.colostate.edu/rovis/Rovis_Group_Website/Home_Page.html.

one anticipates more findings in this area will address these issues. Glorius has further generalized his findings, with cyclizations of the aldehyde onto tethered alkynes. If the latter reaction is conducted in the presence of another aldehyde, a cascade aldehyde alkyne cyclization/intermolecular Stetter sequence takes place.¹⁰

A more salient question, however, is how this reaction operates. Previous work on the benzoin reaction has suggested that it may proceed by simultaneous activation of the carbonyl by a hydrogen bond from the Breslow intermediate (Figure 1). However, the basicity of the carbonyl makes this pathway readily apparent. The Stetter reaction, the addition of the Breslow intermediate to a polarized double bond, lacks this mode of activation, but one may argue that the stability of the generated enolate is such to allow a subsequent rapid proton transfer event to occur. Yates has conducted a DFT study of the Stetter mechanism and has suggested that the resultant enolate is hydrogen bonded to the pendant OH and undergoes a rapid subsequent protonation.^{11,12}

Of course, the unactivated alkene involved in these reactions lacks this stabilization. Glorius has drawn an analogy between the hydroacylation and the Conia ene reaction, comparing the enol of the Breslow intermediate in **A** (Figure 1) and emphasizing its push-pull nature.⁸ One wonders, however, if a more relevant comparison may not be to a reverse-Cope elimination,¹³ with the acyl anion resonance form **B** having the carbanion which mimics the nitrogen in the prototypical reverse-Cope.

All the currently reported examples of aldehydes cyclizing onto unfunctionalized, or rather unpolarized, π systems do so intramolecularly. In that regard, perhaps another finding by the Glorius group holds some promise about a more general solution that may ultimately lead to an intermolecular hydroacylation. The Glorius group has now found that aldehydes add to dehydroamino esters in an intermolecular fashion with high enantioselectivity.¹⁴ Two aspects of this transformation are worthy of note. Our group has demonstrated that asymmetric intermolecular Stetter reactions proceed very well only with the most reactive Michael acceptors such as alkylidene malonates and nitroalkenes.¹⁵ Dehydroaminoacids are clearly far less electrophilic than nitroalkenes. Secondly, this manuscript by Glorius was the first demonstration of a highly enantioselective Stetter that only forms stereocenters alpha to the carbonyl. One wonders whether the unique electronic features of the dehydroamino acid with its partial electron-deficient but also electron-releasing character may not be responsible for the success of the transformation, and reminiscent of the successful cyclization onto unfunctionalized alkenes. If so, it holds significant promise that, given more time, the cyclization of aldehydes onto unpolarized alkenes may prove remarkably general.

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- Putative TS's in the benzoin and Stetter reactions:

- Putative TS's in the hydroacylation reaction:

Figure 1.
Mechanistic Considerations.

She: **Glorius:**

Scheme 1.
Seminal Reports of the NHC-Catalyzed Hydroacylation of Unactivated Alkenes.

Scheme 2.
Asymmetric Intramolecular Hydroacylation of Unactivated Alkenes.