CHIMIA 2001, 55, No. 10

Chimia 55 (2001) 818–820

ISSN 0009–4293

Discovery and Study of New Reaction Chemistry; Applications in Complex Molecule Assembly

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Abstract: The catalytic, *in situ* generation of metal alkynilides under conditions compatible with electrophilic reaction partners provides fresh avenues for the development of new efficient asymmetric processes leading to C–C bond-formation. We have documented that terminal acetylenes undergo stereoselective additions to aldehydes in the presence of catalytic Zn(II), amine, and (+)- or (–)-N-methyl ephedrine to give adducts in useful yields and excellent enantio-induction. The application of this method to natural products syntheses, as exemplified in the epothilone total synthesis, underscores the versatility of the process.

Keywords: Acetylene · Asymmetric catalysis · Natural products synthesis · Zinc

The quest for therapeutics possessing highly specific biological activity of importance to human and animal health demands the identification and synthesis of novel, tailored-made molecules [1]. Regardless of the source of the lead structure, subsequent medicinal chemistry investigations and ultimately the manufacturing process demands that available synthetic methodology facilitate ready access to such entities. In the same vein, advances in materials research benefit not only from novel preparative synthetic methods but also rely on the availability of small-molecule monomers which impact the macroscopic properties of the desired material. Thus, the identification of novel building blocks along with the development of new reaction chemistry that permit ready access is critical to advances in biomedical and materials sciences. In this respect, for example, the discovery of efficient homogeneous, low-molecular weight, well-defined catalysts for olefin metathesis ideally illustrates this point [2]. This reaction has not only found important application in polymer synthesis but also in providing access to non-naturally occurring analogs of natural products that serve as useful probes for understanding cell processes [3].

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The discovery and study of catalytic, enantioselective processes continue to be an active area of research world-wide because not only do such process lead to high-value-added end-products, but also because of the need to advance reaction chemistry to the level where it is increasingly environmentally friendly and economically sound. In this regard, issues of practicality and efficiency are at the core of modern catalytic asymmetric synthesis. In addition to socio-economic pressures driving the field, the identification and development of such methods constitute a challenging chemical problem which ultimately focuses on the most basic of issues: understanding the interrelationship of structure and reactivity. The current state of the field can at best be described as rudimentary; this is best appreciated when one considers how few of the various catalytic enantioselective systems are understood in great detail and how rare are preparatively useful catalytic processes [4]. Indeed, the limitations of the current level of development in this area are evident when one considers the myriad of drawbacks associated with even the best of processes, when measured against the desired goals of atom economy, efficiency, and practicality (simplicity of execution and of starting materials) [5]. These goals can serve to define the boundary conditions in the identification and development of novel reaction chemistry, providing not only difficult fundamental problems in chemistry but also ultimately beneficial to society. When one considers the basic building blocks of organic chemistry, such as CO_2, CO, N_2, ^-CN, NH_3, O_2 along with others, such as alkynes, ketones, aldehydes, esters, acids, it is clear that much more remains to be done in the area of reaction discovery, innovation, and design.

One of the key areas of investigation in our group is the discovery and study of novel processes for C–C bond formation [6]. In particular we focus on enantioselective reactions involving nucleophilic additions to C=O and C=N electrophiles. Such processes not only lead to the production of optically active compounds, but also can lead to rapid increase in molecular complexity, as a consequence of the fact that they can involve fragment coupling. Within this general theme, two interrelated areas, namely, reaction methodology and natural products synthesis constitute the key interests of our research program [7]. In the former, we carry out investigations in both catalytic methods as well as those involving diastereoselective chemistry. Our allied efforts in the development of efficient routes to biologically active natural products is important in two key respects: not only can efficient synthetic routes provide access to quantities of agents of importance to human medicine that may otherwise be difficult to obtain, but also, with respect to basic science, such target-oriented investigations are unfailing in pointing out deficiencies in the state of the art of organic synthesis. The limita-

tions of synthetic methods rear their ugly head every time a route requires extensive protecting group manipulations, or functional group adjustment. Therefore, studies in natural products synthesis fuel the development and study of reaction methodology. Although there have been impressive advances in this area, the day when complex structures can be routinely accessed in useful quantities for important biological studies is still far off. This still remains a fertile area for study, discovery, and innovation. The discussion of two projects in the group serve to illustrate this aspect of our program.

We have recently discovered the *in situ* activation of terminal acetylenes in the presence of Zn(II) and amines to give rise to Zn-alkynylides under remarkably mild conditions (23 °C, ambient atmosphere, various solvents, and solvent-free) [8]. A series of preliminary mechanistic and spectroscopic studies aimed at elucidating the details of this novel process have revealed important details concerning this unprecedented process. In this respect, infra-red spectroscopy has proven very powerful in demonstrating that the combination of amine and Zn(II) leads to rapid deprotonation/metallation of the terminal acetylene with $t_{1/2}$ = 30–60 sec (Scheme 1). In parallel to the spectroscopic studies, we have been interested in utilizing the new metallation process for the development of preparatively useful reaction processes.

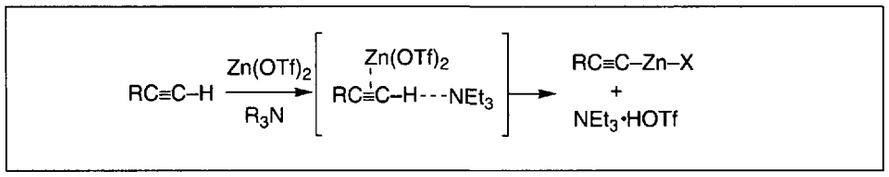
The Zn-alkynilides generated *in situ* participate in processes such as aldehyde and nitrone addition reactions (Scheme 2). For the addition to aldehydes, the presence of an optically active amino alcohol, such as (+)- or (–)-N-methyl ephedrine, leads to propargylic alcohols in high yield and up to 99% ee. The versatility of the process is such that a broad range of both acetylenes and aldehydes participate in the addition reaction (Chart 1).

The reaction belongs to a rare class of processes displaying atom economy, with the starting materials comprising the desired end-products. Further study of this reaction has revealed the addition reaction may be conducted in the absence of solvent and under conditions in which the rigorous exclusion of moisture and oxygen is not necessary. This stands in stark contrast to the more typical carbanionic addition reactions to aldehydes, which in general prescribe rigorous control of the reaction conditions. Using this method not only are a wide range of optically active propargylic alcohols accessible, but also, for the first time, dialkynyl methanols can be synthesized in optically active form. These not only can serve as useful building blocks for synthesis, but also may have important application in materials science (Scheme 3).

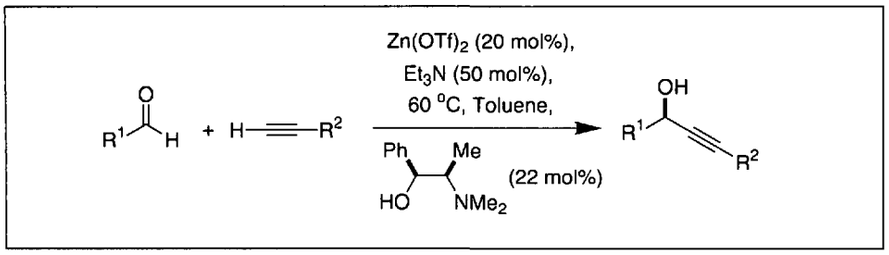
Part of our studies in developing this and related methods involves the examination of the reactions in the context of complex molecule synthesis. Such investigations provide an opportunity to examine the method in the presence of multiple functionality within a complex structure. In this respect, we have developed an efficient synthesis route to epothilones A and B (Chart 2). These polyketide-derived natural products have been the subject of intense research in the pharmaceutical industry as well as academic laboratories as a consequence of their anti-cancer properties [9].

The conversion of **2** to **3** illustrates the use of 3-methyl-butyn-3-ol, or the acetylene-acetone adduct (Scheme 4), in the addition reactions to aldehydes as a synthetic equivalent of C_2H_2. This acetylene is commercially available as an inexpensive commodity chemical and is convenient to use, obviating some of the difficulties in using acetylene in the typical laboratory. The adduct can be readily deprotected in the presence of catalytic K_2CO_3 and 18-C-6, affording a propargylic alcohol, which following reduction with $LiAlH_4$, provides **4**, a key intermediate for the epothilone synthesis route.

We have discussed an area of investigation at the core of our research program in the development of asymmetric C=O and C=N addition reactions. The novel reaction chemistry of acetylenes and Zn(II) allows for the *in situ* generation of the corresponding carbanion under mild conditions. The addition reactions to aldehydes in the presence of N-methyl ephedrine were shown to be highly enantioselective and efficient. More importantly, exploratory work has revealed that



Scheme 1



Scheme 2

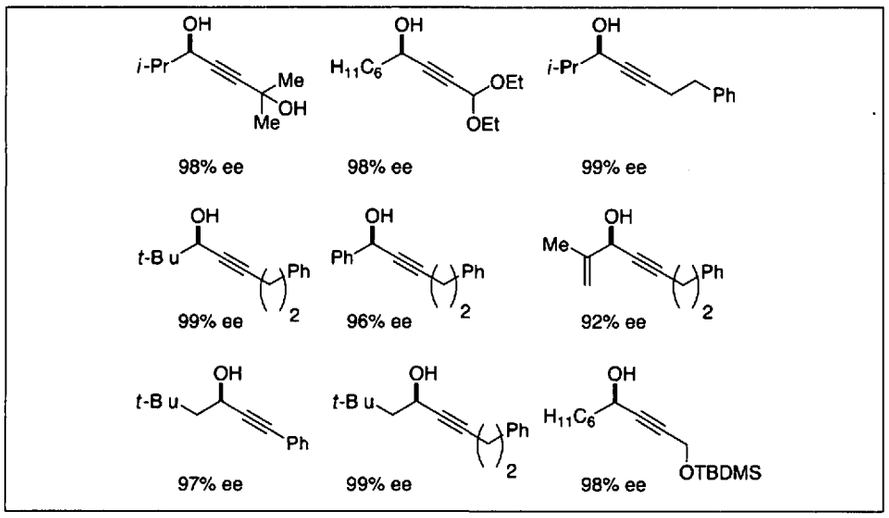
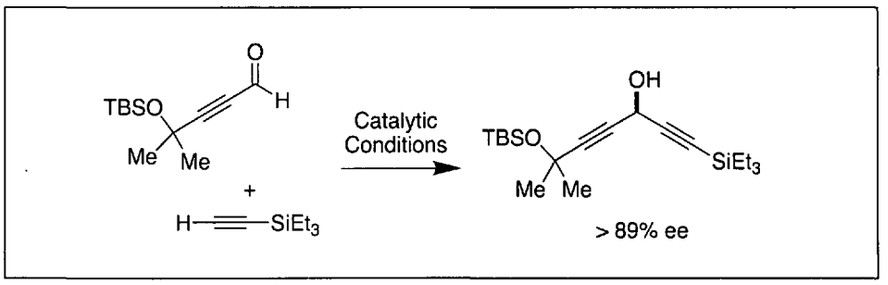


Chart 1

the carbanionic Zn-acetylide generated *in situ* possesses unusual, remarkable tolerance to moisture and oxygen, providing a practical and efficient method for the preparation of optically active propargylic alcohols. The application of this method in the context of complex molecule synthesis illustrates its effectiveness at providing access to key building blocks in the presence of multiple functionality. Work in our group continues to elucidate details of this process that will be helpful in developing and furthering this methodology. Moreover, investigations to identify other novel C–C bond-forming reactions are ongoing.

Received: June 26, 2001



Scheme 3

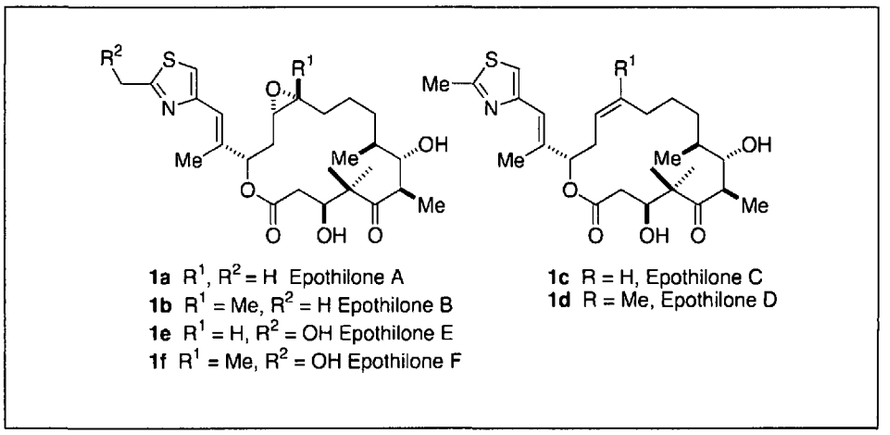
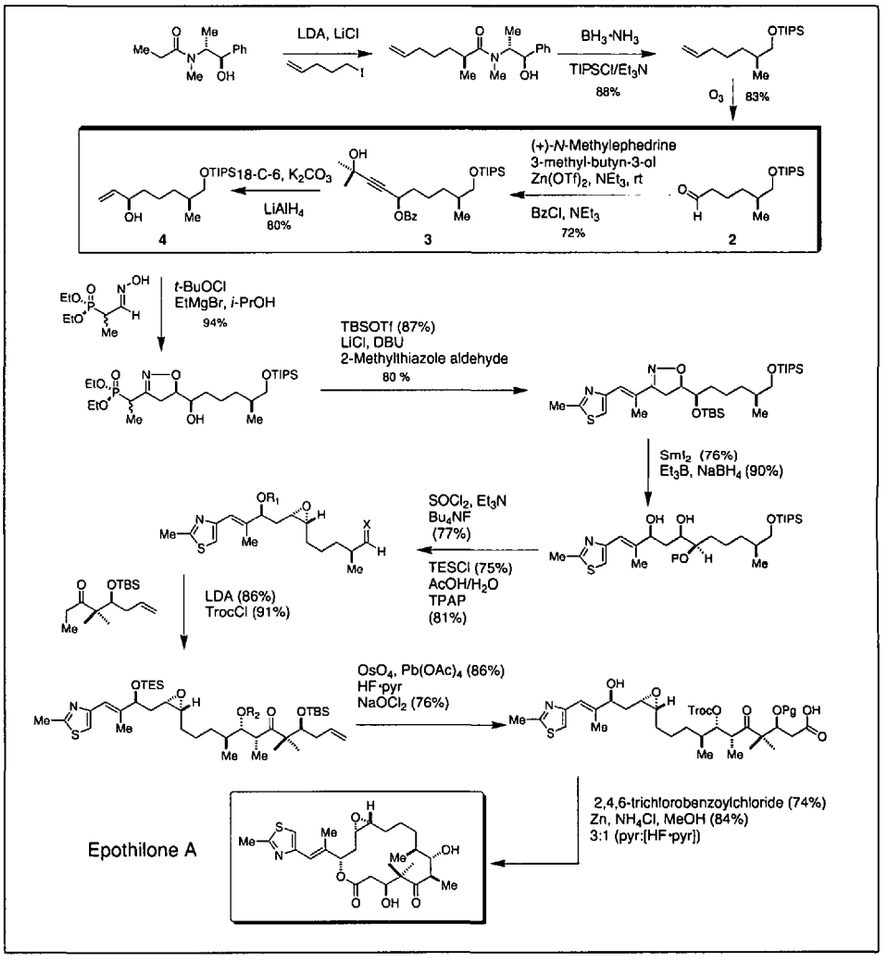


Chart 2



Scheme 4

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