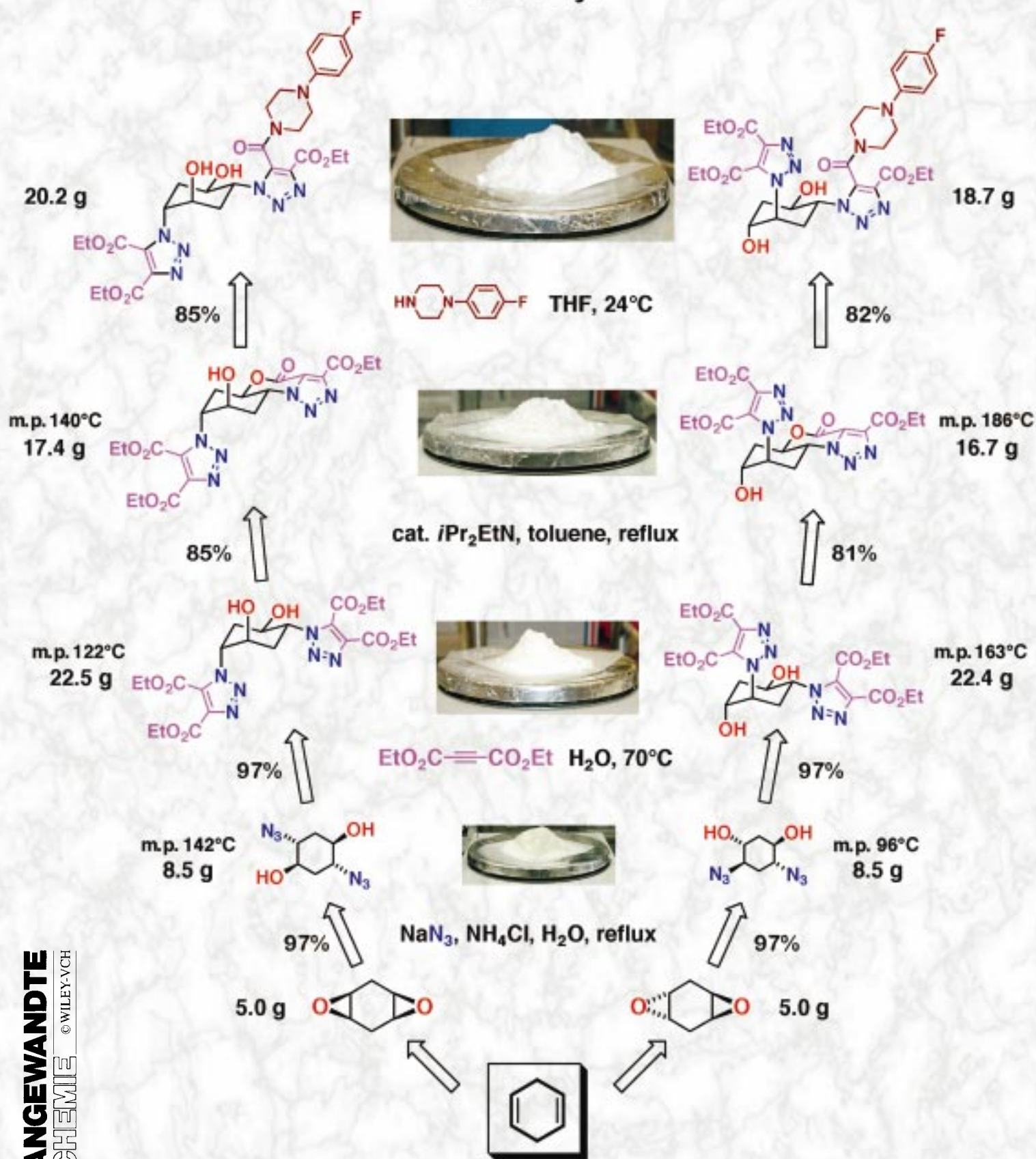# "CLICK" CHEMISTRY

Olefins, spring-loaded electrophiles, and heteroatom connections are key elements in a fast, modular, process-driven approach to molecular discovery.

20.2 g

m.p. 140°C
17.4 g

85%

m.p. 122°C
22.5 g

97%

m.p. 142°C
8.5 g

97%

5.0 g

HN—N—◯—F   THF, 24°C

cat. iPr_2EtN, toluene, reflux

EtO_2C—≡—CO_2Et H_2O, 70°C

NaN_3, NH_4Cl, H_2O, reflux

85%

81%

97%

97%

18.7 g

82%

m.p. 186°C
16.7 g

m.p. 163°C
22.4 g

m.p. 96°C
8.5 g

5.0 g

Click Chemistry: Diverse Chemical Function from a Few Good Reactions

Hartmuth C. Kolb, M. G. Finn, and K. Barry Sharpless*

Dedicated to Professor Daniel S. Kemp

Examination of nature's favorite molecules reveals a striking preference for making carbon–heteroatom bonds over carbon–carbon bonds—surely no surprise given that carbon dioxide is nature's starting material and that most reactions are performed in water. Nucleic acids, proteins, and polysaccharides are condensation polymers of small subunits stitched together by carbon–heteroatom bonds. Even the 35 or so building blocks from which these crucial molecules are made each contain, at most, six contiguous C–C bonds, except for the three aromatic amino acids. Taking our cue from nature's approach, we address here the development of a set of powerful, highly reliable, and selective reactions for the rapid synthesis of useful new compounds and combinatorial libraries through heteroatom links (C–X–C), an approach we call "click chemistry". Click chemistry is at once defined, enabled, and constrained by a handful of nearly perfect "spring-loaded" reactions. The stringent criteria for a process to earn click chemistry status are described along with examples of the molecular frameworks that are easily made using this spartan, but powerful, synthetic strategy.

Keywords: combinatorial chemistry · drug research · synthesis design · water chemistry

1. Introduction:
Beyond the Paradigm of Carbonyl Chemistry

Life on Earth requires the construction of carbon–carbon bonds in an aqueous environment. Carbonyl (aldol) chemistry is nature's primary engine of C–C bond formation. Not only do the requisite carbon electrophiles (carbonyls) and nucleophiles coexist in water, but water provides the perfect environment for proton shuttling among reactants, which is required for reversible carbonyl chemistry.

With CO_2 as the carbon source and a few good carbonyl chemistry based reaction themes, nature achieves astonishing structural and functional diversity. Carbonyl chemistry is used to make a modest collection of approximately 35 simple building blocks, which are then assembled into biopolymers. The enzymatic polymers serve, in concert with increments of energy provided by adenosine triphosphate, as selective catalysts which prevent nature's carbonyl chemistry based syntheses from collapsing into chaos. Since many biosynthetic pathways require a unique enzyme for each step, the enzyme-control strategy required a heavy investment of time and resources for catalyst development. With a few billion years and a planet at her disposal, nature has had both time and resources to spare, but we, as chemists on a human timescale, do not.

Nevertheless, carbonyl-based reactions have always been profoundly appealing to students and practitioners of organic chemistry. It is our contention that organic synthesis conducted, as it has been, in imitation of nature's carbonyl chemistry is ill-suited for the rapid discovery of new molecules with desired properties.

Many transformations that form "new" carbon–carbon bonds are endowed with only a modest thermodynamic driving force. In particular, equilibrium "aldol" reactions are often energetically favorable by less than 3 kcal mol^{-1}.[1] For these processes to reach completion in the laboratory, an additional "push" must be provided, often by application of Le Chatelier's principle (for example, azeotropic removal of water), by coupling the desired process to an exothermic co-reaction (for example, a strong "base" + a strong "acid"), or by virtue of favorable entropic considerations (such as intramolecular ring closure) without enthalpic penalties (such as formation of strained rings). Thus, due in effect to the loss of one "equivalent" of ester, resonance stabilization, the first

[*] Prof. K. B. Sharpless, Prof. M. G. Finn
Department of Chemistry
The Scripps Research Institute
10550 North Torrey Pines Road
La Jolla, CA 92037 (USA)
Fax: (+1)858-784-7562
E-mail: sharpless@scripps.edu

Dr. H. C. Kolb
Vice President of Chemistry
Coelacanth Corporation
East Windsor, NJ 08520 (USA)

step of the intermolecular Claisen condensation (for example, two molecules of ethyl acetate →ethyl acetoacetate+ethanol), is endothermic by approximately 11 kcal mol^{-1}, but the next step—deprotonation of the β-ketoester to its enolate—is highly exothermic and drives the process to completion when a stoichiometric amount of the alkoxide base is provided. Approximately 30 years ago the development of *kinetically controlled* enolate chemistry, enabled by even stronger bases like lithium diisopropylamide, provided the ultimate form of this type of reaction control. Natural products of bewildering complexity are synthesized almost routinely in this manner by the elite practitioners of the art, so it is obviously a powerful strategy, and the best work in this area is fascinating to study as a rich source of new insights into factors which affect chemical reactivity. However, as discussed below, we believe that this approach ultimately pulls organic synthesis in troubling directions, the most insidious problem being the complexity engendered by the need for global protection and deprotection of protic functional groups.

"The most fundamental and lasting objective of synthesis is not production of new compounds, but production of properties."

George S. Hammond, Norris Award Lecture, 1968

If useful properties are our goal—for example, better pharmaceuticals—then the use of complicated synthetic strategies is justified only if they provide the best way to achieve those properties. The bioactive natural products that have most intrigued synthetic organic chemists have frameworks which are difficult to construct largely because there are too many contiguous carbon–carbon bonds. However, these are not the only kinds of molecules that can have useful biological effects. The long and admirable history of natural products synthesis, culminating as it has in the protection-laden schemes of kinetic carbonyl chemistry, perhaps blinds us to the possibility of developing synthetic strategies that enable much more rapid discovery and production of molecules with a desired profile of properties.

K. Barry Sharpless and his co-workers have discovered and developed many widely used catalytic oxidation processes, including the first general methods for stereoselective oxidation—the Sharpless reactions for asymmetric epoxidation, dihydroxylation, and aminohydroxylation of olefins. His mentors at Dartmouth College (BA in 1963), Stanford University (PhD in 1968 and postdoctoral research), and Harvard University (further post-doctoral research) were Prof. T. A. Spencer, Prof. E. E. van Tamelen, Prof. J. P. Collman, and Prof. K. Bloch, respectively. Before 1990, when he became W. M. Keck Professor of Chemistry at The Scripps Research Institute, Prof. Sharpless was a member of faculty at the Massachusetts Institute of Technology (1970–77, 1980–90) and Stanford University (1977–80). Prof. Sharpless's honors include the Chemical Sciences Award of the National Academy of Sciences (of which he is a member), the Roger Adams and Arthur C. Cope Awards from the American Chemical Society, the Tetrahedron Award, the King Faisal Prize, the Prelog Medal, the Wolf Prize, and honorary doctorates from five American and European universities. The Sharpless research group continues to search for new homogeneous oxidation catalysts and for transition metal catalyzed asymmetric processes.*

K. B. Sharpless   M. G. Finn   H. C. Kolb

M. G. Finn received his PhD degree from the Massachusetts Institute of Technology, working with Prof. K. B. Sharpless. This was followed by an NIH postdoctoral fellowship with Prof. J. P. Collman at Stanford University. He joined the faculty of the University of Virginia in 1988, and moved to his present position on the faculty of the Department of Chemistry and The Skaggs Institute for Chemical Biology at The Scripps Research Institute in 1998. His group has studied the reactivity of Fischer carbene complexes, metal-substituted phosphorus ylides, and a variety of transition metal catalyzed processes. His current interests include methods for combinatorial catalyst discovery and the use of viruses as molecular building blocks.

Hartmuth Kolb received his PhD in synthetic organic chemistry under the supervision of Prof. S. V. Ley at Imperial College in London. After two years of postdoctoral study with Prof. K. B. Sharpless at The Scripps Research Institute, he joined the Central Research Laboratories of Ciba–Geigy in Basel. Four years later, he moved to Princeton, New Jersey, to join the Coelacanth Corporation, a high-performance chemistry company founded by K. B. Sharpless and A. Bader. Currently, he is Vice President of Chemistry at the Coelacanth Corporation. His research interests include natural product and carbohydrate synthesis, investigation of reaction mechanisms, molecular modeling, medicinal chemistry, process chemistry, and combinatorial chemistry.

2006

Angew. Chem. Int. Ed. **2001**, 40, 2004–2021

2. A "Process Chemistry" Point of View

The molecules produced by living systems have always fascinated and inspired synthetic organic chemists. As our skills and tools have advanced, the compounds chosen for synthesis have become ever more challenging. So it is no surprise that today's favorite targets are found among the most diabolically complex natural substances ever discovered—the various *secondary metabolites* produced by plants and microorganisms for self-defense. No expense or effort is spared to synthesize even minute quantities of these extraordinary molecules.[2, 3]

The pharmaceutical industry, a direct scion of natural products chemistry,[4] has not been put off by difficult syntheses and many compounds being explored today as drug candidates represent substantial synthetic challenges.[5] While it sharpens the skill and fraternal esteem of the research team, implicit in the decision to pursue a complex drug target is the acceptance of enormous constraints on the scope of the structure space to be explored. When natural products are the models, it usually takes so long to synthesize analogues in a given series that even the most ambitious exploratory efforts, viewed objectively, are often superficial. The process of probing structure–activity relationships (SAR) in these situations has a perverse tendency to discover the "best" candidates in difficult synthetic territory, near the outer limits of "accessibility." Difficult syntheses also tend to arise when trying to reach patentable structural territory after original discoveries have been made by a competitor.

The time required for SAR probing and then synthesis of enough of the better compounds for pharmacokinetic and toxicity profiling is staggering, and goes a long way toward explaining why this phase of pharmaceutical research takes so long. And yet, buoyed by the eventual success in obtaining complex target structures, discovery chemists and top executives alike display little concern for issues of synthetic accessibility. Ignored is the fact that any lead or development series that has supply problems risks inadequate SAR conclusions and development decisions. The story of the carbapenem antibiotic thienamycin[6–8] is illustrative: it required *six years* of superb effort by several research groups in both industry and academia to develop the final therapeutic agent (meropenem,[9] a derivative of thienamycin) after the initial synthesis of thienamycin was published.[10a] The AIDS protease inhibitor Crixivan (indinavir) provides a more recent example—a very difficult synthesis at nearly commodity-chemical scale.[10b]

Only at the end are issues of process development considered, and synthesis on production scale is often expensive. Nevertheless, the prospect of a blockbuster drug is such a powerful motivator for a synthesis team that the job nearly always gets done. The crucial point is that the cost which complex synthesis adds to the final drug, while substantial, is insignificant compared to all the "hidden" costs imposed on the speed and quality of the discovery/development phase by this same complex style of synthesis. In other words, *the way organic synthesis is done has pervasive effects on the entire process of drug discovery, development, and*

Thienamycin

Meropenem

Indinavir
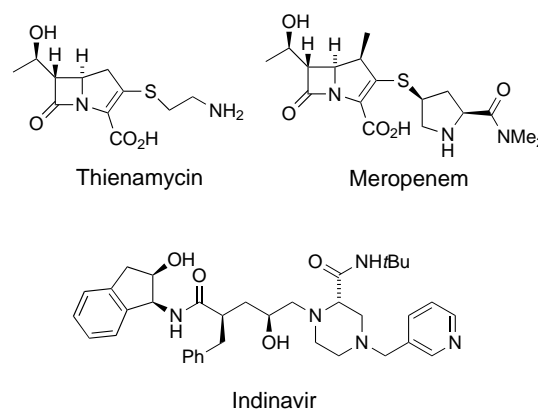
manufacture. If a more modular, faster style of synthesis were to prove effective, lower manufacturing costs should be the least of its benefits. Lead structures should not be synthetically "precious", and one should be able to jump easily from one series to another. As it is now, most discovery endeavors suffer from being too invested in *structure*, when *function* is what is sought.

Consider how nature synthesizes her most important molecules, the *primary metabolites*. While the aforementioned secondary metabolites have extensive networks of contiguous carbon–carbon bonds, and have claimed the lion's share of synthetic organic chemists' attention, it is reversible condensation processes involving carbon–heteroatom connections that are used to assemble polynucleotides, polypeptides, and polysaccharides—the three families of macromolecules that are central to life processes. By embracing the strategy of making large oligomers from small building blocks,

Polynucleotides

Polypeptides

Polysaccharides
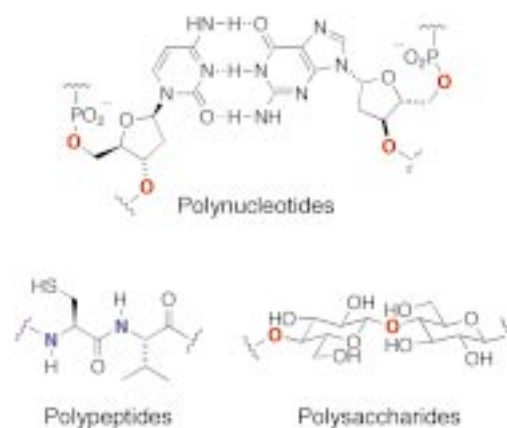
nature is also a consummate combinatorial chemist[11] and achieves astonishing diversity from less than 40 monomers. These building blocks contain at most six contiguous C−C bonds, with the exception of the three aromatic amino acids. Thus, nature is a promiscuous creator of carbon–heteroatom connections, choosing this method to encode and express information.

Nature's ability to create and control biomolecular diversity is largely dependent on the exquisitely selective catalysts she deploys. Our devices for managing reactivity and selectivity are much less sophisticated, particularly with respect to C−C

bond formation. Therefore, the chemist who plans a synthesis that requires the construction of C−C bonds that are not present or latent (for example, CH−CX+base →C=C) in the available starting materials is asking for trouble, particularly if such a synthesis must be reliable for a number of substrates (as for combinatorial searches or SAR studies) or applicable to practical, large-scale production. Problems are less likely if one only needs to unite, functionalize, and/or reorganize starting materials and intermediates in ways which do not require de novo C−C bond construction. If such "new" C−C bonds are required, it is best to make them *intra*molecularly,[12] but it is better still to leave the really tough C−C bond synthesis to nature.[13]

There is, however, still plenty of room for discovery: Guida and co-workers have estimated the pool of "reasonable" drug candidates (≤ 30 non-hydrogen atoms; ≤ 500 daltons; consisting of only H, C, N, O, P, S, F, Cl, and Br; likely to be stable at ambient temperature in the presence of water and oxygen) at between 10^{62} and 10^{63} discrete molecules.[14] With this kind of structure space available,[15] we contend that it makes little sense to search in hard-to-reach places for a desired function. Instead, we present here synthetic methods for drug discovery that adhere to one rule: *all searches must be restricted to molecules that are easy to make*. We hope to convince the reader that a wide diversity of interesting molecules *can* be easily made, and that the chances for achieving desirable biological activity are at least as good with such compounds as with the traditional target structures now favored by medicinal chemists.

2.1. "Click Chemistry"

Following nature's lead, we endeavor to generate substances by joining small units together with heteroatom links (C−X−C). The goal is to develop an expanding set of powerful, selective, and modular "blocks" that work reliably in both small- and large-scale applications. We have termed the foundation of this approach "click chemistry," and have defined a set of stringent criteria that a process must meet to be useful in this context. The reaction must be *modular*, *wide in scope*, give *very high yields*, generate only *inoffensive byproducts* that can be removed by nonchromatographic methods, and be *stereospecific* (but not necessarily enantioselective). The required process characteristics include *simple reaction conditions* (ideally, the process should be insensitive to oxygen and water), *readily available starting materials and reagents*, the use of *no solvent or a solvent that is benign* (such as water) *or easily removed*, and *simple product isolation*. Purification—if required—must be by nonchromatographic methods, such as crystallization or distillation, and the product must be stable under physiological conditions.

It is important to recognize that click reactions achieve their required characteristics by having a high thermodynamic driving force, usually greater than 20 kcal mol^{-1}. Such processes proceed rapidly to completion and also tend to be highly selective for a single product: we think of these reactions as being "spring-loaded" for a single trajectory. Carbon−heteroatom bond forming reactions comprise the

most common examples, including the following classes of chemical transformations:

- cycloadditions of unsaturated species, especially 1,3-dipolar cycloaddition reactions, but also the Diels−Alder family of transformations;
- nucleophilic substitution chemistry, particularly ring-opening reactions of strained heterocyclic electrophiles such as epoxides, aziridines, aziridinium ions, and episulfonium ions;
- carbonyl chemistry of the "non-aldol" type, such as formation of ureas, thioureas, aromatic heterocycles, oxime ethers, hydrazones, and amides; and
- additions to carbon−carbon multiple bonds, especially oxidative cases such as epoxidation, dihydroxylation, aziridination, and sulfenyl halide addition, but also Michael additions of Nu−H reactants.

2.2. Olefin-Based Organic Synthesis

Consider, as a counterpoint to the pharmaceutical industry, the world of petrochemicals and the materials it has spawned (textiles, resins, plastics, etc.). The petrochemist's starting materials are "gifts" prepared by the carbonyl-based syntheses of ancient organisms; in fossil oils are stored the energy of CO_2-based photosynthesis, and, more importantly, countless carbon−carbon bonds. However, natural petroleum, being almost completely saturated, is useless for most organic synthesis needs. The petroleum industry is therefore based upon the manipulation of C−C bond "currency", which entails exchanging C−C σ bonds for new C−C π bonds by "cracking", and creating new C−C π bonds at the expense of C−H bonds by "reforming". The products of these processes are a small number of reactive monomers, which are then assembled, with a battery of selective catalysts, into myriad useful materials. Thus, the manufacture of petrochemical products, based as it is on a modular, and supremely efficient, synthetic strategy, makes the energy expended on "upgrading" saturated hydrocarbons to olefins seem insignificant.

In a general sense, life chemistry and petrochemistry have evolved identical strategies for the synthesis of substances with diverse functions/properties: modular assembly of specially synthesized monomers under the control of selective catalysts. That one depends on *reversible* carbonyl chemistry and the other on *irreversible* olefin chemistry should not obscure the striking similarity at the heart of the two approaches. We are denied the ability to realistically imitate nature's modular carbonyl-based synthesis style (see above), so the modular olefin-based style given to us by the petroleum chemist is the model we choose to follow.[16]

The concept of the C−C bond as a unit of "currency" is central to an appreciation of the value of click chemistry in organic synthesis. Scheme 1 depicts examples of how the currency can be exchanged. The bookkeeping device to keep track of the "total C−C bond count" is often, but not necessarily, connected to demonstrable interconversions. Starting with *n*-octane, the total C−C bond count remains constant at seven regardless of the number of transformations of a saturated C−C bond into a C=C π bond, for example, $C^1-C^2-C^3-H \rightarrow C^1-H+C^2=C^3$. Such a transformation is of

2008

Angew. Chem. Int. Ed. **2001**, *40*, 2004−2021
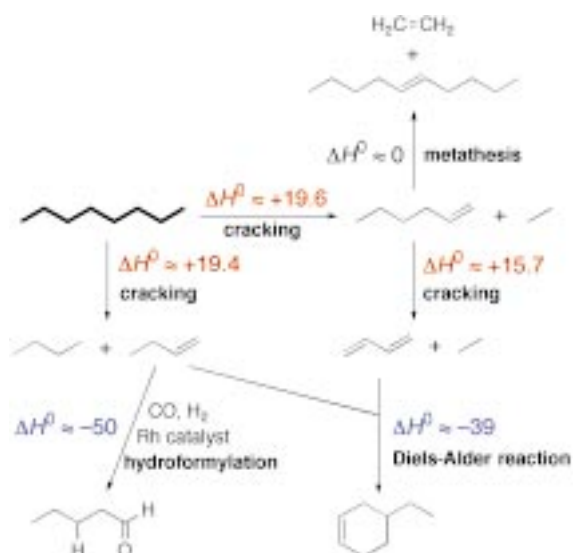
Scheme 1. The C−C bond as a unit of "currency" (ΔH^0 in kcal mol^{-1}; the value given for hydroformylation compares olefin and aldehyde only). No *new* C−C bonds are formed in these processes.

course endothermic, but becomes favorable at high temperatures, thanks to a substantial positive entropy term. The petrochemical industry practices "steam cracking" (a gas-phase process at approximately 850 °C) on enormous scales, to make available a family of inexpensive olefins. The newly created C=C π bonds are highly reactive, having about 22 – 25 kcal mol^{-1} greater free energy content[17] than a C−C σ bond; in effect, the energy expended in "cracking" is partly captured/stored in the C=C linkage. This becomes apparent in processes such as the Diels – Alder reaction and hydroformylation, which gain σ links by reorganizing π C=C links, again without altering the total C−C bond count. Olefin metathesis provides an extraordinarily facile way to redistribute C=C links for further manipulation. (Acetylene links (counting as 3 C−C bonds), with two unstable π bonds, are even better than olefins for driving a host of useful π →σ carbon – carbon bond reorganizations.) Many such processes are highly reliable precisely because no "new" C−C bonds are created; all are nascent in the reactant's π bonds.

Olefins are the most attractive starting materials available to the synthetic chemist, readily accessible in large quantities and in many varieties, especially if one includes the naturally abundant terpenes. The simplest are the handful of C$_1$–C$_8$ blocks shown in Scheme 2. Produced by the petrochemical
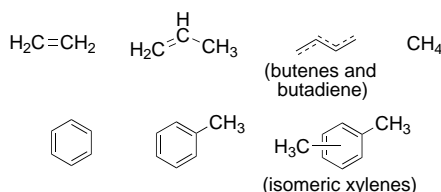

Scheme 2. Small carbon building blocks from petroleum.

industry on a massive scale, they are the ultimate starting materials for 90 % by weight of all useful man-made organic compounds.[18] The Wilke cyclooligomerizations of butadiene

to cyclooctadiene and cyclododecatriene are perfect examples of processes that further expand the core olefin structures available to us at modest cost.[19] The π bonds of butadiene are reorganized effortlessly by the catalyst, to regio- and stereoselectively create sophisticated new carbon skeletons while leaving behind one olefinic linkage per butadiene monomer for the "decoration" steps to follow. Thus, between natural olefin sources (terpenes, fatty acids,[20] etc.) and "reworked" natural hydrocarbons (olefins derived from petroleum) we have been richly endowed by living systems with a diverse olefinic starting material platform. It would be fitting if we could devise short sequences for assembling these "gift" olefins into new substances with beneficial biological functions.

The importance of olefins is dramatically enhanced by their role as progenitors of still higher energy intermediates, such as epoxides, aziridines, episulfonium ions, and aziridinium ions— all nearly perfect for click chemistry transformations (Scheme 3). This sequence of oxidative creation/nucleophilic
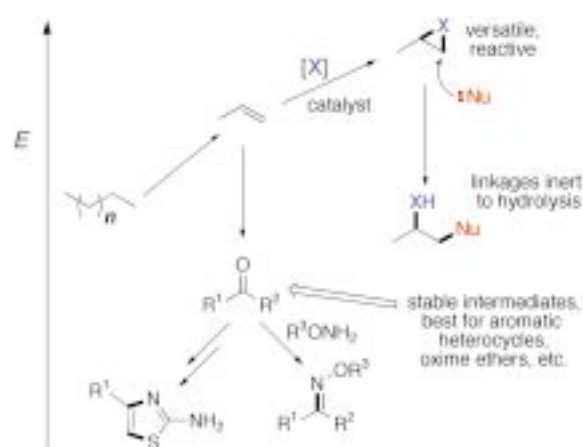
Scheme 3. Examples of the genesis and relative energetics of click chemistry components. New bonds made with click reactions are in bold. Nu = nucleophile.

quenching of reactive electrophiles is what most enables the crucial block ligation steps at the heart of click chemistry. Thus, the chemistry of olefins provides for the creation of diverse scaffolds and the attachment and display of myriad functionality through oxidative addition of heteroatoms to specifically placed olefinic sites.[21] The robust nature of these reactions is predicated on the irreversible progression from systems of high energy to systems of lower energy in a *stepwise* fashion. Each step has a high driving force, the *sine qua non* condition of click chemistry, which enables reliable *intermolecular* connections to be established.

Carbonyl compounds, by contrast, are quite stable thermodynamically relative to olefins and even relative to their hydrocarbon progenitors. Hence, their repertoire of click chemistry transformations is limited. Among the few general and highly reliable reactions starting from aldehydes and ketones are their *imine-forming condensations* to give oximes and hydrazones, and particularly to generate aromatic heterocycles (see below). Also noteworthy, are the few *intermolecular* carbonyl-based new C−C bond forming reactions which approach perfection (Scheme 4): 1) hydroxymethylation and
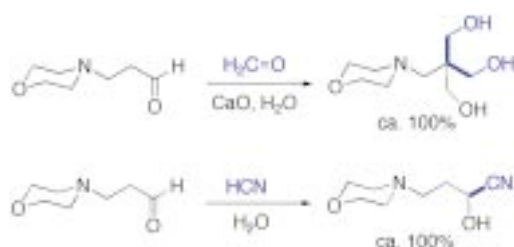
Scheme 4. Strongly driven *intermolecular* C−C bond forming reactions.

aminomethylation reactions using formaldehyde, the least stable carbonyl representative, and 2) HCN additions to carbonyl compounds, driven by the great stability of the resulting cyanohydrin unit (primarily due to the nitrile group's attachment through an sp-hybridized bond, made even stronger by a substantial dipolar contribution). Another excellent carbonyl-based process for intermolecular C−C bond formation is the Michael reaction, an exception which proves the rule, since no new C−C bond is created. Its > 20 kcal mol^{-1} driving force is provided by the C=C bond which is consumed in the H−Nu addition step.

Since click chemistry is intended to provide a foundation for the rapid assembly of new and *pure* molecular entities, stereochemistry is important. The ideal click reactions are based on *stereospecific* processes, but absolute stereochemistry need not be so stringently controlled. In any case, when only one stereogenic element is involved, generation of the racemate for initial biological screening will be preferred. Even when two stereogenic elements are united or created in a ligation step, it should be advantageous to test the racemic mixtures of two or three diastereomers in the first pass at a biological target.[22] With the accelerating development of improved analytical and separation techniques for deconvolution of complicated mixtures,[23] even greater relaxation of stereochemical restrictions on assembly reactions will be feasible in the near future.

Nature achieves highly specific syntheses of complex substances by the uniquely selective action of enzyme catalysts. However, the success of a desired click chemistry sequence requires that virtually all of the control elements and the enabling "energy packets" be present in the reactive components. At first, this plan may sound fanciful—how could any but the most trivial set of reactive components be "self-contained" regarding the instructions and potential energy needed to direct a reaction cascade to a unique synthetic endpoint? Happily, we are finding that this goal is not so difficult, provided one plans carefully and, above all, uses only the handful of "perfect" reactions for the crucial intermolecular block ligation steps.

2.3. Click Chemistry in Water

Over the past two years, we have found that many of the reactions that meet click chemistry standards often proceed better in water than in an organic solvent. This is a natural outcome of one or more of the following five factors.

1) Click reactions often proceed readily in hot water, to give a single product, *even when one or more of the reactants, as well as the product, appear to be insoluble in this medium.* The fact that reactions between organic species in aqueous solution can have higher apparent rate constants than the same processes in organic media has been observed and exploited by a number of laboratories.[24] Among the many explanations offered for such phenomena, we call particular attention to the notion that the free energies of organic molecules are substantially greater when poorly solvated in water, and often impart increased reactivity, which compensates for the low concentration of the participants.[25]

2) Nucleophile additions to epoxide[26] ("homocarbonyl") and aziridine ("homoimine") electrophiles (as well as aziridinium and episulfonium ions) are favored by solvents best able to respond continuously to the demanding range of hydrogen-bonding situations that arise during these processes. In this respect, water is unique, and for the same reasons, it is the perfect milieu for reversible carbonyl chemistry.

3) Two important subsets of olefin and acetylene click reactions are oxidations by electrophilic reagents and cycloaddition reactions. These processes are either concerted or involve polarizable nucleophiles/electrophiles, so that water is not an interfering medium.[27] More generally, it should be appreciated that the use of water offers the greatest leverage for differentiating the reactivities of competing "hard" (nonpolarizable) and "soft" (polarizable) species.

4) A highly favorable reaction of two solutes (say at 0.1 M concentration) is usually much faster than a low driving force side-reaction of one of the solutes with solvent water (55 M).[28] The Schotten–Baumann method for making amides from acyl or sulfonyl halides in water is a well-known example [Eq. (1)].[29]

$$ (1) $$
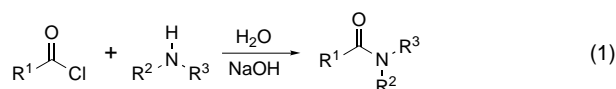
5) Water is a superb heat sink, due to its high heat capacity, and has a convenient boiling temperature; both are useful for large-scale processes.

Water is usually regarded as an ideal solvent in terms of its environmental impact and low cost. A benefit which is little appreciated but has enormous consequences is that most hydroxy O−H and amide N−H groups will not interfere with click reactions performed in water. As a consequence, the installation and removal of protecting groups is avoided—probably the best single reason for adopting this style of synthesis. Indeed, we view many of the best reactions for installing "protecting groups" as good click reactions in their own right (see Section 3.3).

These considerations highlight the fact that, although click reaction components are necessarily highly reactive, their chemoselectivity profiles are quite narrowly defined, that is, "orthogonal" to an unusually broad range of reagents,

solvents, and other functional groups. This attribute allows for reliable and clean sequential transformations of broad scope.[30] For example, opening epoxide or aziridine rings by "HN$_3$" installs a highly reactive "sticky spot" for [3+2] cycloaddition with alkynes, but one that is "invisible" to most other functional groups.

The types of reactions, and especially reaction conditions, that fall into the click chemistry category were more common in the organic literature of 50 to 100 years ago.[31] Few solvents were used then, and heat was the preferred way to speed up reactions. The dearth of available purification techniques meant that processes were chosen for their reliability in giving a single isolable product. Without seeking to collect an exhaustive list of click or click-like reactions,[31] an attempt is made here to illustrate the scope of this approach with a number of representative examples taken both from the literature and from our own work. We focus on nucleophilic openings of the reactive small-ring species readily made by oxidative addition of heteroatoms to olefins, and on concerted cycloadditions and carbonyl/imine condensation reactions to aromatic heterocycles.

2.4. Comments on "Solid-Phase" Synthesis

We are proposing here the use of click reactions in combinatorial style to generate molecules of highly diverse structure and function. Much of the enormous effort in library synthesis currently pursued in academic and industrial laboratories makes use of polymeric supports for the stepwise construction of products.[32] In our view, solid-phase organic synthesis is popular precisely because it allows reactions that fall short of "click" status to be employed as click reactions— that is, in situations where extremely high yields and simple purification procedures are required. These attributes are achieved by using a large excess of the reactants in the mobile phase. While this approach has been very effective for the synthesis of large libraries, the final products tend to be too lipophilic to probe the full range of biological interactions. The hydrophobic character of these collections may, in part, be due to the absence of "bystander" protic functional groups, which tend to be omitted, intentionally or otherwise, to avoid extra protection/deprotection steps.

Most importantly, the solid-phase approach is ill-suited to "process-driven" discovery: it is very expensive and highly wasteful of reagents and solvents; it is difficult to make large amounts of products, and when such large-scale syntheses are attempted, the yield per unit volume is poor; intermediates bound to polymeric supports are difficult to analyze directly by standard spectrometric methods; and another layer of chemical technology— the installation and cleavage of a "linker"—is required. In other words, since solid-phase

combinatorial approaches to the discovery of biologically active compounds ignore most of the issues that constrain practical organic syntheses, the most likely outcome is a trend toward drugs that are even harder to manufacture.

## 2.5. Creation of Modules by Oxidative Addition of Heteroatoms to Olefins

The potential of olefins for generating diversity is unlocked by their oxidative functionalization. Much of our effort for the past three decades has centered on this goal, and a useful set of reliable transformations has emerged from a number of laboratories including our own. The broad scope and high yields of many olefin oxidation processes, and the fact that olefins are the primary organic starting materials, render these reactions the most fundamental enablers of click chemistry. The oxidation step generates highly reactive, yet stable intermediates such as epoxides and aziridines. Both the oxidations to the intermediates *and* their subsequent fusion with nucleophiles are stereospecific, and thus very predictable; Table 1[33–39] shows the processes we use most often. Most of the oxidation steps depend on transition metal catalysis for which efficient enantioselective versions are well established.

A nearly ideal case is our recent discovery of a class of olefins that exhibits unique reactivity in osmium-catalyzed aminohydroxylation and dihydroxylation reactions performed in water or water/organic mixtures. Unlike most olefins, these special substrate classes undergo rapid and nearly quantitative aminohydroxylation, with very low catalyst loading, in the *absence* of cinchona alkaloid ligands, and with only one equivalent of the haloamine salt. Moreover, the reactions can be conducted at molar concentrations in substrate, whereas the standard asymmetric aminohydroxylation process is best performed at ≤ 0.1 molar concentration. Among the substrates that exhibit this type of enhanced reactivity are α,β-unsaturated acids and amides; Scheme 5 gives five examples.[40]

3. Click Chemistry Reaction Types

Below appears a description of the three most useful click reactions presently in use in our laboratory. The best are *pure*

Table 1. Processes used to create oxidized electrophiles or their precursors from olefins.[33–39]

racemic	TsNNaCl,[a] PhNMe$_3^+$Br$_3^-$	cat. MeReO$_3$, H$_2$O$_2$, pyridine	cat. OsO$_4$, cooxidant	RN(Cl)Na, cat. OsO$_4$
asymmetric		*allylic alcohols:* Ti(O*i*Pr)$_4$, Me$_3$COOH, dialkyl tartrate; *unfunctionalized olefins:* [(salen)Mn^{III}],[b] oxidant	cat. OsO$_4$, cooxidant, cinchona alkaloid	RN(Cl)Na, cat. OsO$_4$, cinchona alkaloid

[a] Ts = tosyl = toluene-4-sulfonyl. [b] H$_2$salen = N,N'-bis(salicylidene)ethylenediamine.

Angew. Chem. Int. Ed. **2001**, *40*, 2004 – 2021

2011
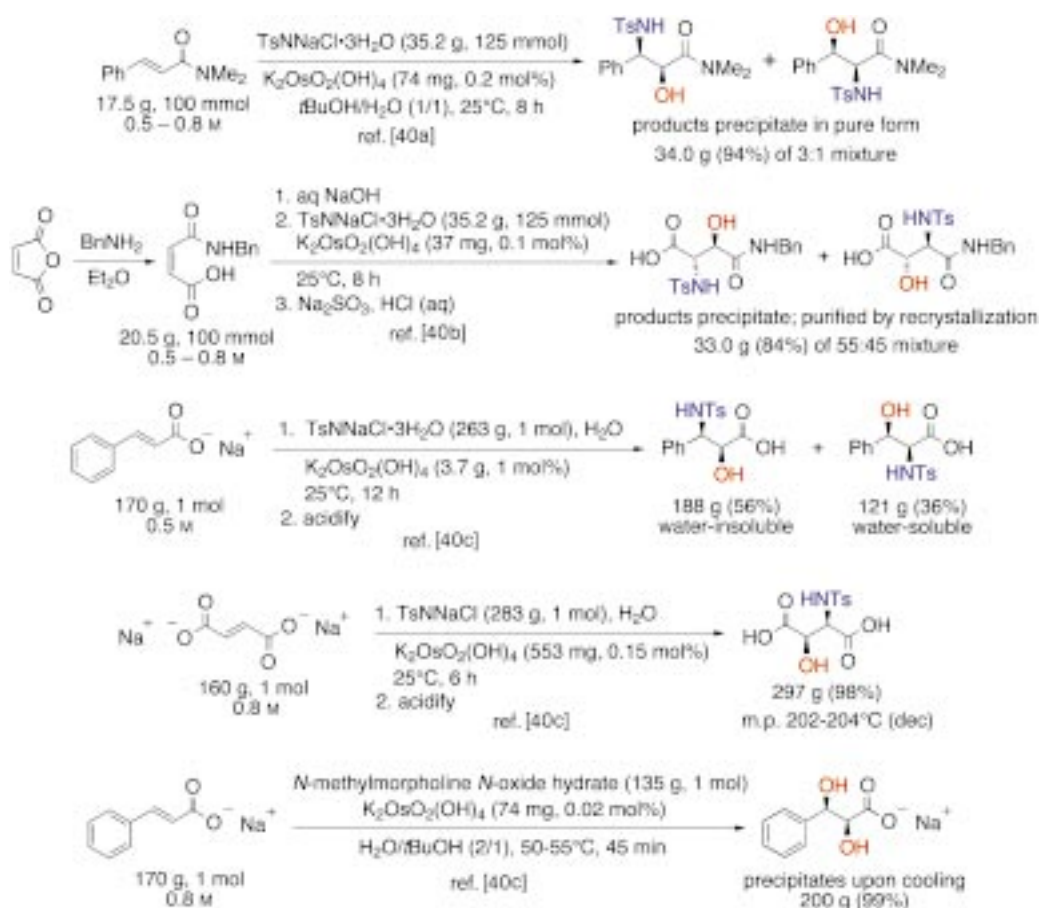
Scheme 5. Examples of unusually efficient osmium-catalyzed aminohydroxylation and dihydroxylation of olefins. Bn = benzyl.

fusion processes, which means that the combined formulae of the reactants equals the formula of the product.[41] They can be divided into two classes: those in which protons must be shuffled about (epoxide ring opening, for example) and those in which no σ-bond connections are severed (cycloaddition reactions, the most useful and reliable being the Huisgen dipolar cycloadditions). The former tend to benefit dramatically from an aqueous environment, while the latter reveal little solvent dependence and are better overall in their adherence to click chemistry ideals. Indeed, the azide + acetylene → triazole version of Huisgen's [2+3] cycloaddition family of processes is about as good as a reaction can get. Nevertheless, it is the "less ideal" epoxide and aziridine opening processes which are the workhorses for installing, often in the penultimate step of a block synthesis, the azide or alkyne moieties.

3.1. Nucleophilic Opening of Spring-Loaded Rings

The four types of primary olefin oxidation products shown in Table 1 are themselves high-energy species or may be readily converted into such intermediates. The S_N2 ring-opening reactions of these molecules—epoxides, aziridines, cyclic sulfates, cyclic sulfamidates, aziridinium ions, and episulfonium ions—are reliable, stereospecific, often highly regioselective, and nearly quantitative—all in all, surpassingly

useful (Scheme 6). We focus here on the chemistry of three-membered ring heterocyclic electrophiles.

The paramount advantage of nucleophilic openings of three-membered rings is that competing elimination processes are stereoelectronically disfavored,[42] which results in high yields and easy product isolation. All of the ring opening reactions shown in Scheme 6 are fusion events, and most can be performed in the absence of solvents[43] or in water, alcohol, or water/alcohol mixtures. In a number of cases, the regioselectivity can be controlled by the choice of solvent, a perfect example being the reaction of *cis*-cyclohexadiene diepoxide 1[44] with amines[45] (Scheme 7). In the absence of solvents, the bis-epoxide reacts with amines to give the amino alcohol 2, in which the entering nucleophiles are 1,3-related. When protic solvents are added, the same reactants give regioisomer 3, with the entering nucleophiles in the 1,4-relationship.[46, 47] In both cases, the diamino diol products are isolated in pure form by direct crystallization from the crude reaction solution, which enables reactions at any scale. Regioselectivity is similarly well-controlled for the ring opening of the *trans* diepoxide 4; the example in Scheme 7 shows the one-pot stitching of three diepoxide units with two equivalents of ammonia to give 5 (85% yield) as a mixture of its three possible racemic diastereomers.

Aziridines, the aza analogues of epoxides, are readily prepared by direct aziridination of olefins,[48] by manipulation

2012

Angew. Chem. Int. Ed. **2001**, *40*, 2004 – 2021
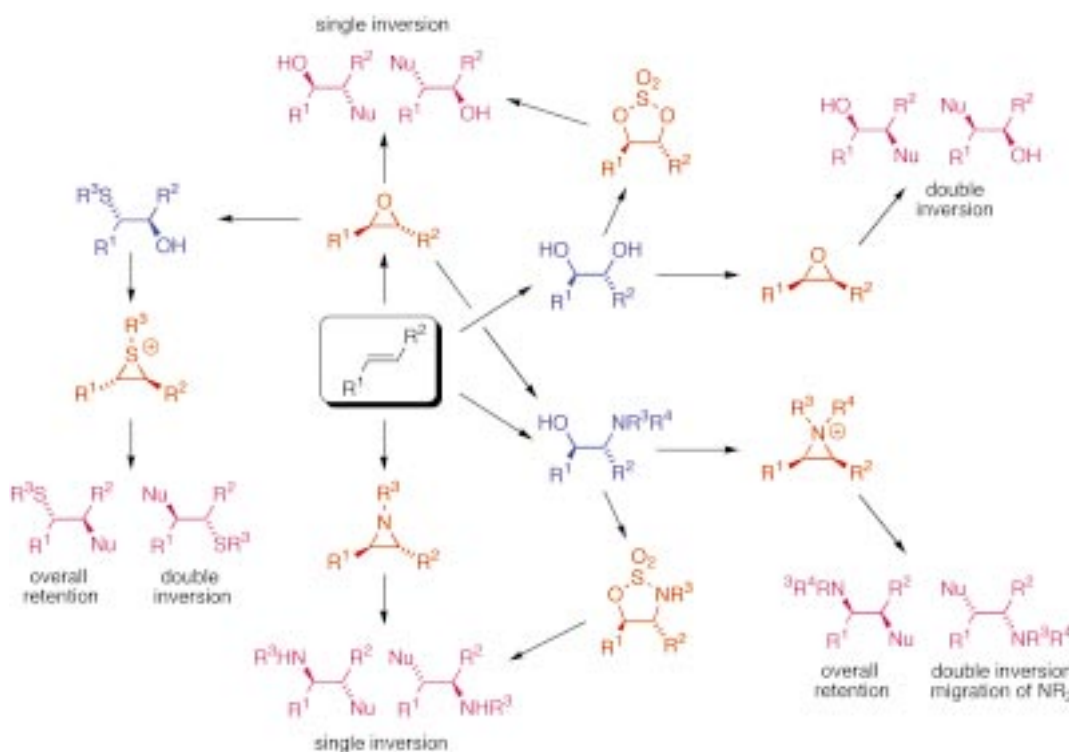
Scheme 6. Generation and opening of spring-loaded cyclic electrophiles (shown in red) from olefins or their oxidation products (blue).
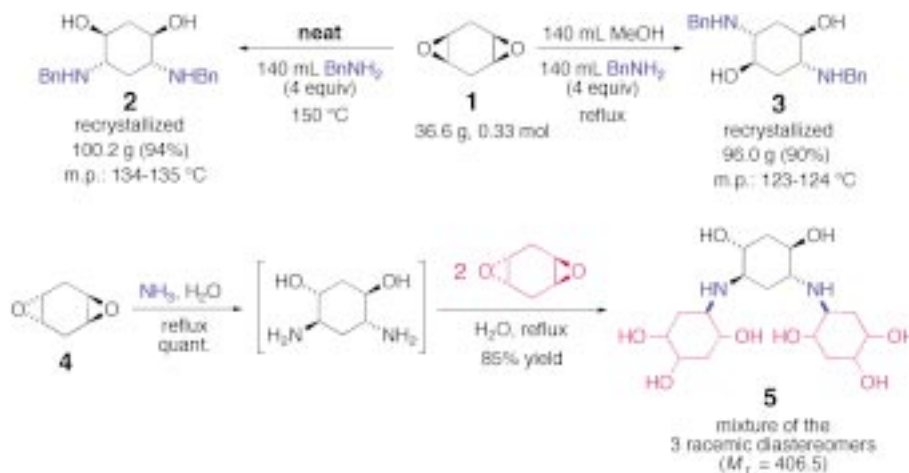
Scheme 7. Amine reactivity with cyclohexadiene diepoxides.

of epoxides[49] or amino alcohols,[50] and by haloazidation of olefins followed by reductive cyclization.[51] Through variation of the substituent on the ring nitrogen, aziridines enable much greater product diversity than epoxides. Their ring-opening reactivities can be modulated over an enormous range,[52] and, most importantly, the nitrogen substituent and the nature of the solvent can be used to control the regioselectivity of ring opening in unsymmetrical cases.[53] The example in Scheme 8 from Stamm and co-workers reveals just how dramatic the effect of the nitrogen substituent can be.[54] Effects deriving from the tendency of sulfonamides to be pyramidal at nitrogen and amides to be planar cause N-sulfonyl aziridines usually to furnish the regioisomer derived from attack of the nucleophile at the sterically least hindered center, while N-acyl aziridines favor the opposite regioisomer.[53] Thus,

aziridines have even more potential than epoxides from the standpoint of click chemistry applications.[55]

While N−H and N−alkyl aziridines are perfectly stable under basic conditions, we and others have found that they can be readily opened, particularly by heteroatom nucleophiles, under buffered conditions in various solvents including water.[56, 57] The examples in Scheme 9 illustrate the practicality of aziridine-based click chemistry.[58a] A solvent is often not required,[58b] so that the ring-opened compounds **7** and **8** are obtained in pure form by neat fusion of **6** with the appropriate secondary amine at ap-
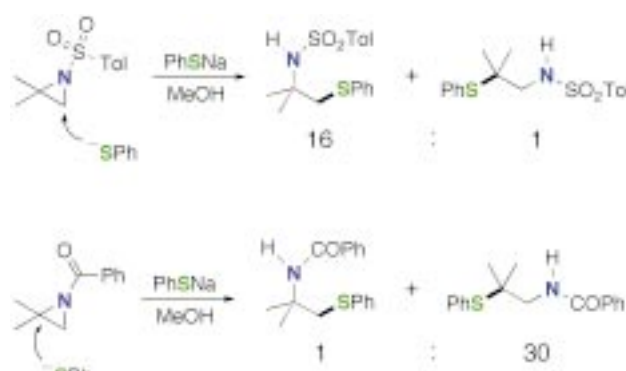
Scheme 8. Influence of the nitrogen substituent (sulfonyl, acyl) on the regioselectivity of aziridine opening.[54] Tol = tolyl.

Angew. Chem. Int. Ed. **2001**, *40*, 2004–2021

2013
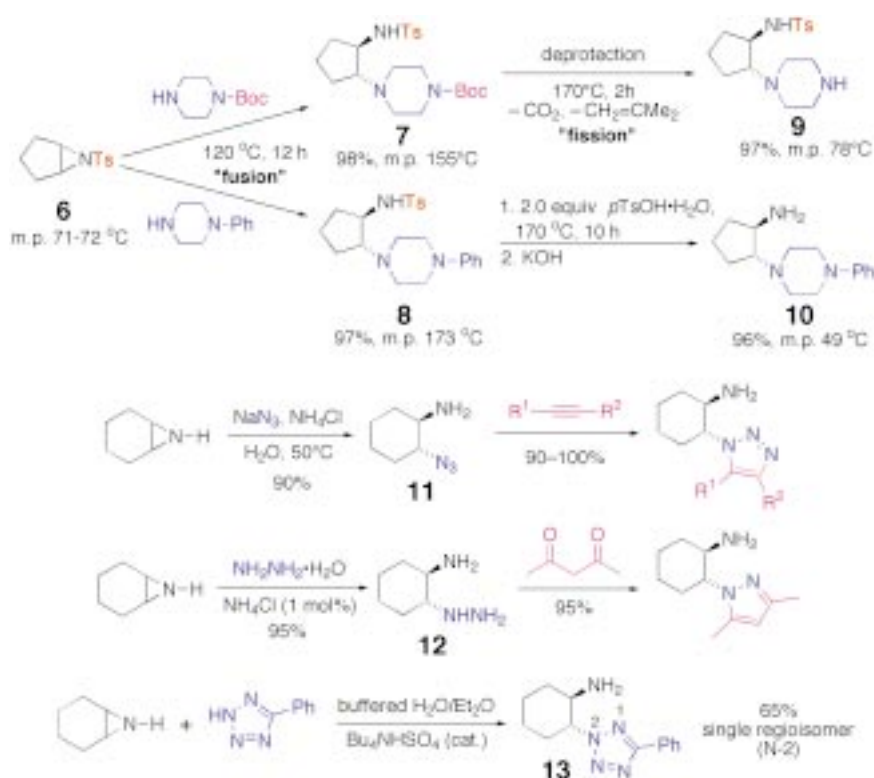
Scheme 9. Use of activated and nonactivated aziridines as building blocks. Boc = *tert*-butoxycarbonyl.

hydrazine (to give **12** at 25 °C). The resulting intermediates are highly useful; their cycloadditions and condensations with alkynes and β-diketones, respectively, are reliable click reactions in their own right (see Section 3.2). Water is often the solvent of choice, as illustrated by the opening of a simple aziridine with 5-phenyltetrazole to give heterocycle **13**. Such a modular approach allows for the formation of a large variety of useful organic intermediates.

Highly activated aziridinium systems are easily generated in situ in the course of neighboring group assisted nucleophilic substitution starting from amino alcohols,[59] or β-halo amines[60] and related compounds[61] (Scheme 6). The reactions of the analogous episulfonium systems[62] are even more facile.[63] All these substitutions are stereospecific and proceed with double inversion, and hence net retention of configuration in cases where the nucleophilic attack on the aziridinium or episulfonium ion occurs at the center bearing the leaving group, or with inversion of both centers in cases where the amino or thioether group undergoes a 1,2-shift. The broad scope of these reactions

proximately 120 °C. Neat thermal fission then removes the *N*-Boc group in **7** to provide the secondary amine **9**, while the primary amine in **10** is unmasked in excellent yield by heating compound **8** at 170 °C with two equivalents of *p*-TsOH · H₂O, again in the absence of solvent. The high temperatures of these solvent-free processes are presented to highlight the reliability of the bond-forming events under any conditions. Each of these reactions can also be done in standard solvents at ≤ 70 °C.

The opening of even unactivated aziridines proceeds readily in water with buffered azide (to give **11** at 50 °C) and with

and the easy access to the starting materials from the corresponding epoxides makes them perfectly suited for the rapid generation of building blocks and combinatorial libraries (Scheme 10).[64] An example of the swift access provided by aziridinium chemistry to "druglike" molecules is shown by the preparation of a 1,5-benzodiazepine derivative (Scheme 11).

Aziridinium and episulfonium chemistry is particularly well-suited to the aqueous phase because the spring-loaded three-membered ring intermediates bear a positive charge, balanced by the anionic counterion which served as the
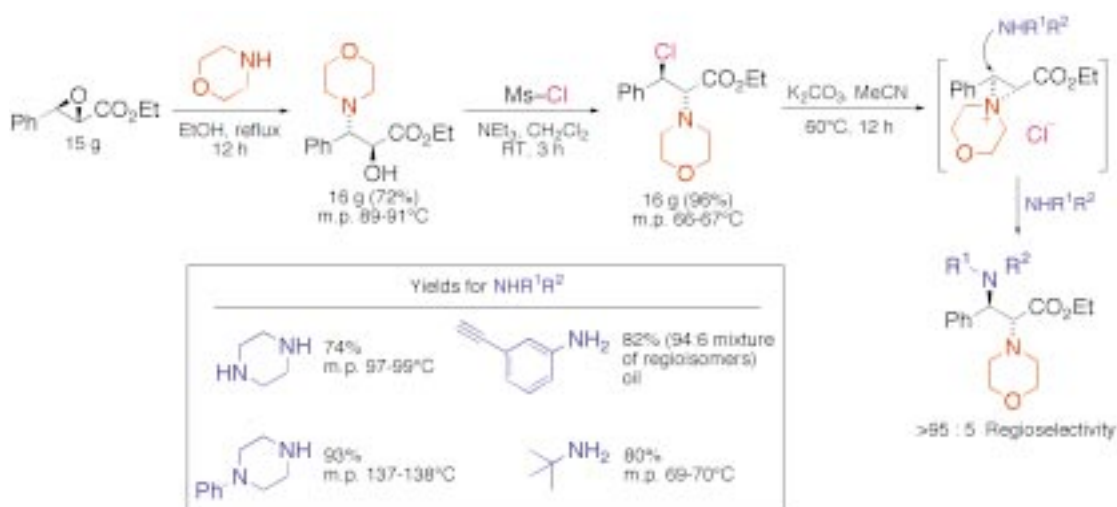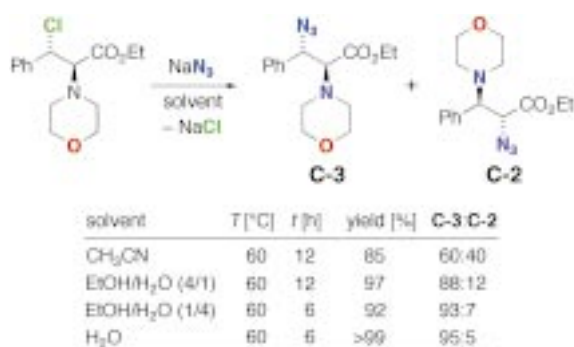

Scheme 10. Aziridinium intermediates in combinatorial assembly. Ms = mesyl = methane sulfonyl.
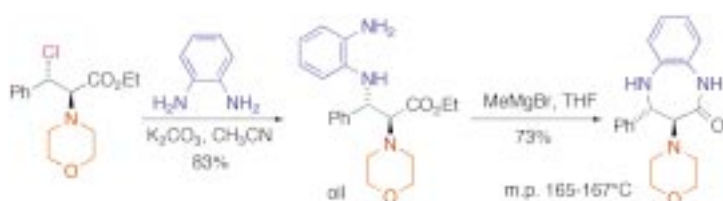
Scheme 11. Efficient assembly of a benzodiazepine via an aziridinium intermediate.

Scheme 13. Generation and reactions of activated sulfonium (thiiranium) electrophile **14**.

leaving group. We have noted that, when this leaving group is chloride or, particularly, sulfonate, the beneficial effects of water are most apparent, whereas little or no improvement is noted on changing the solvent from acetonitrile to water when the leaving group is iodide or bromide.[65] The greater stabilization offered by strong protic solvation of the harder anions in water is probably the dominant factor. Furthermore, these "homocarbonyl" electrophiles, like the acyl halides that participate in Schotten–Baumann reactions, are much more reactive toward a range of heteroatom nucleophiles in water than toward the solvent. An example of the beneficial effects of performing these types of reactions in water is given in Scheme 12, in which both yield and selectivity are shown to be

Scheme 12. Solvent dependence of aziridinium ring opening by azide.

solvent	T [°C]	t [h]	yield [%]	C-3:C-2
CH₃CN	60	12	85	60:40
EtOH/H₂O (4/1)	60	12	97	88:12
EtOH/H₂O (1/4)	60	6	92	93:7
H₂O	60	6	>99	95:5

improved as the water content of the reaction medium is increased. For the last two sets of conditions shown, which lead to the highest selectivities, neither the starting material nor the products are soluble in the reaction solvent.

In this context, it should also be noted that the mustard-type sulfur compounds are directly accessible from olefins in very high yields by addition of sulfenyl halides (RSX)[66] or the inorganic parent SCl_2[67] (Scheme 13, top). The addition often proceeds under thermodynamic control, allowing reliable prediction of the products. The exceptional reactivity of the resulting compounds such as **14** enables many additional click chemistry transformations through neighboring-group participation, which provides episulfonium intermediates such as **15**.[68] These pathways, and especially the required ejection of anionic leaving groups (for example, the chloride in **14**), are uniquely assisted by an aqueous environment. In the cases shown at the bottom of Scheme 13,[69] the reactions proceed cleanly and rapidly from solid-to-solid in aqueous suspension; presumably, the episulfonium ion intermediates are the only water-soluble species on the path from starting materials to
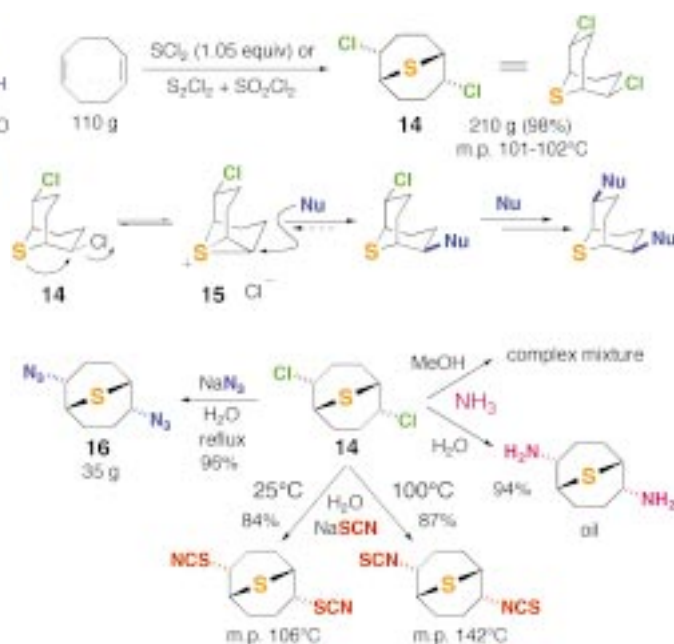
products. The dramatically different outcomes for reaction of **14** with saturated solutions of NH_3 in CH_3OH or H_2O underscore the crucial role played by solvation in these substitutions and the unique properties of water as a solvent, especially when solvent separation of ion pairs and/or efficient proton shuttling through solvent hydrogen-bonding networks are important.

3.2. Cycloaddition Reactions

Click chemistry ideals are beautifully represented among cycloaddition reactions involving heteroatoms, such as hetero-Diels–Alder[70, 71] and, especially, 1,3-dipolar[72–74] cycloadditions. These modular fusion reactions unite two unsaturated reactants and provide fast access to an enormous variety of interesting five- and six-membered heterocycles.[75]

As already mentioned, in this powerful class of concerted click reactions we have come to regard the Huisgen dipolar cycloaddition of azides and alkynes[76] as the "cream of the crop". However, probably because of concerns about the safety of the azide moiety,[77] medicinal chemists have not given these transformations the special attention they deserve.[78] The actual cycloaddition step may be as reliable for other types of [2+3] reactions, but the azide group is by far the most convenient of the 1,3-dipolar components to introduce and to "carry" until needed. Indeed, it may be the only one which is stable toward dimerization and/or hydrolysis. While azides are widely valued for their ease of introduction and reduction to primary amino groups, the remarkable stability (orthogonality) of *aliphatic* azides to a wide variety of other standard organic synthesis conditions seems largely unappreciated. With a few interesting exceptions, they remain "invisible" unless a good dipolarophile is present.

Angew. Chem. Int. Ed. **2001**, *40*, 2004–2021

2015

Two typical examples of azide cycloadditions are shown in Scheme 14.[79] Bis(azide) **16** readily adds two molecules of alkyne to give bis(triazole) **17**. A wide variety of alkynes

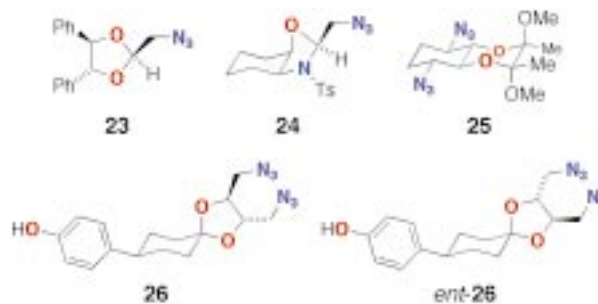Scheme 14. Examples of azide cycloaddition reactions.

engage in such reactions, with electron-deficient cases usually being the most reactive. Azide **18** reacts with the cyanoacetylene equivalent, 2-chloroacrylonitrile, to give only one regioisomer of triazole **19**, which retains its isolated olefins for further decoration.

Other (that is, non-azide) 1,3-dipolar cycloaddition processes provide interesting five-membered heterocycles, such as the examples shown in Scheme 15, in good yields.[80] The

Scheme 15. Cycloaddition reactions based on the hydrazine-derived [2+3] dipole **22**.[80a]

sequence starts with addition of hydrazine to the aziridinium intermediate generated from **20**. The resulting cyclic hydrazide **21** then undergoes condensation with aromatic aldehydes to give azomethine ylides **22**, which react with a variety of unsaturated components to give [3+2] cycloadducts. The rich array of functionality displayed by these products provides opportunities for the creation of unique combinatorial libraries.

3.3. "Protecting Group" Reactions

While hydroxy groups are nearly "invisible" in aqueous solution, in the absence of water a pair of *neighboring* hydroxy groups often exhibit unique reactivity. Thus, acid-catalyzed reactions with aldehydes and ketones provide cyclic 1,3-dioxolane rings in high yields. Instead of their ubiquitous role as diol protecting groups, should not acetals, ketals, and some of their aza-analogues be better viewed as an attractive class of heterocycles for medicinal chemistry applications? They are generally stable at physiological pH,[81a] have already appeared as components in orally available drugs,[81b] contribute several hydrogen bond acceptor sites and interesting dipole effects, provide constrained scaffolds with well-defined projections and spatial orientations of their substituents, are assembled from modular and abundant components, and represent one of the rare click chemistry modules based on *reversible* carbonyl chemistry.
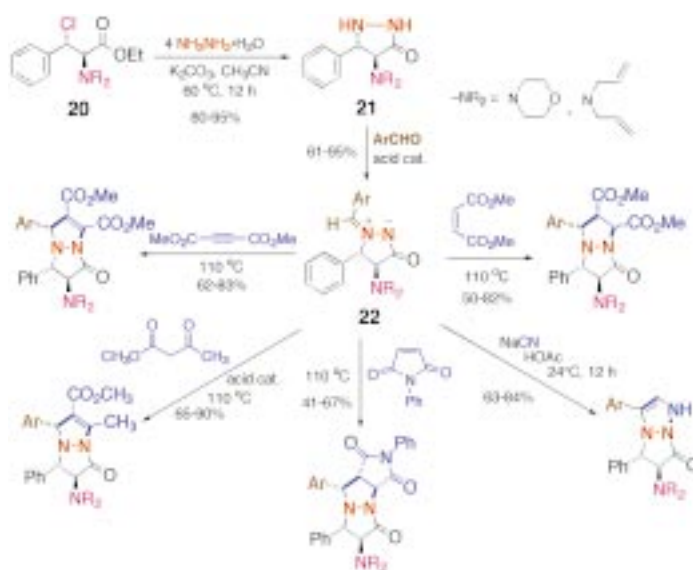
The five acetal-like derivatives (**23**–**26** and *ent*-**26**) were easily prepared on multigram scales from the appropriate diols or hydroxysulfonamides.[82] As a consequence of their

heteroatom substituent inductive effects, they are resistant to standard acidic hydrolysis conditions, all the more so if the azide group is reduced to the amine. The saturated dioxolane cores can be regarded as permanent elements of the block's structure under most physiological and chemical conditions, and if further transformations are desired the pendant azide substituents offer many diverse and reliable options.
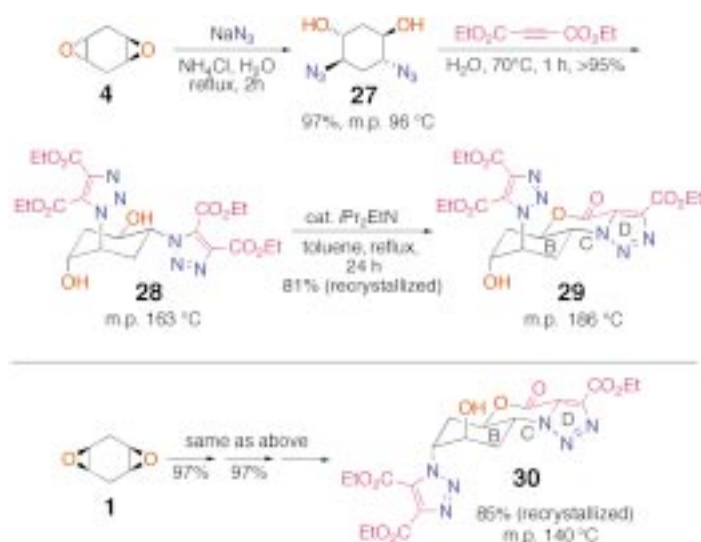
4. Examples of Click Chemistry Sequences— Diversity with Ease

Complex structures can be rapidly assembled using short sequences of simple click chemistry transformations. An example is the formation of the tricyclic molecule **29** in just three steps, conducted sequentially in one pot and starting from bis-epoxide **4**[34, 44] (Scheme 16).[83] The nucleophilic opening of **4** with buffered azide is highly regioselective, resulting in the formation of the crystalline azido alcohol **27** in excellent yield. The bis-triazole **28**, formed by 1,3-dipolar addition of the bis-azide with diethylacetylene dicarboxylate, can be collected from the reaction mixture by filtration. The C_2-symmetry of the system is then broken during base-catalyzed lactonization to furnish lactone **29**, the three rings of which resemble the B, C, and D rings found in

2016

*Angew. Chem. Int. Ed.* **2001**, *40*, 2004 – 2021

Scheme 16. Steroid-like skeletons assembled from cyclohexadiene diepoxides.

steroids. The analogous *cis*-diepoxide **1**, through the same three-step sequence, gives the related lactone **30**, which is identical to **29** except that the two "B"-ring substituents have switched positions. All steps for both sequences proceed in excellent yield. (See the frontispiece for large-scale sequences in this series.)

The capabilities of such reaction sequences for library synthesis are illustrated in Scheme 17. Epoxide ring opening with hydrazine and subsequent condensation with a variety of β-dicarbonyls or other bis-electrophiles provide entry to an enormous range of heterocyclic structures. Library synthesis using these protocols is highly efficient, and achieves excellent diversity from the large, available pool of epoxides.[84]

The facile osmium-catalyzed aminohydroxylation of α,β-unsaturated amides is also an attractive starting point for the synthesis of diverse molecules based on the previously rare α,β-diamino acid motif (Scheme 18). In this sequence, the hydroxysulfonamide regioisomers **31a** and **31b** produced in the aminohydroxylation step conveniently provide the same *cis*-*N*-sulfonylaziridine intermediates **32** upon cyclization.[85]
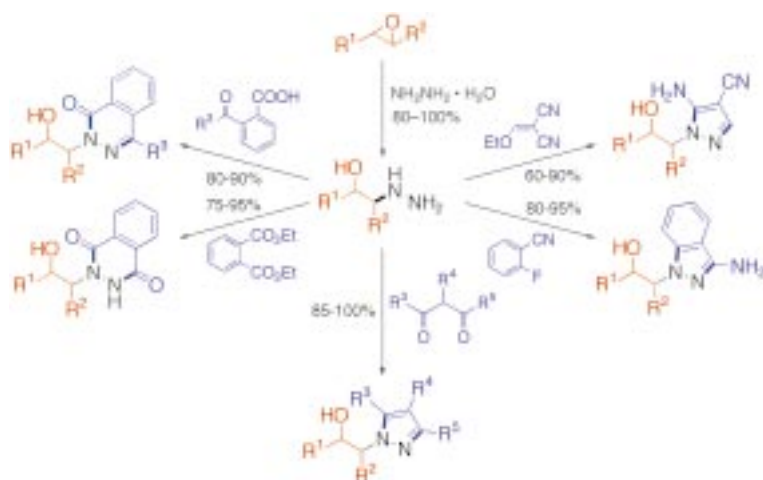
Scheme 17. Click chemistry sequences from epoxides and hydrazine.[84]
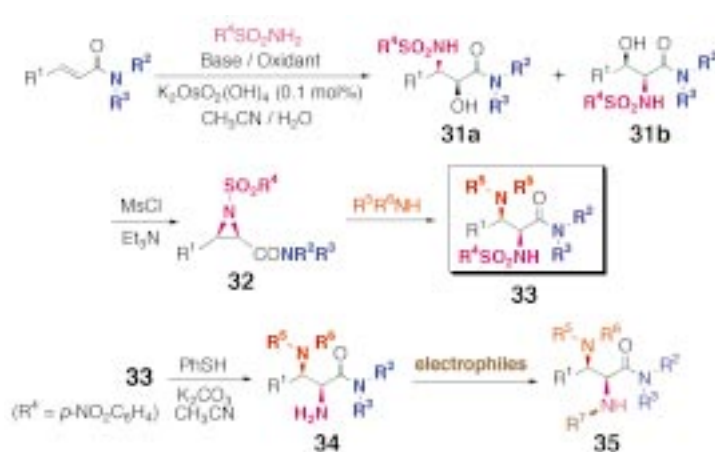
Scheme 18. A click chemistry library sequence from olefinic acids.[88]

Regioselective aziridine ring opening by a diverse set of primary and secondary amines then yields the *threo*-3-amino-2-sulfonamides **33**. The aminohydroxylation was also performed with the chloramine salt of *p*-nosyl sulfonamide (see above), and the β-aminosulfonamide products **33** (R⁴ = *p*-NO₂C₆H₄ (*p*-nosyl)) were freed of their sulfonamide group through the Fukuyama deprotection method,[86] to give **34**. The resulting primary 2-amino group of compounds **34** have been capped with more than sixty electrophiles to date, including acid chlorides, sulfonyl chlorides, anhydrides, isocyanates, and isothiocyanates, to give structures of the general form **35**.[87] The biological activities discovered in various screens of this library will be reported elsewhere.

5. Summary and Outlook

We have described here the basic elements of a new style of organic synthesis, or, perhaps more accurately, the reinvigoration of an old style of organic synthesis. Its purpose is to accelerate the discovery of substances with useful properties, new medicines being the example emphasized. The approach derives from a keen awareness of nature's preferred methods of synthesis, but does not seek to emulate them too closely.

Nature is a matchless creator of C−C linkages and we propose leaving the tough job of C−C bond synthesis as much as possible to her. Instead, it is sensible for us to specialize in quick and easy chemistry that nature uses only sparingly, by focusing on the high driving force reactions that emanate from the olefins that she has provided either directly (for example, terpenes) or that are produced by the petroleum industry.

It is no accident, given the high energy content of the olefinic π bond, that the most reliable and most useful organic reactions all involve olefins, their unsaturated cousins, or their uniquely accessible heteroatom oxidative addition products. The latter compounds either are, or can easily be transformed into, the reactive building blocks that are ideal for the fast, irreversible assembly (for example, through

Angew. Chem. Int. Ed. **2001**, *40*, 2004–2021

2017

click chemistry) of diverse molecules with druglike structural features. Three-dimensional space is efficiently accessed by the stereospecific nucleophilic openings of such spring-loaded rings, and when these spring-loaded units are embedded in cyclohexane frameworks, the level of regio- and stereochemical control available for core creation/decoration sequences reaches a zenith. Nature certainly uses heteroatom connections, but not in this fashion. Therefore, the structures assembled by opening aziridines and epoxides are usually novel, and almost invariably so when the assembly sequence involves two or more such ligations.

Nature's giant molecules are constructed from a small set of building blocks using a few types of reactions for stitching them together. If we are to build small molecules which interact specifically with these large and diverse structures, we will need more components than nature has developed. While new building blocks will always be welcome, we expect that a good set of 500 or so will prove effective for many targets.

Our thinking about C−C bonds as gifts of nature has been a constant source of inspiration during the framing and the ongoing refinement of this minimalist synthetic strategy. In any event, endeavoring to transform these matchless building blocks into substances with diverse and useful functions seems an appropriate way to honor the bestowal of such an embarrassment of riches.

[1] For equilibrium constants in a series of simple aldol condensations, see: J. P. Guthrie, *Can. J. Chem.* **1978**, *56*, 962–973.

[2] E. J. Corey, X.-M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, **1989**; K. C. Nicolaou, E. J. Sorensen, *Classics in Total Synthesis*, VCH, Weinheim, **1996**.

[3] For reviews, see: a) I. T. Baldwin, C. A. Preston, *Planta* **1999**, *208*, 137–145; b) O. C. Yoder, *Dev. Plant Pathol.* **1998**, *13*, 3–15; c) T. Hartmann, *Entomol. Exp. Appl.* **1996**, *80*, 177–188; d) E. Haslam, *Chemoecology* **1995**, *5/6*, 89–95; for a review of antifeedant secondary

metabolites, see: D. P. Singh, A. K. Pant, R. K. Rai, *Chem. Environ. Res.* **1993**, *2*, 3–18.

[4] For an eloquent account of the history of medicinal chemistry, see: W. Sneader, *Drug Prototypes and their Exploitation*, Wiley, New York, **1996**. Here Sneader traces the origins of modern medicines back to approximately 200 natural product prototypes, the majority of which are toxic secondary metabolites created by plants and microorganisms for self-defense.

[5] Some delightful exceptions do exist, such as Celebrex (celecoxib): T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang, P. C. Isakson, *J. Med. Chem.* **1997**, *40*, 1347–1365.

[6] Structure elucidation: G. Albers-Schönberg, B. H. Arison, O. D. Hensens, J. Hirshfield, K. Hoogsteen, E. A. Kaczka, R. E. Rhodes, J. S. Kahan, F. M. Kahan, R. W. Ratcliffe, E. Walton, L. J. Ruswinkle, R. B. Morin, B. G. Christensen, *J. Am. Chem. Soc.* **1978**, *100*, 6491–6499.

[7] Antibacterial properties: F. P. Tally, N. V. Jacobus, S. L. Gorbach, *Antimicrob. Agents Chemother.* **1978**, *14*, 436–438; S. S. Weaver, G. P. Bodey, B. M. LeBlanc, *Antimicrob. Agents Chemother.* **1979**, *15*, 518–521; J. S. Kahan, F. M. Kahan, R. Goegelman, S. A. Currie, M. Jackson, E. O. Stapley, T. W. Miller, A. K. Miller, D. Hendlin, S. Mochales, S. Hernandez, H. B. Woodruff, J. Birnbaum, *J. Antibiot.* **1979**, *32*, 1–12.

[8] Process optimization: D. G. Melillo, T. Shinkai, T. Liu, K. Ryan, M. Sletzinger, *Tetrahedron Lett.* **1980**, *21*, 2783–2786; I. Shinkai, T. Liu, R. A. Reamer, M. Sletzinger, *Tetrahedron Lett.* **1982**, *23*, 4899–4902; see also: D. L. Hughes, R. A. Reamer, J. J. Bergan, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1988**, *110*, 6487–6491.

[9] a) Meropenem synthesis: M. Sunagawa, H. Matsumura, T. Inoue, M. Fukasawa, K. Masatomo, M. Kato, EU-A EP126587, **1984**; A. S. Prashad, N. Vlahos, P. Fabio, G. B. Feigelson, *Tetrahedron Lett.* **1998**, *39*, 7035–7038; b) structure–activity discussion: M. Sunagawa, H. Matsumura, T. Inoue, M. Fukasawa, M. Kato, *J. Antibiot.* **1990**, *43*, 519–532.

[10] a) Synthesis: D. B. R. Johnston, S. M. Schmitt, F. A. Bouffard, B. G. Christensen, *J. Am. Chem. Soc.* **1978**, *100*, 313–315; T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen, F. A. Bouffard, *J. Am. Chem. Soc.* **1980**, *102*, 6161–6163; b) S. Redshaw, G. J. Thomas, *Emerging Drugs* **1997**, *2*, 127–154.

[11] While nature was the *first* combinatorial chemist, Ivar Ugi may be regarded as the *second*. His idea of using one-step *solution-phase* processes, such as his four-component coupling reaction, in such applications was a stroke of genius, and about 30 years ahead of its time: "Since four different starting materials take part in the four-component condensation, the reaction is extremely versatile. If, for example, 40 each of the different components are reacted with one another, the result is $40^4 = 2\,560\,000$ reaction products, which is quite a high figure considering that it is of the same order of magnitude as the total number of chemical compounds described to date." (G. Gokel, G. Lüdke, I. Ugi, in *Isonitrile Chemistry* (Ed.: I. Ugi), Academic Press, New York, **1971**, pp. 145–199; see also: I. Ugi, R. Meyr, U. Fetzer, C. Steinbrückner, *Angew. Chem.* **1959**, *71*, 386). When the pharmaceutical industry "discovered" combinatorial chemistry about 20 years later, the *solid-phase* approach, pioneered by Merrifield for multistep synthesis of large biopolymers, was adapted for multistep syntheses of druglike molecules. Only recently, following ArQule's lead, has the drug-discovery community realized the power of Ugi's vision for quickly generating molecular diversity through robust, yet simple, reaction cascades that assemble multiple components in solution.

[12] The venerable Robinson annelation sequence is an example. The components are first connected intermolecularly by the Michael reaction (no new C−C bonds made, only the favorable exchange of a π for a σ bond; $\Delta H < -20\,\text{kcal mol}^{-1}$) and only then is the hard part (the aldol step) accomplished intramolecularly. The Dieckman condensation has enormous scope because it is intramolecular, whereas the intermolecular parent reaction (Claisen condensation) is only reliable for the simplest case (R = H in RCH_2COOR').

[13] We do not consider here the many polymerization (Ziegler–Natta) reactions of olefins and acetylenes and related processes, which account for the vast majority of man-made materials based on contiguous carbon–carbon bond networks. Being strongly exothermic and superbly efficient, these polymerizations are clearly based on click reactions, but ones which are hard to control for the construction of small molecules in the stepwise "modular" fashion of the reactions discussed above.

[14] R. S. Bohacek, C. McMartin, W. C. Guida, *Med. Res. Rev.* **1996**, 16, 3–50. K.B.S. thanks Prof. Daniel Rich for calling this paper to his attention during a visit to the University of Wisconsin in 1997.

[15] The portion of this drug candidate "universe" that has been synthesized to date is approximately one part in 10^{57}, or roughly the ratio of the mass of one proton to the mass of the sun! The distance from Earth to the edge of the visible universe is traversed in only 25 powers of ten ($10^0 \rightarrow 10^{25}$ meters) or so: P. Morrison, P. Morrison, *Powers of Ten*, Scientific American, New York, **1982**.

[16] For further discussion of this approach, and its relation to process chemistry, see: Foreword by K. B. Sharpless in *Practical Process Research & Development* (Ed.: N. G. Anderson), Academic Press, San Diego, **2000**.

[17] The free energy of the hydrogenation of ethylene to ethane is $-24.1 \, \mathrm{kcal\,mol^{-1}}$, and of acetylene to ethylene is $-33.7 \, \mathrm{kcal\,mol^{-1}}$. Other convenient comparisons, such as the ones shown in Scheme 1, can be made with the aid of the Benson group-additivity method: S. W. Benson, *Thermochemical Kinetics*, 2nd ed., Wiley, New York, **1976**.

[18] H. A. Wittcoff, B. G. Reuben in *Industrial Organic Chemicals*, Wiley, New York, **1996**.

[19] G. Wilke, A. Eckerle, *Appl. Homogeneous Catal. Organomet. Compd.* **1996**, 1, 358–373; b) P. W. Jolly, G. Wilke, *The Organic Chemistry of Nickel*, *Vol. I* and *II*, Academic Press, New York, **1975**; c) G. W. Parshall, W. A. Nugent, *CHEMTECH* **1988**, 18, 314–320.

[20] U. Biermann, W. Friedt, S. Lang, W. Lühs, G. Machmüller, J. O. Metzger, M. Rüsch gen. Klaas, H. J. Schäfer, M. P. Schneider, *Angew. Chem.* **2000**, 112, 2292–2310; *Angew. Chem. Int. Ed.* **2000**, 39, 2206–2224.

[21] It should be appreciated that nature does make sparing use of olefin-based chemistries. In general, their high reactivity toward oxidation and addition makes olefins a liability for biology, in that harmful, irreversible reactions are possible. But occasionally, necessity seems to have been the mother of spectacular invention, as in the cationic cyclization of squalene epoxide to lanosterol. In this and related polyene cyclizations, we see that nature discovered the unique effectiveness of olefin oligomerization processes for turning unstable C=C networks into stable (C—C) ones some years before the petroleum chemist.

[22] a) *Tetrahedron* **1998**, *54*(16) (special issue devoted to solution-phase combinatorial chemistry); b) H. An, P. D. Cook, *Chem. Rev.* **2000**, 100, 3311–3340.

[23] For example, see: R. H. Griffey, H. An, L. L. Cummins, H. J. Gaus, B. Haly, R. Herrmann, P. D. Cook, *Tetrahedron* **1998**, 54, 4067–4076.

[24] a) C.-J. Li, T.-H. Chan, *Organic Reactions in Aqueous Media*, Wiley, New York, **1997**; b) *Aqueous Phase Organometallic Catalysis* (Eds.: B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, **1998**; c) *Organic Synthesis in Water* (Ed.: P. A. Grieco), Blackie, London, **1998**; d) R. Breslow, *Acc. Chem. Res.* **1991**, 24, 159–164; e) R. Breslow, *Pure Appl. Chem.* **1998**, 70, 1933–1938.

[25] J. J. Gajewski, *Acc. Chem. Res.* **1997**, 30, 219–225.

[26] See, for example: F. Fringuelli, O. Piermatti, F. Pizzo, L. Vaccaro, *J. Org. Chem.* **1999**, 64, 6094–6096.

[27] For an example of the beneficial effects of aqueous solvent on 1,3-dipolar cycloaddition reactions, see: D. van Mersbergen, J. W. Wijnen, J. B. F. N. Engberts, *J. Org. Chem.* **1998**, 63, 8801–8805.

[28] With the concentrations indicated and the assumption of simple second-order kinetics, the click reaction has to have a rate constant approximately 50 000 times that of the competing reaction with water in order for the side product to constitute less than one percent of the total. At room temperature, this translates to a difference in activation energy of approximately $6.4 \, \mathrm{kcal\,mol^{-1}}$. The situation is more complicated when, as is often the case, either or both of the reaction components are poorly soluble in water.

[29] Note, however, that amide bond synthesis by this or other methods, in spite of being strongly favorable thermodynamically, does not often reach the level of yield, generality, simplicity, and ease of product isolation that characterizes click reactions. For example, compare amide synthesis with the synthesis of ureas from amines and isocyanates. The latter process is a nearly perfect transformation, and like all the best click reactions it is a pure fusion process requiring no adjuvants of any kind. Amide bond formation, in contrast, usually requires external reagents and generates nontrivial by-products, factors contributing to uncertain outcomes in new circumstances. Reactions such as these are good enough for making building blocks, but not for the final assembly sequences.

[30] A similar theme may be found in the development of sequential ("domino") reaction schemes for the rapid synthesis of single compounds or compound libraries. See, for example: L. F. Tietze, A. Modi, *Med. Res. Rev.* **2000**, 20, 304–322; L. F. Tietze, M. E. Lieb, *Curr. Opin. Chem. Biol.* **1998**, 2, 363–371; L. F. Tietze, *Chem. Rev.* **1996**, 96, 115–136; L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, 105, 137–170; *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 131–163; A. Orita, Y. Nagano, K. Nakazawa, J. Otera, *Synlett* **2000**, 599–602.

[31] The series *Houben-Weyl: Methods of Organic Chemistry*, Thieme Verlag, Stuttgart remains unchallenged as the best source of information of this type.

[32] a) J. I. Crowley, H. Rapoport, *Acc. Chem. Res.* **1976**, 9, 135–144; b) J. S. Früchtel, G. Jung, *Angew. Chem.* **1996**, 108, 19–46; *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 17–42; c) P. H. H. Hermkens, H. C. J. Ottenheijm, D. C. Rees, *Tetrahedron* **1996**, 52, 4527–4554; d) P. H. H. Hermkens, H. C. J. Ottenheijm, D. C. Rees, *Tetrahedron* **1997**, 53, 5643–5678.

[33] Aziridination: a) J. U. Jeong, B. Tao, I. Sagasser, H. Henniges, K. B. Sharpless, *J. Am. Chem. Soc.* **1998**, 120, 6844–6845; b) A. V. Gontcharov, H. Liu, K. B. Sharpless, *Org. Lett.* **1999**, 1, 783–786.

[34] Olefin epoxidation using methylrhenium trioxide as a catalyst in the presence of amine additives: a) H. Adolfsson, A. Converso, K. B. Sharpless, *Tetrahedron Lett.* **1999**, 40, 3991–3994; b) W. A. Herrmann, R. W. Fischer, D. W. Marz, *Angew. Chem. Int. Ed. Engl.* **1991**, 30, 1638–1641; c) W. A. Herrmann, F. E. Kühn, *Acc. Chem. Res.* **1997**, 30, 169–180; d) J. Rudolph, K. L. Reddy, J. P. Chiang, K. B. Sharpless, *J. Am. Chem. Soc.* **1997**, 119, 6189–6190.

[35] Reviews of the asymmetric epoxidation of allylic alcohols: a) T. Katsuki, V. S. Martin, *Org. React.* **1996**, 48, 1–299; b) R. A. Johnson, K. B. Sharpless in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, New York, **1993**, pp. 101–158.

[36] Reviews of the asymmetric epoxidation of unfunctionalized olefins: a) T. Katsuki, *J. Mol. Catal. A* **1996**, 113, 87–107; b) E. N. Jacobsen, in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, New York, **1993**, pp. 159–202.

[37] Osmium-catalyzed dihydroxylation of olefins: a) H. C. Kolb, K. B. Sharpless, *Transition Met. Org. Synth.* **1998**, 2, 219–242; b) H. C. Kolb, M. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, 94, 2483–2547.

[38] Review of the osmium-catalyzed aminohydroxylation of olefins: a) H. C. Kolb, K. B. Sharpless, *Transition Met. Org. Synth.* **1998**, 2, 243–260; b) G. Schlingoff, K. B. Sharpless in *Asymmetric Oxidations Reactions: A Practical Approach* (Ed.: T. Katsuki), Oxford University Press, in press; c) use of amino-substituted heterocycles as nitrogen source: L. J. Goossen, H. Liu, K. R. Dress, K. B. Sharpless, *Angew. Chem.* **1999**, 111, 1149–1152; *Angew. Chem. Int. Ed. Engl.* **1999**, 38, 1080–1083; K. R. Dress, L. J. Goossen, H. Liu, D. M. Jerina, K. B. Sharpless, *Tetrahedron Lett.* **1998**, 39, 7669–7672; d) Z. P. Demko, M. Bartsch, K. B. Sharpless, *Org. Lett.* **2000**, 2, 2221–2223.

[39] For a recent review of the asymmetric synthesis of aziridines from amino alcohols, epoxides, alkenes, and imines, see: H. M. I. Osborn, J. Sweeney, *Tetrahedron: Asymmetry* **1997**, 8, 1693–1715.

[40] a) A. E. Rubin, K. B. Sharpless, *Angew. Chem.* **1997**, 109, 2751–2754; *Angew. Chem. Int. Ed. Engl.* **1997**, 36, 2637–2640; b) W. C. Pringle, K. B. Sharpless, unpublished results; c) V. V. Fokin, K. B. Sharpless, *Angew. Chem.*, in press; *Angew. Chem. Int. Ed.*, in press; d) see also: W. Pringle, K. B. Sharpless, *Tetrahedron Lett.* **1999**, 40, 5151–5154.

[41] For an appreciation of the virtues of fusion processes from the viewpoint of "atom economy", see: B. M. Trost, *Science* **1991**, 254, 1471–1477.

Angew. Chem. Int. Ed. **2001**, 40, 2004–2021

2019

[42] a) The fact that stereoelectronic factors disfavor eliminations in small rings has allowed the stereoselective alkylation of the α-carbon of carboxylic acids, with oxygen-containing functionality in the β-position, through heterocyclic enolates with an exocyclic double bond (D. Seebach, J. D. Aebi, M. Gander-Coquoz, R. Naef, *Helv. Chim. Acta* **1987**, *70*, 1194 – 1216). For other uses of oxiranyl anions, see: b) T. Satoh, *Chem. Rev.* **1996**, *96*, 3303 – 3325; c) Y. Mori, *Rev. Heteroat. Chem.* **1997**, *17*, 183 – 211; d) T. Satoh, S. Kobayashi, S. Nakanishi, K. Horiguchi, S. Irisa, *Tetrahedron* **1999**, *55*, 2515 – 2528; e) Y. Mori, K. Yaegashi, H. Furukawa, *J. Am. Chem. Soc.* **1997**, *119*, 4557 – 4558.

[43] Care must be exercised with these reactive electrophiles, since the ring-opening reactions are exothermic and often autocatalytic when performed neat with basic amines as the nucleophile. In large-scale applications without solvent, it is essential to start at a temperature where the reaction at hand has been shown to be self-sustaining and the amines then added at a rate to maintain the desired temperature. If water alone cannot be used as solvent, we often employ boiling *n*-propanol or boiling toluene for large-scale applications (depending on whether or not a protic or aprotic environment is desired (see refs. [44b] and [45]); in the former case, the addition of water after cooling often results in precipitation of the product.

[44] Synthesis of *cis*-1,4-cyclohexadiene epoxides: a) T. W. Craig, G. R. Harvey, G. A. Berchtold, *J. Org. Chem.* **1967**, *32*, 3743 – 3749; b) G. Kavadias, S. Velkof, B. Belleau, *Can. J. Chem.* **1978**, *56*, 404 – 409; c) T. Suami, S. Ogawa, H. Uchino, Y. Funaki, *J. Org. Chem.* **1975**, *40*, 456 – 461; for ring-opening reactions of six-membered ring di- and triepoxides, see: d) R. Kuehlmeyer, R. Keller, R. Schwesinger, T. Netscher, H. Fritz, H. Prinzbach, *Chem. Ber.* **1984**, *117*, 1765 – 1800; e) J. Schubert, R. Keller, R. Schwesinger, H. Prinzbach, *Chem. Ber.* **1983**, *116*, 2524 – 2545; f) C. Rucker, H. Muller-Botticher, W. D. Braschwitz, U. Reifenstahl, H. Irngartinger, *Liebigs Ann.* **1997**, 967 – 989; g) S. Kagabu, S. Kaiser, R. Keller, P. G. Becker, K. H. Mueller, L. Knothe, G. Rihs, H. Prinzbach, *Chem. Ber.* **1988**, *121*, 741 – 756.

[45] a) H. T. Chang, J. P. Chiang, K. L. Reddy, M. A. Winter, A. K. Yudin, K. B. Sharpless, unpublished results; b) for previous studies on the regioselectivity of the ring opening of *cis*- and *trans*-1,4-cyclohexadiene diepoxides, see: G. Kavadias, R. Droghini, *Can. J. Chem.* **1979**, *57*, 1870 – 1876; F. Haviv, B. Belleau, *Can. J. Chem.* **1978**, *56*, 2677 – 2680; T. Suami, S. Ogawa, H. Uchino, Y. Funaki, *J. Org. Chem.* **1975**, *40*, 456 – 461.

[46] The 1,3-selectivity in the neat reaction (that is, **1**→**2**) probably stems from the interplay of two effects: *trans*-diaxial epoxide opening and intramolecular epoxide activation by the hydroxy group that is released in the first step (see Scheme 19). The latter effect is much less important in the presence of a protic solvent, and thereby allows the intermediate hydroxy epoxide to react from the other, more stable chair conformer, which gives rise to the diamine from 1,4-attack (that is, **1**→**3**, Scheme 7).
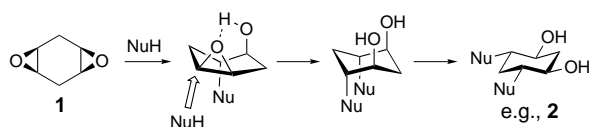
Scheme 19.

[47] For the nucleophilic opening of epoxides derived from tetrahydronaphthalene and hexahydroanthracene, see: a) E. Vogel, F. Kuebart, J. A. Marco, R. Andree, *J. Am. Chem. Soc.* **1983**, *105*, 6982 – 6983; b) E. Vogel, W. Klug, A. Breuer, *Org. Synth. Coll. Vol.* **1988**, *6*, 862 – 865; c) E. Vogel, M. Biskup, A. Vogel, H. Günther, *Angew. Chem.* **1966**, *78*, 755 – 756; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 734 – 735; d) A. K. Yudin, J. P. Chiang, K. B. Sharpless, unpublished results.

[48] See ref. [33a]; synthesis by transition metal catalyzed aziridination of olefins, see: H. Kwart, A. A. Kahn, *J. Am. Chem. Soc.* **1967**, *89*, 1951 – 1953; D. Mansury, J.-P. Mahy, D. Annie, B. Gustave, P. Battioni, *J. Chem. Soc. Chem. Commun.* **1984**, 1161 – 1163; D. A. Evans, M. M. Faul, M. T. Bilodeau, *J. Org. Chem.* **1991**, *56*, 6744 – 6746; E. Vedejs, H. Sano, *Tetrahedron Lett.* **1992**, *33*, 3261 – 3264; M. J. Sodergren, D. A. Alonso, A. V. Bedekar, P. G. Andersson, *Tetrahedron Lett.* **1997**, *38*, 6897 – 6900; asymmetric transition metal catalyzed aziridination of olefins: D. A. Evans, M. M. Faul, M. T. Bilodeau, B. A. Anderson, D. M. Barnes, *J. Am. Chem. Soc.* **1993**, *115*, 5328 – 5329; R. E. Rowenthal, S. Masamune, *Tetrahedron Lett.* **1991**, *32*, 7373 – 7376; Z. Li, K. B. Conser, E. N. Jacobson, *J. Am. Chem. Soc.* **1993**, *115*, 5326 – 5327; H. Nishikori, T. Katsuki, *Tetrahedron Lett.* **1996**, *37*, 9245 – 9248; aziridination of olefins with PhI=NTs: Y. Yamada, T. Yamamoto, *Chem. Lett.* **1975**, 361.

[49] a) D. Tanner, C. Birgersson, *Tetrahedron Lett.* **1991**, *32*, 2533 – 2536; b) D. Tanner, A. Almario, T. Högberg, *Tetrahedron* **1995**, *51*, 6061 – 6070; c) Z. Wang, L. S. Jimenez, *J. Org. Chem.* **1996**, *61*, 816 – 818; d) P. Besse, H. Veschambre, R. Chenevert, M. Dickman, *Tetrahedron: Assymmetry* **1994**, *5*, 1727 – 1744; e) P. Wipf, P. C. Fritch, *J. Org. Chem.* **1994**, *59*, 4875 – 4886; f) V. C. O. Njar, R. W. Hartmann, C. H. Robinson, *J. Chem. Soc. Perkin Trans. 1* **1995**, 985 – 991; g) P. Crotti, V. Di Bussolo, L. Favero, F. Macchia, M. Pineschi, *Tetrahedron: Asymmetry* **1996**, *7*, 779 – 786; h) N. A. J. M. Sommerdijk, P. J. J. A. Buynsters, H. Akdemir, D. G. Geurts, R. J. M. Nolte, B. Zwanenburg, *J. Org. Chem.* **1997**, *62*, 4955 – 4960.

[50] a) H. Wenker, *J. Am. Chem. Soc.* **1935**, *57*, 2328; b) P. A. Leighton, W. Perkins, M. L. Renquist, *J. Am. Chem. Soc.* **1947**, *69*, 1540; c) C. F. H. Allen, F. W. Spangler, E. R. Webster, *Org. Synth. Coll. Vol.* **1963**, *4*, 433 – 435; d) A. Galindo, L. Orea, D. Gnecco, R. G. Enríquez, R. A. Toscano, W. F. Reynolds, *Tetrahedron: Asymmetry* **1997**, *8*, 2877 – 2879.

[51] a) I.-C. Chiu, H. Kohn, *J. Org. Chem.* **1983**, *48*, 2857 – 2866; b) D. van Ende, A. Krief, *Angew. Chem.* **1974**, *86*, 311 – 312; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 279 – 280.

[52] For a study on the influence of Lewis acids on the nucleophilic opening of *N*-acyl aziridines versus their rearrangement to oxazolines, see: D. Ferraris, W. J. Drury III, C. Cox, T. Lectka, *J. Org. Chem.* **1998**, *63*, 4568 – 4569.

[53] a) H. Stamm, *J. Prakt. Chem.* **1999**, *341*, 319 – 331; b) K. Bellos, H. Stamm, *J. Org. Chem.* **1995**, *60*, 5661 – 5666.

[54] P.-Y. Lin, K. Bellos, H. Stamm, A. Onistschenko, *Tetrahedron* **1992**, *48*, 2359 – 2372.

[55] See, for example: a) D. Tanner, *Angew. Chem.* **1994**, *106*, 625 – 646; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599 – 619; b) Y. L. Bennani, G.-D. Zhu, J. C. Freeman, *Synlett* **1998**, 754 – 756.

[56] H.-T. Chang, Z. Chen, H. C. Kolb, K. B. Sharpless, unpublished results.

[57] Opening of aziridines with thiols, see: a) G. Meguerian, L. B. Clapp, *J. Am. Chem. Soc.* **1951**, *73*, 2121 – 2124; b) J. Legters, L. Thijs, B. Zwanenburg, *Recl. Trav. Chim. Pays-Bas* **1992**, *111*, 1 – 15; c) H. Shao, Q. Zhu, M. Goodman, *J. Org. Chem.* **1995**, *60*, 790 – 791.

[58] a) Z.-M. Wang, J. E. Pease, K. R. Dress, K. B. Sharpless, unpublished results; b) **WARNING**: When the neat synthesis of **7** (Scheme 9) was performed on a 3-gram scale, it took off with a "pop" and most of the white crystalline product ended up on the ceiling of the fume hood. The autocatalysis mentioned in ref. [43] is especially dramatic in such neat amine openings of *N*-sulfonylaziridines, since the newly created sulfonamide N−H bond, being almost 10^6 times more acidic than an alcohol O−H group, is especially good at assisting in the opening process. Such cases need a solvent if the scale is greater than approximately 5 mmol.

[59] For selected examples, see: a) S. E. De Sousa, P. O'Brien, P. Poumellec, *J. Chem. Soc. Perkin Trans. 1* **1998**, 1483 – 1492; b) P. A. Grieco, W. A. Carroll, *Tetrahedron Lett.* **1992**, *33*, 4401 – 4404; c) S. V. D'Andrea, E. T. Michalson, J. P. Freeman, C. G. Chidester, J. Szmuszkovicz, *J. Org. Chem.* **1991**, *56*, 3133 – 3137; d) P. Gmeiner, *Heterocycles* **1991**, *32*, 1499 – 1504; e) R. K. Dieter, N. Deo, B. Lagu, J. W. Dieter, *J. Org. Chem.* **1992**, *57*, 1663 – 1671; f) S. Zhao, J. P. Freeman, C. G. Chidester, P. F. von Voigtlander, S. A. Mizsak, J. Szmuszkovicz, *J. Org. Chem.* **1993**, *58*, 4043 – 4048; g) H. H. Wasserman, C. B. Vu, *Tetrahedron Lett.* **1994**, *35*, 9779 – 9782; h) S. Zhao, A. Ghosh, S. V. D'Andrea, J. P. Freeman, P. F. von Voigtlander, D. B. Carter, M. W. Smith, J. R. Blinn, J. Szmuszkovicz, *Heterocycles* **1994**, *39*, 163 – 170; i) D.-K. Kim, G. Kim, Y.-W. Kim, *J. Chem. Soc. Perkin Trans. 1* **1996**, 803 – 808; j) G. Miao, B. E. Rossiter, J. S. Bradshaw, *J. Org. Chem.* **1995**, *60*, 8424 – 8427; k) C. Perrio-Huard, C. Ducandas, M. C. Lasne, B. Moreau, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2925 – 2932.

[60] For selected examples, see: a) T. R. Webb, C. Eigenbrot, *J. Org. Chem.* **1991**, *56*, 3009–3016; b) M. Shrimali, R. Kalsi, S. S. Parmar, J. P. Barthwal, *Arzneim. Forsch.* **1991**, *41*, 101–103; c) S. Corsano, G. Strappaghetti, A. Codagnone, R. Scapicchi, G. Marucci, *Eur. J. Med. Chem.* **1992**, *27*, 545–549; d) M. A. Williams, H. Rapoport, *J. Org. Chem.* **1994**, *59*, 3616–3625; e) T. Morie, S. Kato, H. Harada, I. Fujiwara, K. Watanabe, J. Matsumoto, *J. Chem. Soc. Perkin Trans. 1* **1994**, 2565–2569; f) S. Corsano, G. Strappaghetti, R. Scapicchi, G. Marucci, *Arch. Pharm.* **1996**, *329*, 468–470; g) E. J. Corey, R. Naef, F. J. Hannon, *J. Am. Chem. Soc.* **1986**, *108*, 7114–7116; h) L. F. Lindoy, B. W. Skelton, S. V. Smith, A. H. White, *Aust. J. Chem.* **1993**, *46*, 363–375.

[61] P. F. Richardson, L. T. J. Nelson, K. B. Sharpless, *Tetrahedron Lett.* **1995**, *36*, 9241–9244.

[62] a) J. A. J. M. Vincent, P. Schipper, A. deGroot, H. M. Buck, *Tetrahedron Lett.* **1975**, 1989–1992; b) W. H. Mueller, *Angew. Chem.* **1969**, *81*, 475–484; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 482–492.

[63] K. Burow, B. Tao, A. Converso, M. G. Finn, K. B. Sharpless, unpublished results.

[64] T.-H. Chuang, K. B. Sharpless, *Org. Lett.* **1999**, *1*, 1435–1437.

[65] T.-H. Chuang, A. Converso, K. Burow, K. L. Reddy, A. Marzinzik, K. B. Sharpless, unpublished results.

[66] For a review, see: E. Kühle, *Synthesis* **1971**, 563–586.

[67] a) For a review, see: M. Mühlstädt, D. Martinetz, *Z. Chem.* **1974**, *14*, 297–304; b) formation of macrocycles by reaction of nonconjugated dienes with SCl₂: M. Mühlstädt, M. Ecke, K. Hollmann, M. Möder, DE-B 288 603 A5, **1983**; c) addition of SCl₂ to cycloheptadienones: P. H. McCabe, W. Routledge, *Tetrahedron Lett.* **1976**, 85–86; d) reaction with aryl allyl ethers: M. Mühlstädt, K. Hollmann, R. Widera, *Tetrahedron Lett.* **1983**, *24*, 3203–3204; reaction with acyclic nonconjugated dienes: F. Lautenschlaeger, *J. Org. Chem.* **1968**, *33*, 2620–2627; e) reaction with cyclic polyolefins: F. Lautenschlaeger, *J. Org. Chem.* **1968**, *33*, 2627–2633; F. Lautenschlaeger, *Chemistry in Sulfides Conference* (Ed.: A. V. Tobolsky), Interscience, New York, **1968**, pp. 73–81; E. D. Weil, K. J. Smith, R. J. Gruber, *J. Org. Chem.* **1966**, *31*, 1669–1679; F. Lautenschlaeger, *J. Org. Chem.* **1966**, *31*, 1679; E. J. Corey, E. Block, *J. Org. Chem.* **1966**, *31*, 1663–1668; F. Lautenschlaeger, *Can. J. Chem.* **1966**, *44*, 2813–2817; f) reaction with vinyl cyclohexenes: G. A. Tolstikov, B. M. Lerman, N. G. Komissarova, L. M. Zelenova, *Zh. Org. Khim.* **1983**, *19*, 321–332; G. A. Tolstikov, B. M. Lerman, N. G. Komissarova, *Zh. Org. Khim.* **1983**, *19*, 299–310.

[68] A. Converso, A. Marzinzik, A. R. Vaino, K. Burow, K. P. M. VanHessche, H. C. Kolb, M. G. Finn, K. B. Sharpless, unpublished results.

[69] A. Converso, K. Burow, A. Marzinzik, K. B. Sharpless, M. G. Finn, *J. Org. Chem.*, in press.

[70] For a review of the use of the hetero-Diels–Alder reaction in organic chemistry, see: L. F. Tietze, G. Kettschau, *Top. Curr. Chem.* **1997**, *189*, 1–120.

[71] For a review of the asymmetric hetero-Diels–Alder reaction, see: H. Waldmann, *Synthesis* **1994**, 535–551.

[72] a) R. Huisgen in *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Padwa), Wiley, New York, **1984**, pp. 1–176; b) A. Padwa in *Comprehensive Organic Synthesis*, *Vol. 4* (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, pp. 1069–1109.

[73] For a review of asymmetric 1,3-dipolar cycloaddition reactions, see: K. V. Gothelf, K. A. Jorgensen, *Chem. Rev.* **1998**, *98*, 863–909.

[74] For a review of synthetic applications, see: J. Mulzer, *Org. Synth. Highlights* **1991**, 77–95.

[75] a) W.-Q. Fan, A. R. Katritzky in *Comprehensive Heterocyclic Chemistry II*, *Vol. 4* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**, pp. 101–126; b) R. N. Butler in *Comprehensive Heterocyclic Chemistry II*, *Vol. 4* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**, pp. 621–678; c) K. Banert, *Chem. Ber.* **1989**, *122*, 911–918.

[76] a) R. Huisgen, *Pure Appl. Chem.* **1989**, *61*, 613–628; b) R. Huisgen, G. Szeimies, L. Moebius, *Chem. Ber.* **1967**, *100*, 2494–2507; c) W. Lwowski in *1,3-Dipolar Cycloaddition Chemistry*, *Vol. 1* (Ed.: A. Padwa), Wiley, New York, **1984**, Chap. 5; d) J. Bastide, J. Hamelin, F. Texier, V. Q. Ven, *Bull. Soc. Chim. Fr.* **1973**, 2555–2579; J. Bastide, J. Hamelin, F. Texier, V. Q. Ven, *Bull. Soc. Chim. Fr.* **1973**, 2871–2887.

[77] "Azidophobia" seems to be largely based on the fact that a number of metallic azides are shock sensitive. However, certain organic azides, especially small ones, are also explosive. The following points are noteworthy. Sodium azide is relatively safe, especially in aqueous solution, unless acidified to form HN₃, which is volatile and highly toxic. For organic azides, the "rule of six" is very useful: six carbons (or other atoms of about the same size) per energetic functional group (azide, diazo, nitro, etc.) provides sufficient dilution to render the compound relatively safe. Note that the presence of acetylenic groups or other energy producers with an azide makes for increased hazard. Decomposition of organic azides can be catalyzed by certain transition metal species (especially those from the Fe and Co triads) and by strong acids (that is, the same catalysts that are most effective for decomposition of organic peroxides). Azide groups attached directly to olefinic, aromatic, or carbonyl moieties are much less stable and, other things being equal, more dangerous than aliphatic azides (the approximate activation energies for unimolecular loss of N₂ being 29 and 49 kcal mol⁻¹, respectively). For these reasons, azides should not be distilled or treated in a careless fashion. However, when common sense is employed, they can be prepared, stored, and used without risk in the standard organic chemistry laboratory: We have never experienced a safety problem with these materials. See: M. Peer, *Spec. Chem.* **1998**, *18*, 256–263.

[78] Recent examples of the use of this process include: a) M. Yamashita, K. Suzuki, Y. Kato, A. Iida, K. Ikai, P. M. Reddy, T. Oshikawa, *J. Carbohydr. Chem.* **1999**, *18*, 915–935; b) M. Moore, P. Norris, *Tetrahedron Lett.* **1998**, *39*, 7027–7030; c) D. J. Hlasta, J. H. Ackerman, *J. Org. Chem.* **1994**, *59*, 6184–6189; d) F. Palacios, A. M. Ochoa de Retana, J. Pagalday, *Heterocycles* **1994**, *38*, 95–102; e) W. H. Pearson, S. C. Bergmeier, J. A. Chytra, *Synthesis* **1990**, 156–159.

[79] a) A. Marzinzik, A. V. Gontcharov, K. B. Sharpless, unpublished results; b) R. Portmann (Novartis AG), WO-A 9802423, **1998** [*Chem. Abstr.* **1998**, *128*, 140707].

[80] a) T.-H. Chuang, K. B. Sharpless, *Helv. Chim. Acta* **2000**, *83*, 1734–1743; b) J. Svete, A. Preseren, B. Stanovnik, L. Golic, S. Golic-Gradadolnik, *J. Heterocycl. Chem.* **1997**, *34*, 1323–1328.

[81] a) P. Deslongchamps, Y. L. Dory, S. Li, *Tetrahedron* **2000**, *56*, 3533–3537, and references cited therein; b) orally available drugs must be stable to the acidic environment of the stomach. For acetal and ketal examples, see: M. Jung, S. Lee, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1003–1006; for ketoconazole, itraconazole, and derivatives, see: J. Heeres, L. J. J. Backx, J. H. Mostmans, J. Van Cutsem, *J. Med. Chem.* **1979**, *22*, 1003–1005; T. Bergan, *Antiinfect. Drugs Chemother.* **1995**, *13*, 149–150; N. Sonino, F. Fallo, M. Boscaro, *Med. Sci. Res.* **1989**, *17*, 131–134; J. Bolos, S. Gubert, L. Anglada, A. Sacristan, J. A. Ortiz, *J. Heterocycl. Chem.* **1997**, *34*, 1709–1713; L.-F. Huang, J.-W. Kim, L. Bauer, G. Doss, *J. Heterocycl. Chem.* **1997**, *34*, 469–476.

[82] Z. Demko, D. Michel, B. Chao, K. B. Sharpless, unpublished results.

[83] M. A. Winter, K. B. Sharpless, unpublished results.

[84] E. Stevens, A. V. Gontcharov, K. B. Sharpless, unpublished results.

[85] See ref. [40a] for 10- to 100-gram preparations of these crystalline aziridines.

[86] T. Fukuyama, C.-K. Jow, M. Cheung, *Tetrahedron Lett.* **1995**, *36*, 6373–6374.

[87] It should be noted that the simple 1,2-diamine motif is almost completely absent from that part of the ≤ 500-dalton drug candidate "universe" to have been explored so far, due to a woeful underutilization of the aziridine group as an intermediate in exploratory medicinal chemistry. For us, this omission highlights the vast regions of structural and functional "space"—the 10⁶³ candidates of Guida and co-workers in ref. [14]—that remain unexplored for the discovery of biologically active molecules.

[88] a) A. E. Rubin, PhD thesis, The Scripps Research Institute (USA), 1999; b) D. S. Nirschl, PhD thesis, The Scripps Research Institute (USA), 2000.

Angew. Chem. Int. Ed. **2001**, *40*, 2004–2021

2021