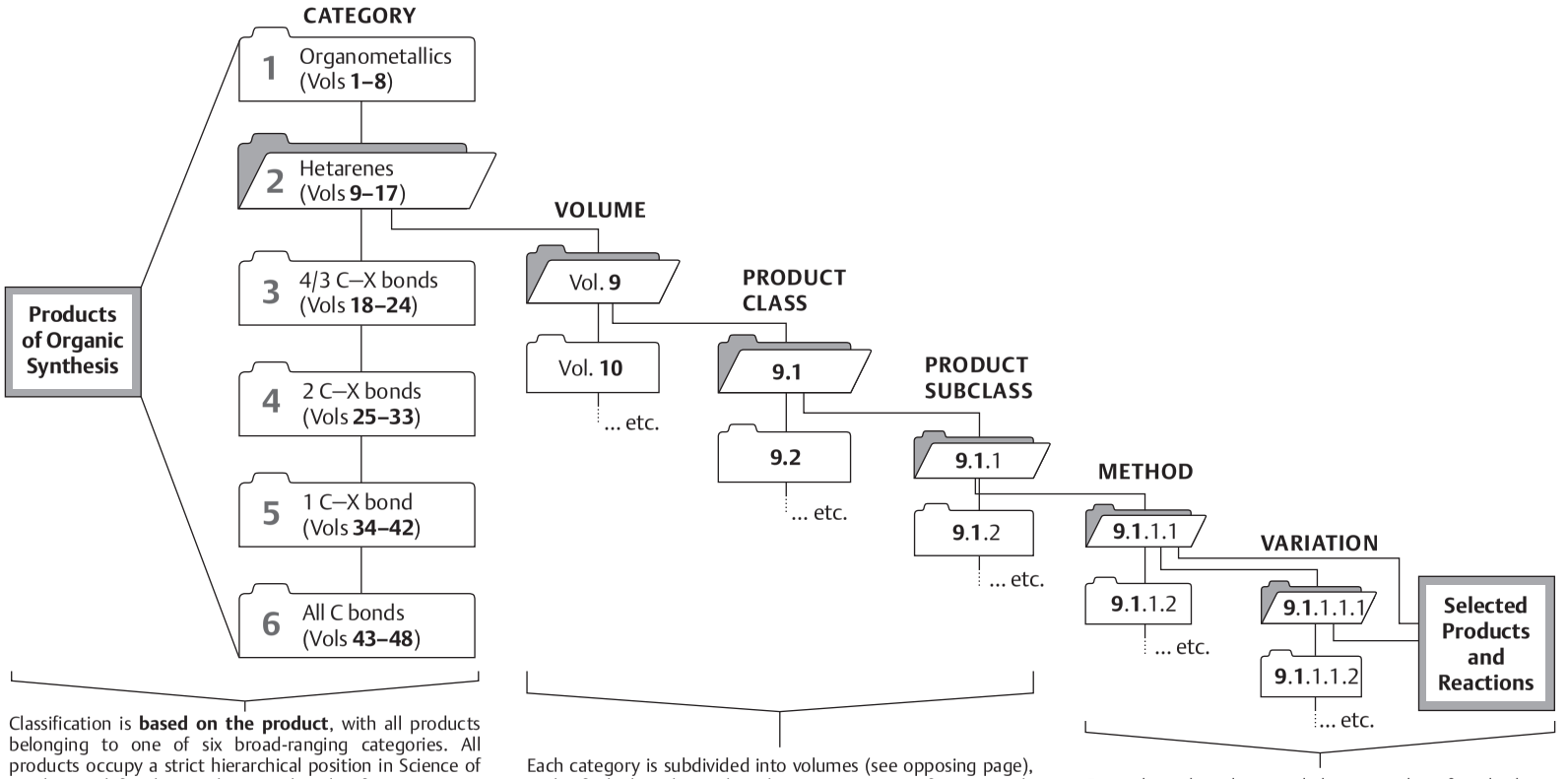
Science of Synthesis

Knowledge Updates 2013/3

Thieme

Organizational Structure of Science of Synthesis*

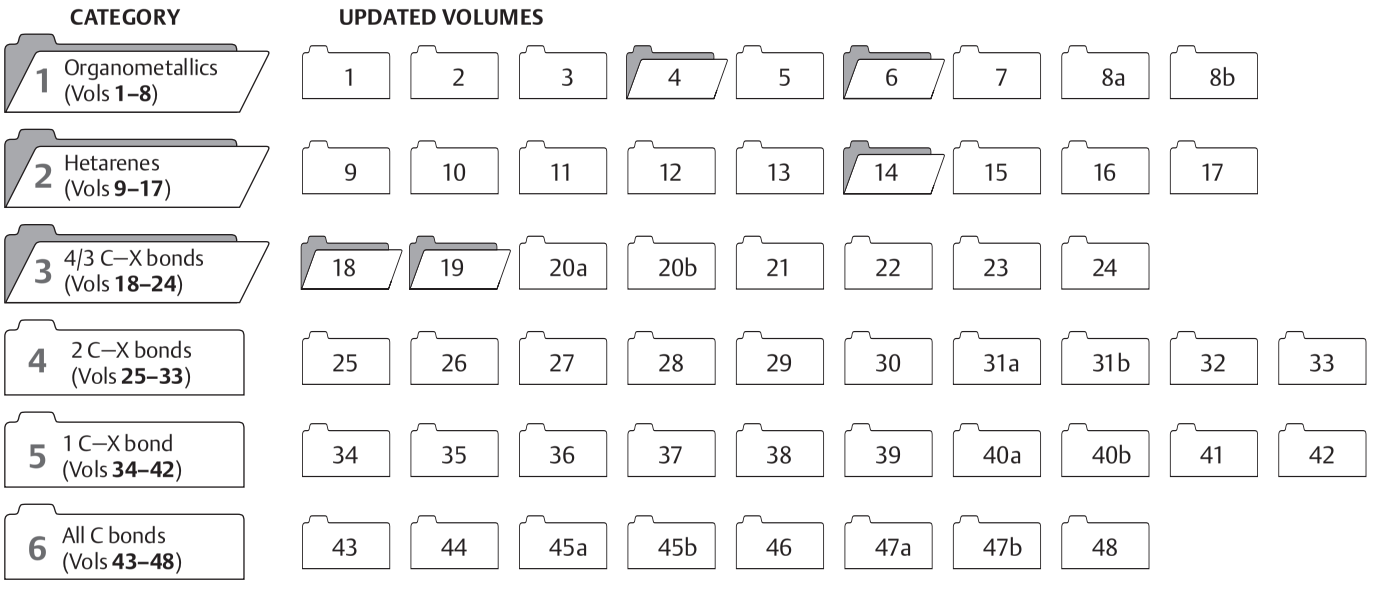
* A complete description of the full classification principles can be found in the **Science of Synthesis Guidebook.**



Classification is **based on the product**, with all products belonging to one of six broad-ranging categories. All products occupy a strict hierarchical position in Science of Synthesis, defined according to the classification principles*. Products in Categories 3–6 are organized according to oxidation state, with products containing the greatest number of carbon–heteroatom (C—X) or C—C π-bonds to a single carbon occupying the highest positions (e.g., carboxylates, enolates, and alcoholates are covered in Categories 3, 4, and 5, respectively).

Each category is subdivided into volumes (see opposing page), each of which is devoted to discrete groupings of compounds called **product classes** (e.g., "Thiophenes" is Product Class 10 of Volume 9). Product classes may be further subdivided into **product subclasses**, (e.g., "Thiophene 1,1-Dioxides" is Product Subclass 3 of Product Class 10 of Volume 9). Consequently, the relationship between heading name and heading number varies below product class level within individual volumes.

For each product class or subclass, a number of methods are described for synthesizing the general product type. Often there are variations on a method given. Both methods and variations contain experimental procedures with relevant background information and literature references. **Selected products and reactions** display the scope and limitations of the methods.



4 Compounds of Group 15 (As, Sb, Bi) and Silicon Compounds
6 Boron Compounds
14 Six-Membered Hetarenes with One Chalcogen
18 Four Carbon–Heteroatom Bonds: X–C≡X, X=C=X, X_2C=X, CX_4
19 Three Carbon–Heteroatom Bonds: Nitriles, Isocyanides, and Derivatives

* Detailed listings of product classes and subclasses, methods, and variations can be found in the **Table of Contents** sections of every volume.

Science of Synthesis

Science of Synthesis is the authoritative and comprehensive reference work for the entire field of organic and organometallic synthesis.

Science of Synthesis presents the important synthetic methods for all classes of compounds and includes:

- Methods critically evaluated by leading scientists
- Background information and detailed experimental procedures
- Schemes and tables which illustrate the reaction scope

Science of Synthesis

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Preface

As the pace and breadth of research intensifies, organic synthesis is playing an increasingly central role in the discovery process within all imaginable areas of science: from pharmaceuticals, agrochemicals, and materials science to areas of biology and physics, the most impactful investigations are becoming more and more molecular. As an enabling science, synthetic organic chemistry is uniquely poised to provide access to compounds with exciting and valuable new properties. Organic molecules of extreme complexity can, given expert knowledge, be prepared with exquisite efficiency and selectivity, allowing virtually any phenomenon to be probed at levels never before imagined. With ready access to materials of remarkable structural diversity, critical studies can be conducted that reveal the intimate workings of chemical, biological, or physical processes with stunning detail.

The sheer variety of chemical structural space required for these investigations and the design elements necessary to assemble molecular targets of increasing intricacy place extraordinary demands on the individual synthetic methods used. They must be robust and provide reliably high yields on both small and large scales, have broad applicability, and exhibit high selectivity. Increasingly, synthetic approaches to organic molecules must take into account environmental sustainability. Thus, atom economy and the overall environmental impact of the transformations are taking on increased importance.

The need to provide a dependable source of information on evaluated synthetic methods in organic chemistry embracing these characteristics was first acknowledged over 100 years ago, when the highly regarded reference source **Houben–Weyl Methoden der Organischen Chemie** was first introduced. Recognizing the necessity to provide a modernized, comprehensive, and critical assessment of synthetic organic chemistry, in 2000 Thieme launched **Science of Synthesis, Houben–Weyl Methods of Molecular Transformations**. This effort, assembled by almost 1000 leading experts from both industry and academia, provides a balanced and critical analysis of the entire literature from the early 1800s until the year of publication. The accompanying online version of **Science of Synthesis** provides text, structure, substructure, and reaction searching capabilities by a powerful, yet easy-to-use, intuitive interface.

From 2010 onward, **Science of Synthesis** is being updated quarterly with high-quality content via **Science of Synthesis Knowledge Updates**. The goal of the **Science of Synthesis Knowledge Updates** is to provide a continuous review of the field of synthetic organic chemistry, with an eye toward evaluating and analyzing significant new developments in synthetic methods. A list of stringent criteria for inclusion of each synthetic transformation ensures that only the best and most reliable synthetic methods are incorporated. These efforts guarantee that **Science of Synthesis** will continue to be the most up-to-date electronic database available for the documentation of validated synthetic methods.

Also from 2010, **Science of Synthesis** includes the **Science of Synthesis Reference Library**, comprising volumes covering special topics of organic chemistry in a modular fashion, with six main classifications: (1) Classical, (2) Advances, (3) Transformations, (4) Applications, (5) Structures, and (6) Techniques. Titles will include *Stereoselective Synthesis*, *Water in Organic Synthesis*, and *Asymmetric Organocatalysis*, among others. With expert-evaluated content focusing on subjects of particular current interest, the **Science of Synthesis Reference Library** complements the **Science of Synthesis Knowledge Updates**, to make **Science of Synthesis** the complete information source for the modern synthetic chemist.

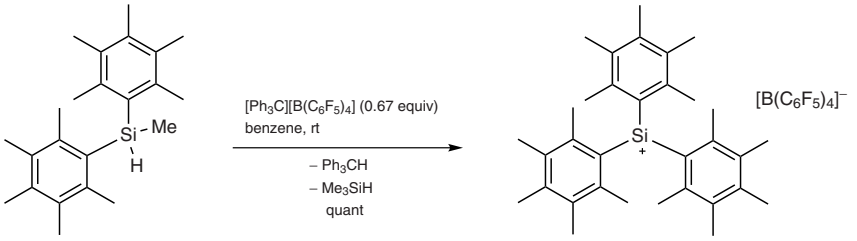
The overarching goal of the **Science of Synthesis** Editorial Board is to make the suite of **Science of Synthesis** resources the first and foremost focal point for critically evaluated information on chemical transformations for those individuals involved in the design and construction of organic molecules.

Throughout the years, the chemical community has benefited tremendously from the outstanding contribution of hundreds of highly dedicated expert authors who have devoted their energies and intellectual capital to these projects. We thank all of these individuals for the heroic efforts they have made throughout the entire publication process to make **Science of Synthesis** a reference work of the highest integrity and quality.

The Editorial Board July 2010

Abstracts

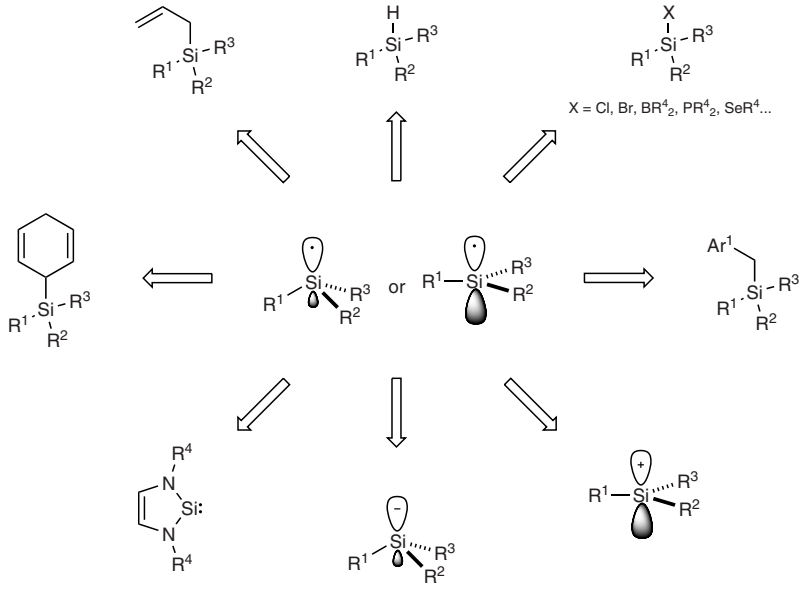
This chapter describes methods for the synthesis of silylium ions and silylium ions stabilized by direct interaction with solvents or counteranions. The applications of these species in Lewis acid catalysis and in bond-activation processes are also summarized.



Keywords: C—F bond activation · borates · Brønsted acids · carbocations · C—Si bonds · hydrosilylation · Lewis acid catalysts · onium ions · silanes · silicon compounds · silyl cations · solvent effects

Silyl radicals are short-lived species that have found widespread use in various areas, including organic and polymer chemistry and, more recently, material science. These silicon-centered radicals are generated from various sources, including silyl hydrides, disilanes, allylsilanes, silyl halides, and silylenes, and by carbon—heteroatom bond cleavage. Silyl radicals are intermediates in important transformations such as hydrosilylation and reduction processes. They add to unsaturated systems (including alkenes, alkynes, arenes, and carbonyl derivatives) with high rate constants, generating carbon-centered radicals which are then involved in subsequent transformations. The understanding of steric and electronic properties of silyl radicals now allows a better prediction of their reactivity. Silyl radical precursors, such as silyl hydrides, are thus commonly used in the synthesis of complex targets including natural products. These radicals efficiently trigger complex radical cascades as well as rearrangements processes, opening an access to elaborate

architectures that would be otherwise difficult to access. Finally, silyl radicals are key intermediates in the functionalization of silicon surfaces, which have recently received a lot of interest due to the importance of organic films for applications as biomaterials and biochips.



Keywords: radicals · silyl hydrides · abstraction · disilanes · allylsilanes · hydrogen transfer · homolytic substitution · silylenes · silyliums · polarity-reversal catalysis

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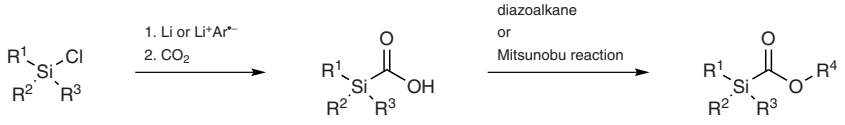
4.4.45 **Product Subclass 45: Silanecarboxylic Acids and Esters**

K. Igawa and K. Tomooka

Silanecarboxylic acids having a carboxy group on the silicon atom are synthesized from chlorosilanes via their reductive lithiation and subsequent carboxylation with carbon dioxide. Silanecarboxylic acid esters are synthesized from silanecarboxylic acids by O-alkylation with diazoalkanes or by the Mitsunobu reaction with alcohols.



Keywords: silanecarboxylic acids · silanecarboxylic acid esters · reductive lithiation · carboxylation · esterification

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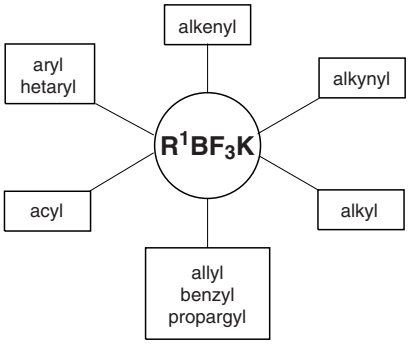
6.1.6 **Product Subclass 6: Haloborates**

G. A. Molander and F. Beaumard

This chapter is a revision of the earlier *Science of Synthesis* contribution describing methods for the synthesis of haloborates. It focuses on the synthesis of organotrifluoroborates and highlights methods published between 1999 and 2013.



Keywords: organotrifluoroborates · organoboron compounds · C—B bonds · C—H bond activation · hydroboration · transmetalation · borylation

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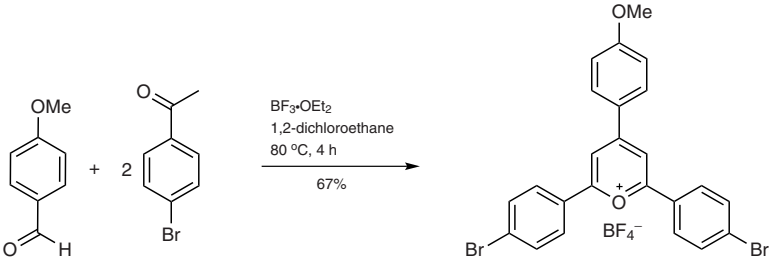
14.1.5 **Pyrylium Salts**

A. T. Balaban and T. S. Balaban

This update covers the literature from 2000 to the end of 2011; it also includes a few references from 1999 that were not discussed in the original *Science of Synthesis* review of pyrylium salts. In addition to methodologies for preparing pyrylium salts, some new applications of these compounds are also described.



Keywords: pyrylium salts · aldehydes · ketones · 1,5-diones · cyclization · aromatization

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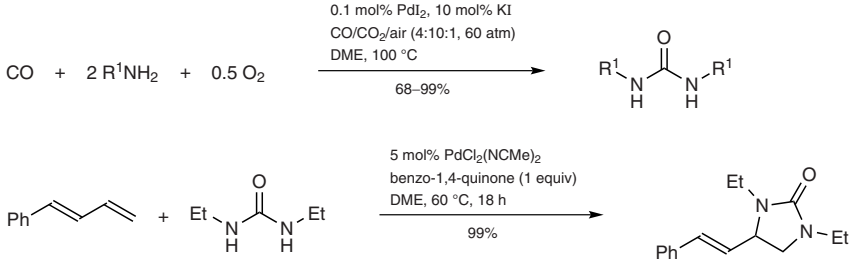
18.8.22 **Acyclic and Cyclic Ureas**

S. Kubik

This update summarizes synthetic approaches to acyclic and cyclic ureas, as well as nonfunctionalized and functionalized derivatives. Syntheses of various urea derivatives are presented that were either not covered, or not treated in such detail, in the earlier *Science of Synthesis* contribution. For example, syntheses of imidazolidine-2,4-diones (hydantoins), 3,4-dihydropyrimidin-2(1*H*)-ones (Biginelli products), and pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones (barbiturates) are presented. The literature is covered between the years 2001 and 2012.



Keywords: barbiturates · Biginelli reaction · carbamates · carbon dioxide · carbonylation · 1,2-diamination · hydantoins · isocyanates · multicomponent reactions · ureas

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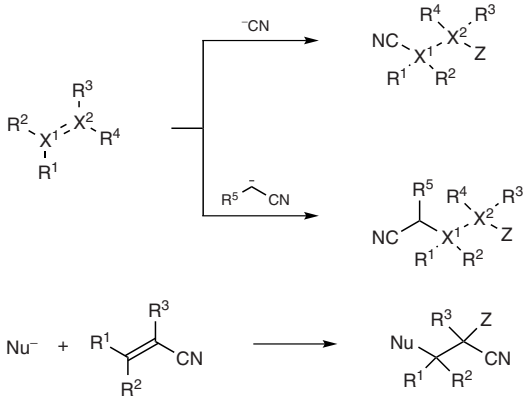
19.5.14.15 **Synthesis from Nitriles with Retention of the Cyano Group**

N. Mase

This is an update to the original Section 19.5.14, which deals with synthesis from nitriles with retention of the cyano group. In order to cover significant recent developments, this update focuses on organocatalytic reactions of nitriles. These reactions are classified into two reaction modes: (1) reactions of nucleophiles containing a cyano group with electrophiles, and (2) reactions of nucleophiles with electrophiles containing a cyano group. In this update, significant achievements made employing asymmetric organocatalysts from the years 2000–2012 are highlighted.



Keywords: organocatalysis · nitriles · cyanides · isocyanides · cyanation · nucleophilic addition · nucleophilic substitution · one-pot processes

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Volume 14: Six-Membered Hetarenes with One Chalcogen

Volume 18: Four Carbon—Heteroatom Bonds: X—C≡X, X=C=X, $X_2C=X$, CX_4

Volume 19: Three Carbon—Heteroatom Bonds: Nitriles, Isocyanides, and Derivatives

4.4.43 Product Subclass 43: Silylium Ions and Stabilized Silylium Ions

T. Müller

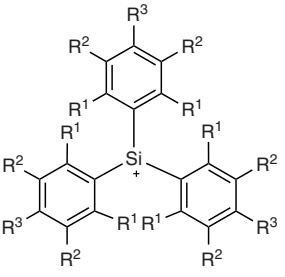
General Introduction

Silylium ions [R_3Si^+] are tricoordinate silicon species with a positively charged silicon atom. The central silicon atom adopts a trigonal planar coordination environment with R—Si—R bond angles close to the ideal value of 120°. The vacant p-type molecular orbital at the central silicon atom is oriented perpendicular to the R_3Si plane. Therefore, these six-valence electron species are isostructural and isolobal to boranes [R_3B] and they are the silicon analogues of classical carbenium ions [R_3C^+]. The history of their synthesis and chemistry has been repeatedly reviewed over the past few decades, describing both transient and stable representatives.[1–9] Carbenium ions are frequent intermediates in many chemical transformations in carbon chemistry, and their existence was recognized and firmly established in 1901.[10,11] In contrast, in organosilicon chemistry, there are only a few examples of reactions with silylium ions as established intermediates, and the first conclusive evidence for a silylium ion in condensed media was only found in 1997.[12,13] This striking difference between these two so closely related species is not a result of the thermodynamic instability of the silicon compound. On the contrary, the silicon cation [R_3Si^+] is, for most of the synthetically important substituents R, more stable than the corresponding carbenium ion [R_3C^+].[8] The major obstacle to the formation of silylium ions in the condensed phase is their high electrophilicity and, as a consequence, their high reactivity toward any nucleophile. The lower electronegativity of silicon compared to carbon leads to an accumulation of positive charge at the central silicon atom for every organic substituent R. This accretion of positive charge is not dispersed by π-conjugation and/or hyperconjugative effects due to less-effective orbital overlap between the silicon atom and the carbon substituents. The larger size of the silicon atom means that steric protection by bulky substituents is less effective than for carbocations, and it allows extension of the coordination sphere at silicon to coordination numbers larger than 4. For these reasons many reactions in organic chemistry that proceed by a dissociative S_N1-type mechanism will in organosilicon chemistry follow an associative course via pentacoordinated transition states or even intermediates. Furthermore, these are also factors that severely hamper the synthesis of silylium ions unfettered by interactions with solvent or counteranion. Silylium salts are prepared by synthetic approaches that are different from those well established in carbon chemistry (see Sections 4.4.43.1–4.4.43.6). The use of unusual solvents for ionic compounds, such as aromatic hydrocarbons, or silanes paired with the application of very robust and extremely weakly coordinating anions {e.g., fluorinated tetraphenylborates of the type $[B(C_6F_{5-n}R^1{}_n)_4]^-$ ($R^1 = SiR^2{}_3$, H; n = 0, 1), or halogenated *closo*-carborates $[HCB_{11}H_{11-n}X_n]^-$ (X = Cl, Br, I; n = 6, 11) or -borates $[B_{12}X_{12}]^{2-}$ (X = Cl, Br)} are absolute prerequisites for their successful generation and isolation.[14,15] As a consequence, only a small number of silylium ions have been synthesized that are fully consistent with the textbook definition of a trigonal planar coordinated silylium ion [R_3Si^+].[12,16–18] These cations **1** are substituted with three bulky aryl groups to prevent reactions with nucleophiles and only one alkyldiarylsilylium ion **2** has been prepared (Scheme 1). In addition, several silylium ions **3–6** in which the positively charged silicon atom is part of a delocalized π-system are known (Scheme 1).[19–23] From the viewpoint of synthetic chemistry, the enormous Lewis acidity, in particular of the aryl-substituted

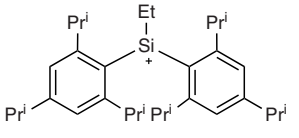
for references see p 40

ions **1** and **2**, is interesting, but the bulky substituents, essential for their successful synthesis, and their high reactivity severely hamper their application in organic synthesis (see, however, Section 4.4.43.10). Silylium ions are easily identified spectroscopically by their ^{29}Si NMR resonance at very low field. For cation **2** a resonance at $\delta^{29}Si = 245$ is reported and the triarylsilylium ions **1** are characterized by ^{29}Si NMR chemical shifts at $\delta^{29}Si = 230–216$.[18] For the silicon atoms in aromatic **3** and homoaromatic **4**, an even stronger deshielding effect is noticed [i.e., $\delta^{29}Si = 316$ for the central tricoordinated silicon atom in the homoaromatic cation **4** and $\delta^{29}Si = 208–288$ in the trisilacyclopropenium ion **3** (Z = Si)].[19–21]

Scheme 1 Stable Silylium Ions[12,16–23]



1 R^1 = Me; $R^2 = R^3$ = H
$R^1 = R^3$ = Me; R^2 = H
$R^1 = R^2$ = Me; R^3 = H
$R^1 = R^2 = R^3$ = Me
$R^1 = R^3$ = iPr; R^2 = H



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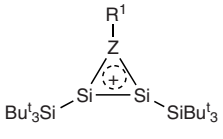
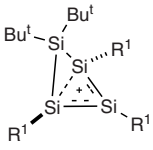
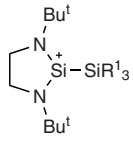


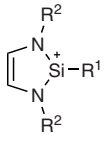
3 Z = Si; R^1 = SiMe*t*-Bu_2
Z = C; R^1 = 1-adamantyl



4 R^1 = SiMe*t*-Bu_2



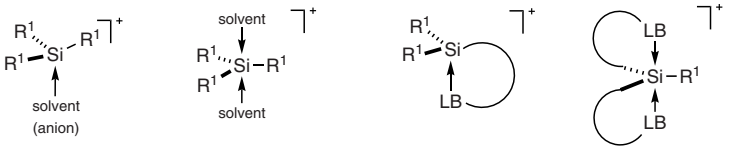
5 R^1 = Et, iPr



6 $R^1 = CH(SiMe_3)_2$; R^2 = *t*-Bu
$R^1 = SiEt_3$; R^2 = *t*-Bu, 2,6-$Me_2C_6H_3$, 2,6-$iPr_2C_6H_3$
$R^1 = Si(iPr)_3$; R^2 = *t*-Bu, 2,6-$Me_2C_6H_3$, 2,6-$iPr_2C_6H_3$

The synthetic efforts toward the isolation of silylium salts with an ideal trigonal planar coordinated positively charged silicon atom created a series of stabilized silyl cations in which either the interaction with the solvent, the counteranion, or intramolecular donor groups pacifies the high reactivity of the silyl cations. This electron donation leads to cationic species **7** in which the silicon atom adopts a distorted tetrahedral coordination environment (Scheme 2). Siliconium ions **8**, in which the silicon atom has expanded its coordination number to 5 by addition of two solvent molecules, have been structurally characterized. Intermolecular species **7** and **8** as well as intramolecular variants **9** and **10**, which have both modes of stabilization, have been characterized.

Scheme 2 Different Modes of Stabilization for Silylium Ions

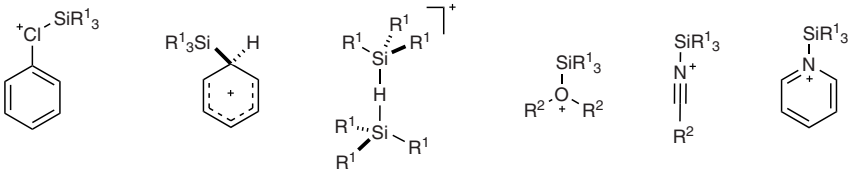


7 **8** **9** **10**

LB = Lewis basic group

Of particular interest are the solvent- or anion-stabilized tetracoordinated silyl cations **7**. In the case of the solvent complexes **11–16**, structural and/or NMR spectroscopic data clearly indicate a covalent interaction between the solvent and the silylium ion (Scheme 3). For example, cations **12** should be described as silylated arenium ions, as indicated by their ^{29}Si NMR chemical shifts of δ^{29}Si = 84 and 98 for R^1 = Me and Et, respectively.[8,23] Nevertheless, cations **12** as well as chloronium ions **11** and the bissilylated hydronium ions **13** are extremely valuable synthetic sources of silylium ions with an unmatched Lewis acidity. From a synthetic point of view, these species might be regarded as solvent-stabilized silylium ions. In particular, their reactivity is significantly greater than those of silylated oxonium ions **14**, nitrilium ions **15**, or pyridinium ions **16**. Benzenium ions **12** are usually prepared using the weakly coordinating perfluorinated tetraphenylborate anion $\{[B(C_6F_5)_4]^-\}$. Switching to carborates as counteranions results in the formation of carborate-stabilized silylium ions; for example, when using the 7,8,9,10,11,12-hexachloro-1-carba-*closo*-dodecaborate(1–) $\{[HCB_{11}H_5Cl_6]^-\}$ anion the silylium carborate **17** is formed (Scheme 4). Extended structural studies of **17** and several related halogenated carborates and borates reveals in each case close contact between one halogen atom of the carborate anion and the silicon atom. This leads to a distorted tetrahedral coordination environment for the silicon atom.[8,24,25] The zwitterionic nature of the silylium carborate **17** is also reflected by the relatively small ^{29}Si NMR chemical shift (δ^{29}Si = 103 in benzene-d_6) compared to that of free silylium ions. This ^{29}Si NMR chemical shift is, however, significantly different from that measured for triisopropylsilylium tetrakis(pentafluorophenyl)borate $\{[iPr_3Si][B(C_6F_5)_4]\}$ in the same solvent (δ^{29}Si = 108).[8] This suggests that, depending on the weakly coordinating anion, different silyl cationic species are present in benzene solution. Although the interaction between the carborate anion and the silicon atom determines the structure and spectroscopic properties of these silylium carborates and distinguishes them from the free silylium ion, they represent possibly the nearest approach to simple trialkyl-substituted silylium ions in the condensed phase. Their high ability for silyl group transfer and their unprecedentedly high Lewis acidity, which outperforms by far those of the conventionally covalently bonded silyl Lewis acids **18–20**, justifies, from a synthetic point of view, their being described as anion-stabilized silylium ions.

Scheme 3 Examples of Solvent-Stabilized Silylium Ions[8]



11 **12** **13** **14** **15** **16**

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