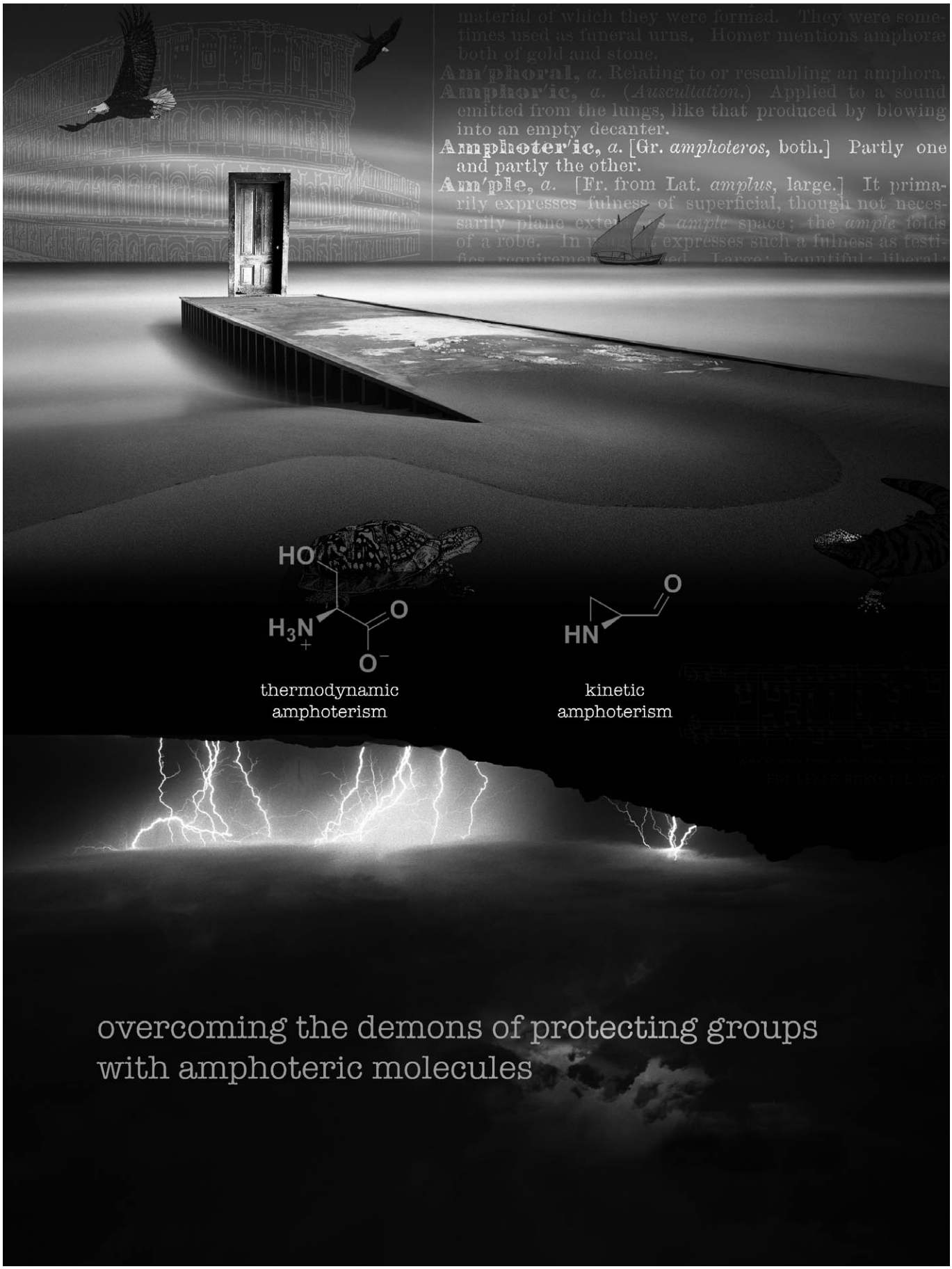
CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200700710



Overcoming the Demons of Protecting Groups with Amphoteric Molecules

Andrei K. Yudin* and Ryan Hili[a]

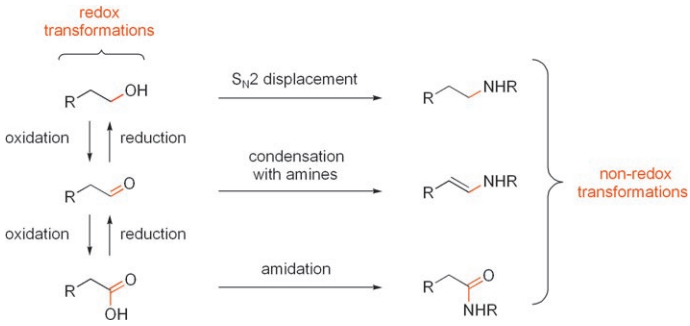
Dedicated to Professor George A. Olah on the occasion of his 80th birthday

Abstract: Synthetic organic chemists have long depended on protecting group manipulations when faced with the challenges of chemoselectivity and functional group incompatibility. Overcoming this dependence will improve the overall efficiency of chemical synthesis. By taking advantage of orthogonally reactive functional groups, *amphoteric* molecules can afford access not only to more efficient and strategic syntheses but also to the development of novel chemical transformations.

Keywords: amino aldehydes · amphoteric molecules · chemoselectivity · organic synthesis · protecting groups

Introduction

Despite a seemingly infinite amount of reactions that involve carbon-containing compounds, the vast majority can be divided into one of two large groups: reactions in which a carbon atom undergoes oxidation state change, and reactions in which its oxidation state remains unaffected. Each oxidation state of carbon has a set of reactions associated with it. A subset of reactions relevant to carbon–nitrogen bond formation illustrates this point (Scheme 1). For instance, primary alcohols can undergo nucleophilic displacement to generate amines, enolizable aldehydes can condense with amines giving enamines, whereas carboxylic acids can be converted into amides. Chemical synthesis of targets of varied complexity is an exercise in interspersing non-redox reactions with the carbon oxidation state adjustments. Chemoselectivity, defined as the preferential reaction of a chemical reagent with one of two or more different functional groups,[1] is one of the biggest challenges facing chemical synthesis. Avoiding the problems of chemoselectivity using protecting groups is commonplace, but comes at the expense of atom[2] and step economy.[3] In this regard, it is instructive to observe that biosynthesis avoids the chemoselectivity problems by molecular shape recognition.[4] The event of binding into an enzyme active site allows precise positioning of the functional group about to undergo transformation. In comparison, very few synthetic reagents obey the Michaelis–Menten kinetics. Instead, electronic and/or steric requirements of different functional groups present in a given reactant have to be taken into account in order to reach high levels of selectivity. Parameters such as pK_a, redox potential, and *A* values, are common metrics used by organic chemists in order to compare and predict reactivity of different molecules. None of these parameters come close to describing the overall property of a given molecule. In contrast, enzymatic systems are holistic in their approach to chemical transformations.



Scheme 1. Redox and non-redox domains of organic reactivity.

In order to find general solutions to protecting group-free synthesis,[5] one approach is to develop reagents and catalysts that emulate enzymatic efficiency with regard to chemoselectivity and practical turnover numbers. On the other hand, new ideas about interrelationships between functional groups are expected to play a significant role. In this article, we outline a strategy for executing orthogonal amine/carbonyl transformations, underscoring a seamless bridge to

[a] Prof. Dr. A. K. Yudin, R. Hili
Davenport Research Laboratories, Department of Chemistry
University of Toronto, 80 St. George Street
Toronto ON, M5S 3H6 (Canada)
Fax: (+1) 416-946-7676
E-mail: ayudin@chem.utoronto.ca

protecting group-free synthesis. In a broader sense, we contend that the search for molecules that are amphoteric on the grounds of kinetics is a useful approach to the discovery of new reactivity.

Discussion

In an ideal world, one would have a capability to chemoselectively manipulate molecules equipped with mutually reactive functional groups. In the realm of acid/base chemistry, the so-called amphoteric molecules have been known for some time. The term amphoteric is of Greek origin: *amphoteros* literally means "both of two".[6] Although the origin of the word is not related to any particular chemical property, this term has been mainly used in order to refer to a molecule that can act as both acid and base. For instance, amino acids are amphoteric compounds, characterized by an isoelectric point at which the molecule exists in its zwitterionic state (e.g. L-serine in Figure 1). Depending on pH, the position of proton can change, affecting the chemical behavior of the amino acid. Accordingly, amphoterism has belonged to the domain of thermodynamics since proton transfer is typically diffusion-limited. The thermodynamics of proton transfer can temporarily stabilize unstable molecules that contain nucleophilic and electrophilic centres. Fischer, who in 1908 prepared glycinal[7] from the reduction of its ester, demonstrated that protection of the amine functional group by proton at acidic pH stabilized the amino aldehyde, albeit briefly. More recently, Myers and co-workers[8] have used a similar method of amine protonation to establish the epimerization-free adduct formation between amino aldehydes with nucleophilic solvent molecules. When the pH of the medium was increased to value greater than 5, the amino aldehydes decomposed through self-condensation reactions.

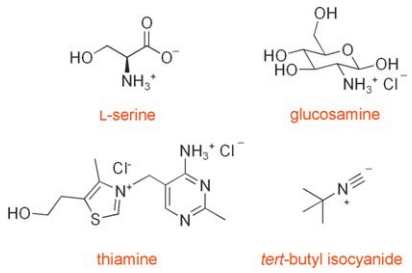
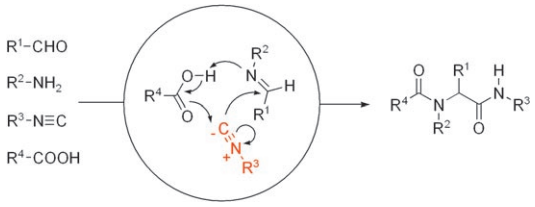


Figure 1. Selected examples of amphoteric molecules.

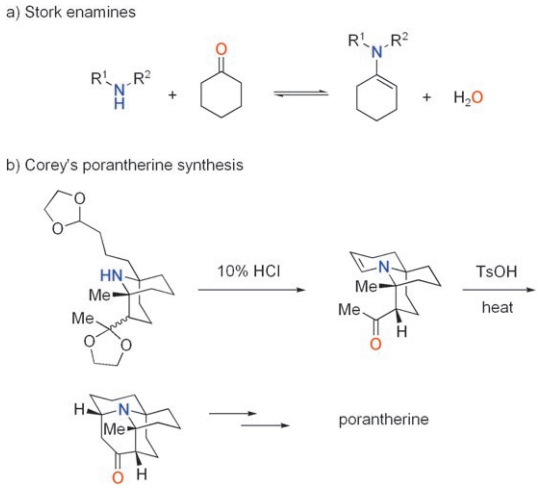
There are few examples of synthetically useful molecules one can consider amphoteric based on kinetic grounds. The most mechanistically instructive case is that of the isocyanide (Figure 1), first synthesized in 1859.[9] Two of the widely used multicomponent reactions owe their efficiency to the amphoteric nature of the isocyanide. The Passerini reaction involves a three component condensation between an isocyanide, an aldehyde, and a carboxylic acid to generate α-acyloxycarboxamides. By introducing another component—an amine—into the reaction, Ugi developed a four-component process, which is used to generate dipeptides and other valuable molecules.[10] The critical mechanistic point of this reaction is that the isocyanide carbon establishes a connection with both nucleophile (carboxylic acid) and electrophile (imine) (Scheme 2). The unique amphoteric nature of the isocyanide carbon centre facilitates the discovery of multicomponent processes using simple building blocks.[11]



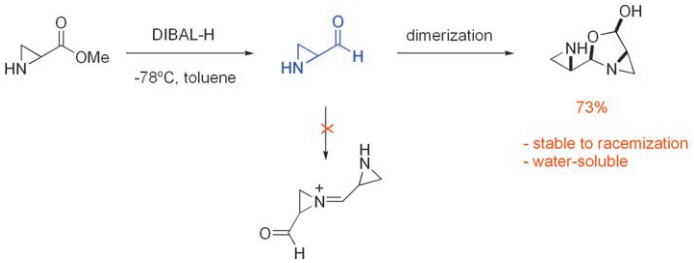
Scheme 2. Strategic significance of isocyanide in the Ugi four-component condensation.

We became interested in expanding the meaning of amphoterism to embrace kinetic considerations that govern nucleophile/electrophile chemistry. Recently, we initiated a search for molecules that contain unprotected functionalities that remain orthogonal to each other throughout their transformations. If these functionalities are reactive towards added reagents, there is a high probability to discover novel processes. In our search for new amphoteric molecules, we have focused our attention on the relationship between amine and carbonyl groups. The latter is arguably the most synthetically useful oxidation state of carbon (Scheme 1) since condensations between amines and carbonyl groups give rise to enamines, some of the most widely used synthetic intermediates.[12] Besides their utility as building blocks in target-oriented synthesis, enamines have many other important applications. For instance, many developments in an active area of current research, organocatalysis, depend on enamine generation for catalytic turnover.[13] Ironically, in the context of synthesis, enamine formation can be regarded as a limitation: due to their inherent reactivity, a secondary amine and an aldehyde or a ketone cannot be carried through a synthetic sequence in their unprotected forms. Unveiling a secondary amine in the presence of an aldehyde or a ketone is done when an instant condensation resulting in an iminium/enamine system is desired (Scheme 3). It is easy to see that if the unprotected derivatives were to have a kinetic barrier against condensation, they would afford a number of strategic as well as tactical advantages.

We hypothesized that an increase in strain upon converting the simplest nitrogen heterocycle, NH aziridine, into an iminium ion should decrease the rate of its formation from an aldehyde. Accordingly, unprotected aziridine aldehydes were prepared by simple reduction of aziridine esters (Scheme 4).[14,15] Upon formation, the aziridine aldehydes dimerize to give stable products that were found to act as aldehydes under suitable reaction conditions. In doing so, we



Scheme 3. Amine/carbonyl reactivity: useful at the right time.



Scheme 4. Synthesis of aziridine aldehyde dimers from aziridine esters.

have generated bench-stable molecules equipped with secondary amine and aldehyde functionalities that resist iminium ion formation from the dimeric amino acetal adduct. The aziridine aldehydes were found to be stable towards epimerization. Because aziridine ring can be regarded as a stepping stone towards a wide variety of amines via well documented ring-opening chemistry,[16] these unprotected building blocks provide a solution to broad challenges faced by protected amino aldehydes[17] in complex amine transformations. Interestingly, the only prior mentioning of unprotected aziridine aldehydes was in the work by Rheinhoudt, who isolated a monomeric aziridine–aldehyde species as an unstable by-product that decomposed during purification.[18]

Which pattern of reactivity can be expected of a kinetically amphoteric molecule? Under the conditions where the orthogonal nodes of reactivity (indicated as Nu and E in Figure 2) behave independently, attack by an external nucleophile (Nu^1 in Figure 2a) should lead to a *nascent* electrophile that should undergo cyclization. The overall process can also be initiated at the other end of the molecule if the external party is of electrophilic character. The ensuing relay will then be driven by a *nascent* nucleophile. Importantly, upon reaction with an amphoteric molecule, all subsequent nucleophile/electrophile interactions are no longer orthogonal and should proceed with favourable kinetics. Each of these processes can incorporate non-trivial steps, such as skeletal rearrangements. It is therefore possible to imagine that many complex reactions can be designed using this simple principle. As a realization of just one of many possibilities, we reported construction of pentacyclic molecules reminiscent of many complex alkaloid skeletons[19] from aziridine aldehydes in one step (Scheme 5). In the course of the reaction, iminium ion formation is followed by intramolecular attack of the indole to generate a spirocyclic intermediate. Subsequently, the aziridine nitrogen adds to the iminium ion to generate the final product. As a result, the bis-nucleophilic *N*-benzyltryptamine acts as a precursor to a bis-electrophile through the action of an amphoteric aziridine aldehyde.

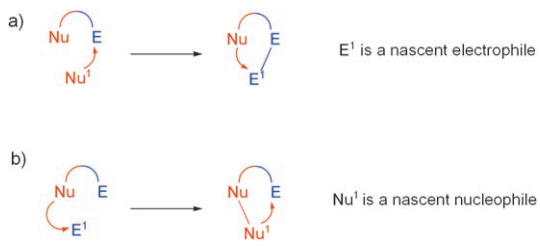
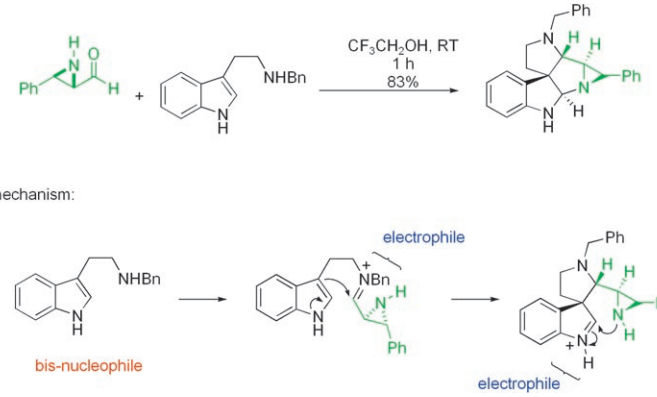


Figure 2. Nascent reactivity triggered by amphoteric molecules.



Scheme 5. One-step synthesis of complex heterocycles from amphoteric aziridine aldehydes.

Concluding Remarks

In effort to discover new reactivity, organic chemists strive to separate kinetic and thermodynamic factors. We have shown that imposing kinetic barriers on functional groups that are known to engage in irreversible and thermodynamically favourable processes can lead to stable molecules in which reactive functional groups remain orthogonal to each other. This concept was demonstrated on a specific example of an aziridine/aldehyde system that does not display iminium ion chemistry on the basis of excess strain in the intermediate iminium ion. Other combinations of functional groups that satisfy the criteria of amphoterism on kinetic grounds are likely to be identified. In fact, many of them al-

ready exist (Figure 1), but their utility in the context of chemoselective synthetic operations has been under-appreciated. Upon identification of the amphoteric pair of functional groups, one can also anticipate creating a myriad of homologous molecules in which additional functional groups separate the opposing nodes of reactivity. The amphoteric nature of these compounds can lead to high bond-forming efficiency indexes[20] and rapid generation of complex molecular skeletons. Thereby, the amphoteric molecules will provide a seamless bridge to atom and step economy and may contribute to the development of useful waste-free technologies.

[1] IUPAC Compendium of Chemical Terminology, 2nd ed., **1997**.
[2] B. M. Trost, *Science* **1991**, *254*, 1471.
[3] P. A. Wender, M. P. Croatt, B. Witulski, *Tetrahedron* **2006**, *62*, 7505.
[4] R. Hili, A. K. Yudin, *Nat. Chem. Biol.* **2006**, *2*, 284.
[5] For recent discussions, see: a) R. W. Hoffman, *Synthesis* **2006**, 3531; b) P. S. Baran, T. J. Maimone, J. M. Richter, *Nature* **2007**, *446*, 404.
[6] Zell's popular encyclopedia; a universal dictionary of English language, science, literature and art by L. Colage, Philadelphia, T. E. Zell, **1871**.
[7] E. Fischer, *Chem. Ber.* **1908**, *41*, 1019.
[8] A. G. Myers, D. W. Kung, B. Zhong, *J. Am. Chem. Soc.* **2000**, *122*, 3236.
[9] W. Lieke, *Justus Liebigs Ann. Chem.* **1859**, *112*, 316.
[10] a) I. Ugi, A. Dömling, *Angew. Chem.* **2000**, *112*, 3300; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168; b) *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley, New York, **2005**.
[11] L. Weber, K. Illgen, M. Almstetter, *Synlett* **1999**, 161.
[12] *The Chemistry of Enamines* (Ed.: Z. Rappoport), New York, **1994**.
[13] a) B. List, *Chem. Commun.* **2006**, 819; b) G. Lelais, D. W. C. Macmillan, *Aldrichimica Acta* **2006**, *39*, 79.
[14] R. Hili, A. K. Yudin, *J. Am. Chem. Soc.* **2006**, *128*, 14772.
[15] L. Yu, A. Kokai, A. K. Yudin, *J. Org. Chem.* **2007**, *72*, 1737.
[16] *Aziridines and Epoxides in Organic Synthesis* (Ed.: A. K. Yudin), Wiley, New York, **2006**.
[17] a) J. Jurczak, A. Golebiowski, *Chem. Rev.* **1989**, *89*, 149; b) M. T. Reetz, *Angew. Chem.* **1991**, *103*, 1559; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531; c) F. J. Sardina, H. Rapoport, *Chem. Rev.* **1996**, *96*, 1825.
[18] M. L. M. Pennings, D. N. Rheinhoudt, S. Harkema, G. J. van Hummel, *J. Org. Chem.* **1983**, *48*, 486.
[19] M. Hesse, *Alkaloids: Nature's Curse or Blessing?*, Wiley, New York, **2002**.
[20] L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115.

Published online: July 10, 2007

