News and Views in Organic Chemistry

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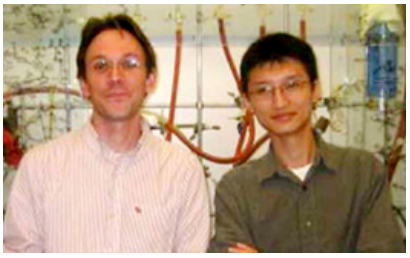
Direct, Catalytic, Stereoselective Conversion of Epoxyaldehydes into β-Hydroxyesters (*J. Am. Chem. Soc.* **2004**, *126*, 8126)

Direct, catalytic, stereoselective and simple: all you want from an organic reaction! These highly desirable features belong to a process recently described by assistant professor Jeffrey W. Bode and graduate student Kenneth Yu-Kin Chow at the Chemistry and Biochemistry Dept., University of California in Santa Barbara (UCSB). "This reaction is part of two larger programs in our group. – said Prof. Bode when contacted by LOC – In the first, we are seeking new reactions for the direct synthesis of carboxylic acid derivatives, such as esters and amides, under truly catalytic, waste-free conditions. In the second, we are exploiting catalyst induced redox reactions to access uniquely reactive



Prof. J.W. Bode (left) and K.Y.-K. Chow (right).

intermediates, such as activated carboxylates and homoenolates." Bode's direct, catalytic esterification of epoxyaldehydes was one of those rare cases where the reaction worked on the first try, just the way one hopes. "In fact, it worked so well that we thought, "Someone *must* have tried this before!". – Bode continued – We searched and searched for a similar process, and finally found a mechanistically similar reaction, the cyanide mediated conversion of chloral to dichloroacetic acid, published by Wallach in 1873 (*Ann. Chem.* **1873**, *6*, 114). It was great fun to learn that we "rediscovered" a very powerful reaction that had lied dormant for so long! Of course, our procedure has some advantages to the Wallach process. First, the reaction proceeds with chiral epoxyaldehydes, which are easily prepared in scalemic form by the Sharpless epoxidation. Second, there are no reactions by products, all of the atoms of both the alcohol and the epoxyaldehyde are incorporated in the product. Third, the reaction uses catalytic amounts of a cheap, non-toxic organocatalyst. Fourth, in some cases we have even been able to dispense with the solvent; simply mixing 1 equiv. of the aldehyde, 1.1 equiv. of the alcohol, 8 mol% thiazolium salt, and 7 mol% Hunig's Base gives the desired product in 86% isolated yield!".

A remarkable feature of this paper is that it is the first from Bode's laboratory. In fact Jeffrey Bode began his independent research career at the UCSB in July 2003. Prior to that he was a graduate student with Prof. Erick M. Carreira at the California Institute of Technology and the Swiss Federal Institute of Technology (ETH-Zurich). His postdoctoral studies were with Prof. Keisuke Suzuki at the Tokyo Institute of Technology. Kenneth Yu-Kin Chow performed this work in his first year of graduate studies at UCSB working with Prof. Bode. He completed his Bachelors of Science in Biochemistry at San Francisco State University in 2003.

Enantioselective Direct Incorporation of O_2 *via* Organocatalysis (*J. Am. Chem. Soc.* **2004**, *126*, 8914)

Natural amino acids are able to catalyze the asymmetric incorporation

Prof. A. Córdova (left) and I. Ibrahem (right).

of singlet molecular oxygen to the α-position of aldehydes. In addition to its synthetic interest, this reaction may suggest a prebiotic entry for α-hydroxy aldehydes, which are of great biological significance as the building blocks of sugars. The striking discovery has been recently done by Prof. Armando Córdova, graduate students Ismail Ibrahem, Magnus Engqvist, Henrik Sundén and post-doc Jesus Casas at the Dept. of Organic Chemistry, Arrhenius Laboratory, of the Stockholm University (Sweden). Based on previous investigations of direct amino acid-catalyzed asymmetric α-oxidations of carbonyl compounds with nitrosobenzene by the same group (*Chem. Eur. J.* **2004**, *10*, 3673), Córdova and coworkers became interested in whether a catalytically generated enamine would be able to react with molecular oxygen and form an oxygenated organic compound. "We found that α-methyl proline catalyzed the biomimetic aerobic α-oxidations of aldehydes with the highest enantioselectivity. – said Prof Córdova, contacted by LOC - The direct catalytic asymmetric α-oxygenations may be considered a metal free entry for the preparation of optically active building blocks such as terminal diols." The α-oxygenations are inexpensive and operationally simple. All materials in this process are from renewable resources thus allowing for a highly sustainable catalytic process. Córdova's results demonstrate that simple amino acids can accomplish catalytic asymmetric oxidations with singlet molecular oxygen, which has been previously considered to be in the domains of enzymes and chiral transition-metal complexes. "The amino acid-catalyzed asymmetric aerobic oxidations have now been expanded to

M. Engqvist

Dr. J. Casas

H. Sundén

ketone substrates. – continued Prof. Córdova referring to a paper in press in *Angew. Chem. Int. Ed.* - The simplest chiral amino acid alanine provided the highest asymmetry in the incorporation of molecular oxygen to ketones. We are currently performing density functional calculations of the reaction in order to get a better understanding of the transition states and to obtain higher stereoselectivity of the transformation."

No-D NMR: RLi and RMgX Titers in Minutes (*Org. Lett.* **2004**, *6*, 2567)

Determining the concentration of solutions of organometallic reagents is an onerous obligation that doesn't get done often enough in most labs. Now Professor Thomas R. Hoye, graduate student Brian M. Eklov, and undergraduate student Mikhail Voloshin at the Chemistry Dept. of the University of Minnesota have reported a method, dubbed No-D (No Deuterium) Proton NMR Spectroscopy (or "No-D"), that reduces this task to a ten minute operation: squirt (cyclooctadiene standard), squirt (R-Met in hexanes or THF), record (the No-D spectrum), and integrate. Quantification is easily reliable to ±2%.

Prof. Hoye

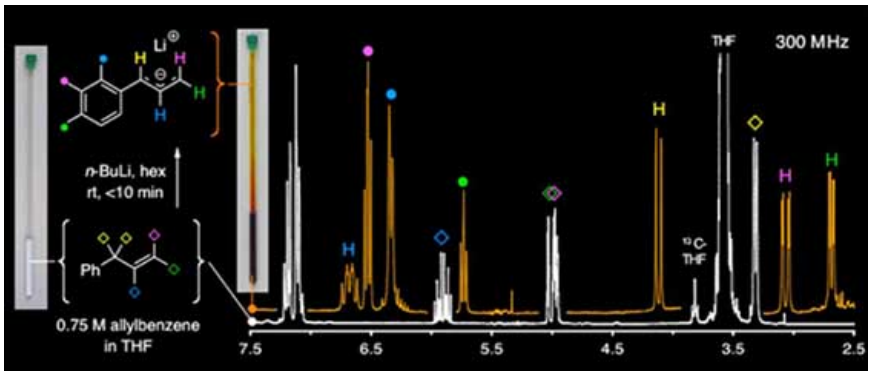
"For some time now in our laboratory we have been routinely recording proton NMR spectra of all types of solutions (*n*-BuLi/hexanes, coffee, an aliquot of an enolate reaction, … you name it) in an unorthodox fashion. – said Prof. Hoye to LOC – Namely, no deuterated sol-vent is present and the spectra, necessarily then, are recorded in unlocked mode. It is important to repeat here what we have pointed out elsewhere; this is not a new idea. We can identify niche applications in the literature (and anecdotally), but there is no doubt that this technique is a) not at all mainstream and b) extremely valuable."

B.M. Eklov

The first paper on the subject (*Org. Lett.* **2004**, *6*, 953) was designed to be a "how to manual" for every synthetic chemist. "Learning to shim and record an unlocked sample is like learning to ride a bicycle—once mastered, it is never forgotten. – added Prof. Hoye – Frankly, the bigger barrier is getting chemists to think to use the technique in the first place. Ever wonder how much of your polar product was lost in an aqueous wash? Take the No-D of the water layer. That the approach is somehow 'unclean' probably contributed to the fact that the first student in the lab to really run with the idea was an undergraduate researcher, Misha Voloshin, who was not unduly biased by habit."

M. Voloshin

Hoye and coworkers have now detailed (*Org. Lett.* **2004**, *6*, 2567) a method for determining the titer of organolithium, -magnesium, and -zinc reagents, and there is no reason it can't be extended to many other classes of reagents as well. Nucleophilic or basic metal hydrides constitute another set for which titers are not easily available. "We are currently preparing a manuscript describing a 'reaction titration' that nicely addresses this problem (for, e.g., $LiAlH_4$, DIBALH, Red-Al®, and NaH). – concluded Prof. Hoye – Finally, because No-D is a non-invasive technique (i.e., no workup), it can be used routinely to assess the generation and stability of reactive intermediates or to monitor their reaction progress. As but one (of dozens of) example(s), consider the formation of phenylallyllithium by the deprotonation of allylbenzene by *n*-BuLi in THF at room temperature (Figure). The beautiful orange-black solution of anion gives rise to an equally beautiful spectrum and remains stable for days in an NMR tube with no special precautions. The bottom line: the technique is easy to use and it is powerful." Eklov and Voloshin reported that "this is so easy, even Professor Hoye can take the spectrum." Consider recording the No-D NMR spectrum of any (every?) solution!

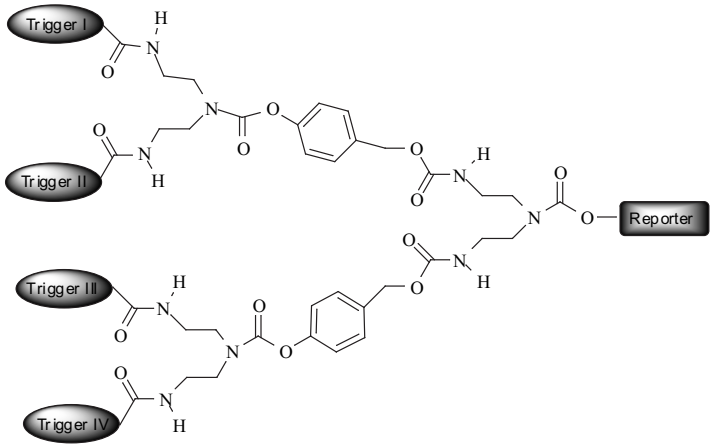


No-D ^{1}H NMR spectrum of, as an example, phenylallyllithium recorded (at RT) within minutes of mixing allylbenzene [0.5 M] and n-butyllithium in hexanes/THF (experiment of James E. Kabrhel).

Self-immolative Dendrimer Biodegradability by Multi-enzymatic Triggering (*Chem. Commun.* **2004**, 1614)

The modern therapy of serious diseases, such as cancer, needs more effective and better controlled drug delivery systems. This, in principle, could be achieved through a drug carrier, which upon proper stimulation, releases multiple loads of active molecule, then is effectively cleared out from circulation avoiding toxic side effects. Recently, the group led by Dr. Doron Shabat, senior lecturer at Tel-Aviv University (Israel), has reported

Dr. D. Shabat (left) and R. Amir (right).

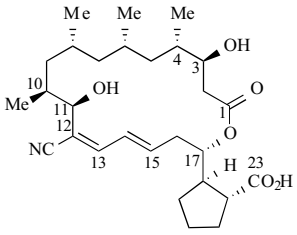


the design and synthesis of novel dendritic molecules, which were termed as Self-Immolative Dendrimers (*Angew. Chem. Int. Ed.* **2003,** *42*, 4494-4499). These dendrimers are designed to undergo a domino like fragmentation, which starts at the core and propagates along the dentritic skeleton towards the periphery with a consequent release of the end groups. Now, Dr. Shabat and graduate student Roey J. Amir have designed and synthesized new self-immolative dendritic molecules. The new dendrons (Figure) are built with a multi-enzymatic triggering mechanism, which initiates their biodegradation through a self-immolative chain fragmentation to release a reporter group from the focal point. The dendritic backbone is constructed from polycarbamate linkages, which are stable to hydrolysis and enhance the dendrons solubility in water. The degradation can readily take place under physiological conditions following enzymatic triggering.

Preliminary studies have shown that such a dendrimer acts like an "OR" molecular logic gate which can be activated by multi-number of orthogonal agents. "Incorporation of different substrates in the dendron's periphery, should allow the use of diverged triggering enzymes. – said Dr. Shabat to LOC - This concept may be particularly important in the field of prodrug mono-therapy, if a drug molecule will be incorporated instead of the reporter unit. Especially in circumstances with more than one tumor-associated or targeted enzyme with different catalytic activity. Further studies of these dendritic molecules are under progress."

New Total Synthesis of the Macrolide Borrelidin (*Angew. Chem. Int. Ed.* **2004**, *43*, 3947)

Initially proposed by Woodward in 1957, the term macrolide has defined an interesting class of bioactive natural products that are structurally characterized by a macrocyclic lactone motif. Despite a common polyketide-based

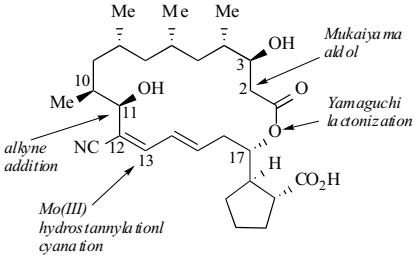


Borrelidin

biogenesis, the chemical structure of macrolides is very diverse and often contains unusual functionalities that contribute substantially to the biological activities of these compounds. The macrolide borrelidin exemplifies such features, by encompassing four 1,3 alternating methyl groups with a distinctive syn/syn/anti relationship. Moreover, the presence of a Z/E conjugated cyanodiene fragment (C12-C15) and the cyclopentane carboxylic acid unit (C18-C23) contribute to an unprecedented chemical structure. Isolated for the first time in 1949, borrelidin was found to possess a broad antibiotic profile and, in fact, it was so named due to its activity against *borrelia*, the spirochete of relapsing fever.

More recent studies indicated that borrelidin inhibits the process of angiogenesis at subnanomolar concentrations underlining its potential as a lead structure for the development of new antiangiogenesis drugs. This information has spurred the development of new methods and strategies towards the chemical synthesis of this natural product. Three total syntheses of borrelidin have been described by James P. Morken (*J. Am. Chem. Soc.* **2003**, *125*, 1458), Stephen Hanessian (*J. Am. Chem. Soc.* **2003**, *125*, 13784), Satoshi Omura (*Org. Lett.* **2004**, *6*, 1865) and their coworkers.

Prof. Theodorakis



In a recent article Prof. Emmanuel Theodorakis, graduate student Binh G. Vong, and Postdoctoral Researchers Dr. Sun Hee Kim, and Dr. Sunny Abraham at the Chemistry and Biochemistry Dept., University of California, San Diego, reported a new stereoselective synthesis of borrelidin. "Crucial to the synthesis was the installation of the cyano group after construction of the 18-membered macrocyclic ring of this natural product. – said Prof. Theodorakis contacted by LOC – This reaction proceeded with excellent regioselectivity by implementing a novel Mo(0)-catalyzed hydrostannation of an enynone precursor. The latter compound could be easily formed by connection of two main fragments *via* a sequence of reactions that includes alkyne addition (formation of C11-C12 bond), Mukaiyama aldol reaction (formation of C2-C3 bond) and Yamaguchi macrolactonization (formation of macrocyclic scaffold), thus adding to the convergence of the overall strategy. Moreover, the late installation of the cyano unit in a fully functionalized macrocyclic motif paves

the way for the preparation of synthetic analogs of this natural product thereby leading to its structure-activity evaluation."