[27] Lankacyclinol (**1**): $R_f = 0.25$ in acetone/benzene (1/1); 0.21 in methyl ethyl ketone/ethyl acetate (2/8); mp 220 °C (uncorrected); synthetic **1**: $[\alpha]_D^{25} -163°$ ($c = 0.3$, EtOH), natural **1**: $[\alpha]_D^{25} -165°$ ($c = 0.35$, EtOH); IR (EtOH) $\tilde{\nu}_{max}$ 3422, 3096, 2996, 1661, 1624, 1105, 1078 cm^{-1}; ^1H NMR (500 MHz, [d_6]acetone): $\delta = 7.18$ (d, $J = 9.5$ Hz, NH), 6.56 (t, $J = 7.8$ Hz, 1H), 5.98 (d, $J = 15.6$ Hz, 1H), 5.70 (d, $J = 15.9$ Hz, 1H), 5.38 (dd, $J = 15.6$, 7.87 Hz, 1H), 5.32 (dd, $J = 15.9$, 7.87 Hz, 1H), 5.22–5.18 (m, 2H), 5.05 (q, $J = 9.9$ Hz, 1H), 4.28–4.20 (m, 1H), 4.10–4.00 (m, 3H), 3.66–3.60 (m, 1H), 2.60–2.54 (m, 2H), 2.42–2.36 (m, 1H), 2.28–2.19 (m, 1H), 1.70 (s, 3H), 1.64 (s, 3H), 1.52 (s, 3H), 1.29 (d, $J = 6.8$ Hz, 3H), 0.95 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (125 MHz, [d_6]acetone): $\delta = 203.2$, 174.64, 139.13, 137.88, 136.29, 135.73, 134.73, 131.76, 131.72, 130.04, 129.07, 74.48, 72.65, 68.97, 49.67, 43.79, 42.44, 38.54, 37.42, 21.74, 16.16, 13.23, 12.66, 12.55; MS (DCI/CH_4), m/z (%) 418 (4) [M^+], 400 (6) [$M^+ - H_2O$]; HR-MS (DCI/CH_4): calcd for $C_{24}H_{36}NO_5$ [MH^+]: 418.2593, found: 418.2573.

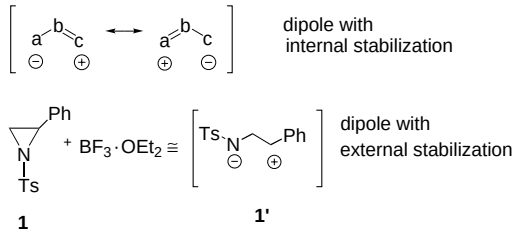
Phenylaziridine as a Masked 1,3 Dipole in Reactions with Nonactivated Alkenes**

Ioana Ungureanu, Philippe Klotz, and André Mann*

In memory of Toshiro Ibuka

Aziridines are known to react with a wide variety of nucleophiles, and their ability to undergo regioselective ring-opening reactions contributes largely to their synthetic value.[1] In our previous work, we disclosed a new type of reactivity for phenylaziridine **1**, a formal [3+2] dipolar cycloaddition on *activated* double bonds (Ts = tosyl = *p*-toluenesulfonyl). Phenylaziridine **1** reacts with allylsilanes[2] or dihydropyran (DHP)[3] in the presence of a Lewis acid to produce highly substituted pyrrolidines. This type of reactivity for aziridines has been noticed before, but has never been systematically investigated.[4]

We concluded that in the presence of $BF_3 \cdot Et_2O$ at −78 °C, **1** reacts via **1′**, a rather uncommon 1,3 dipole (Scheme 1). The two charges of **1′** are isolated by an sp^3-hybridized carbon atom, and therefore, according to Huisgen, an internal stabilization by delocalization, as found in classical 1,3 dipoles,

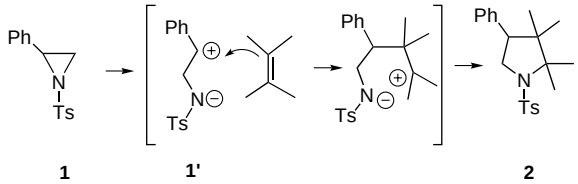


Scheme 1. Possible modes of dipole stabilization.[5]

is not possible.[5] In contrast, **1′** is stabilized externally by the double contributions of the aromatic ring and the arylsulfonyl group. Thus, following the Huisgen classification **1′** can be considered as a zwitterionic 1,3 dipole.[5] More interestingly, **1′** is electron deficient and should thus react with electron-rich partners. Therefore we wondered if **1** reacts with *nonactivated* olefinic double bonds.

Herein we present our results on the reactivity of **1** with alkenes. This new use of **1** as a 1,3-dipole precursor is an advance on our recent work,[3] and of importance, not only from its theoretical, but also from its preparative significance in providing direct access to substituted pyrrolidines.

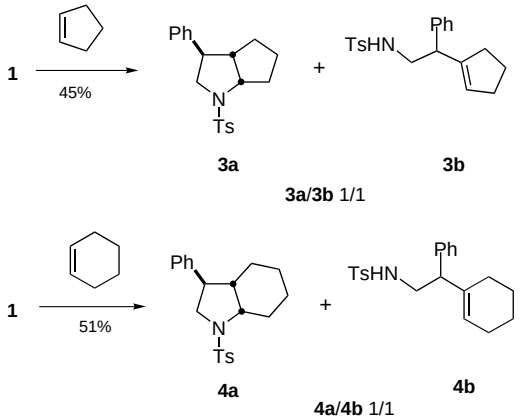
To avoid undesirable problems with regioselectivity we first considered a symmetrically substituted alkene.[6] Therefore we chose to react tetramethylethylene with **1** in the presence of $BF_3 \cdot Et_2O$ in CH_2Cl_2 at −78 °C (the same experimental conditions were used for all reactions with **1**). A fast reaction took place and the only isolated product was the pyrrolidine **2** in 92% yield (Scheme 2).



Scheme 2. Reaction of **1** with tetramethylethylene.

This result shows that **1′** is electron deficient enough to react even with a *nonactivated* alkene. The dipole **1′** is produced at −78 °C, the olefinic π system attacks at the benzylic position giving rise to a stable tertiary carbocation, ready for a ring closure with the adjacent amide. This process constitutes a formal [3+2] cycloaddition that is useful for the synthesis of 2,2,3,3-tetrasubstituted pyrrolidines.

To explore the generality of this heterocyclization, we examined the reactivity of **1** towards cyclopentene and cyclohexene. We identified for each alkene a pair of product compounds **3a**/**3b** and **4a**/**4b**, formed in a 1/1 ratio in a total yield around 50% (Scheme 3). The bicyclic adducts **3a** and **4a** are isolated as single diastereomers, and their relative



Scheme 3. Reaction of **1** with cycloalkenes.

[*] Dr. A. Mann, I. Ungureanu, P. Klotz
Laboratoire de Pharmacochimie de la Communication Cellulaire
UMR 7081, Faculté de Pharmacie
74 route du Rhin, BP 24, 67401 Illkirch (France)
Fax: (+33) 3-88-67-47-94
E-mail: andre.mann@pharma.u-strasbg.fr

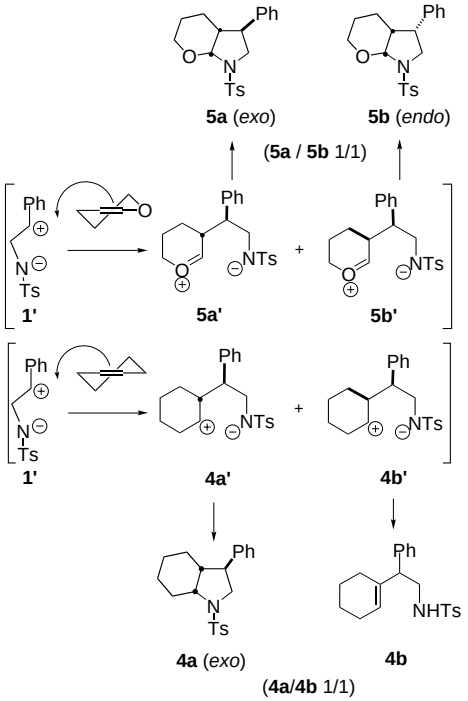
[**] We thank Professor C. G. Wermuth for stimulating discussions.

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

  1433-7851/00/3924-4615 $ 17.50+.50/0

configurations found to be *exo* by single-crystal X-ray analysis.[7]

To investigate the diastereoselectivity of this reaction, we recall that **1** reacts with DHP giving **5a** and **5b** in a 1/1 ratio (Scheme 4).[3] As the steric hindrance at C1 of cyclohexene and C3 of DHP are alike, we can consider that similar stereoelectronic factors govern the two processes, that is, **4a′** and **4b′** should be formed in the same ratio as **5a′** and **5b′**.

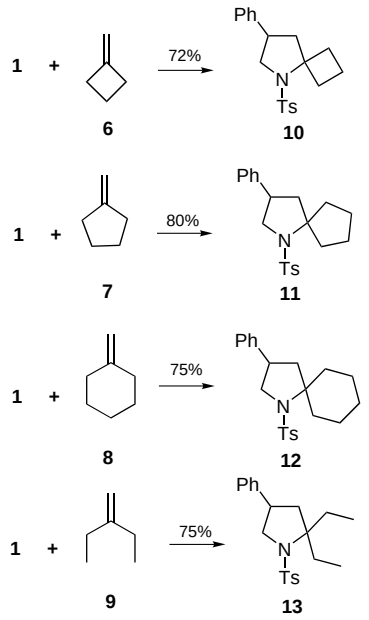


Scheme 4. Diastereoselectivity of the reaction of **1** with dihydropyran and cyclohexene.

The transient carbocations in **4a′**/**4b′** are not stabilized as they are in **5a′** /**5b′**, and side reactions can occur, competing with the formation of **4a**/**4b**. The intermediate dipole **4b′** prefers to eliminate, the ring closure is disfavored, probably for steric reasons. The formation of **3a**/**3b** and **4a**/**4b** in a 1/1 ratio, supports our argumentation. The same explanation can be evoked to account for the formation of **3a** and **3b** in a 1/1 ratio.

Since the nature and the yield of the products obtained in the reaction of **1** with olefins depend on the stability of the carbocation in the 1,5-zwitterionic intermediates, we decided to use geminal disubstituted alkenes. If the reaction pathway is conserved, a more stable, tertiary carbocation is expected in the transition state, and the heterocyclization should be favored. Indeed the olefins **6**–**8**, containing an exocyclic double bond, and the structurally similar open-chain compound **9**, react cleanly with **1**, under the usual conditions, to yield the spiropyrrolidines **10**–**12** and the geminal disubstituted pyrrolidine **13** as the only isolated products (Scheme 5).

To the best of our knowledge, this type of spiroannulation is without precedent. The good yields obtained support our hypothesis that heterocyclization is favored over elimination if the lifetime of the 1,5-zwitterionic intermediate is long



Scheme 5. Reaction of geminal disubstituted alkenes.

enough. Clearly the tertiary carbocations generated by the reaction of **1′** with methylenecycloalkanes have the required lifetime (in contrast to the secondary carbocations produced with cycloalkenes) and are able to cyclize. Elimination products are not observed.

The reactions described above have some similarities with the Prins reaction, where water plays the role of the nucleophile in quenching the carbocation derived from the olefin.[8] In our case the nucleophile is delivered intramolecularly. If we consider the simultaneous formation of a C–C and C–N bond, this reaction could be termed "carboamination" of olefins. Few examples of this type are reported in the literature, in spite of considerable synthetic value for such a reaction.[9] Noteworthy is that the replacement of the tosyl by the nosyl group (nosyl = *p*-nitrobenzenesulfonyl) in **1** did not alter the reactivity of the corresponding aziridine. Finally our results are in line with a recent example of a Lewis acid catalyzed reaction of oxiranes with alkenes.[10]

The new chemical behavior of *N*-tosyl-2-phenylaziridine **1** is of interest from several points of view 1) in the presence of $BF_3 \cdot Et_2O$ the reactivity **1** with *nonactivated* olefins is equivalent to that of a 1,3 dipole, 2) molecular complexity is achieved in a single step, and 3) the obtained adducts are important precursors of biologically active molecules. Indeed the azabicycloadducts **3a**/**4a** are valuable as strained phenylethylamines,[11] and are easily accessible from cheap starting materials, furthermore the production of spiropyrrolidines **10**–**12** is of importance as this structural motive forms the core of some biologically active alkaloids.[12]

Experimental Section

General procedure for the reaction of **1** with alkenes: A solution of $BF_3 \cdot OEt_2$ (0.06 mL, 0.5 mmol, 1 equiv) in CH_2Cl_2 (0.3 mL) was added dropwise under argon to a solution of **1** (140 mg, 0.51 mmol) and alkene (1.4 equiv) in CH_2Cl_2 (5 mL) cooled at $-78\,^{\circ}C$. After 20 min at $-78\,^{\circ}C$, the solution was quenched with water (2 mL). The aqueous phase was extracted twice

  1433-7851/00/3924-4616 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **2000**, *39*, No. 24

with CH_2Cl_2 (5 mL) and dried over Na_2SO_4. The crude material was purified by column chromatography on silica gel eluting with hexane/diethyl ether.

Physical data for selected compounds (full details are in the Supporting Information):

4a: $R_f = 0.37$ (hexane/diethyl ether 1/1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS) $\delta = 7.79$ (d, $J = 8.4$ Hz), 7.36 (d, $J = 7.8$ Hz), 7.34 – 7.19 (m, 3H), 7.02 – 6.93 (m, 2H), 3.97 – 3.78 (m, 2H), 3.43 – 3.31 (m, 1H), 3.22 (dd, $J = 9.7$, 10 Hz, 1H), 2.46 (s, 3H), 2.19 – 2.05 (m, 1H), 1.98 – 1.83 (m, 1H), 1.75 – 1.69 (m, 1H), 1.63 – 1.09 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): $\delta =$ 143.4, 139.6, 135.8, 129.8, 128.8, 127.8, 127.5, 127.3, 60.4, 54.4, 44.9, 44.7, 30.9, 24, 21.7, 20.6; MS (IE) m/z: 355.

10: $R_f = 0.44$ (hexane/diethyl ether 1/1); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C,TMS): $\delta = 7.76$ (d, $J = 8.4$ Hz, 2H), 7.4 – 7.15 (m, 7H), 3.87 (m, 1H), 3.41 – 3.26 (m, 2H), 3.21 (dd, $J = 8.4$, 10.3 Hz, 1H), 2.89 (dd, $J = 10$, 20.3 Hz, 1H), 2.57 (dd, $J = 5$, 11.9 Hz, 1H), 2.43 (s, 3H), 2.11 – 1.74 (m, 4H), 1.71 – 1.49 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 143$, 139.9, 138.5, 129.8, 128.8, 127.2, 127.1, 66.9, 55.7, 47.3, 40.5, 37.4, 34.6, 21.6, 14.5; MS (ESI) m/z: 342 $[M+H]^+$.

Received: May 15, 2000
Revised: October 9, 2000 [Z15128]

[1] For reviews on reactions with aziridines: M. Kasai, M. Kono, *Synlett* **1992**, 778; D. Tanner, *Angew. Chem.* **1994**, *106*, 625; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599; H. M. I. Osborn, J. Sweeney, *Tetrahedron: Asymmetry* **1997**, *8*, 1693; C. M. Rayner, *Synlett* **1997**, 11; T. Ibuka, *Chem. Soc. Rev.* **1991**, *27*, 145.

[2] M.-R. Schneider, A. Mann, M. Taddei, *Tetrahedron Lett.* **1996**, *37*, 8493.

[3] I. Ungureanu, C. Bologa, S. Chayer, A. Mann, *Tetrahedron Lett.* **1999**, *40*, 5315

[4] K. Gaebert, J. Mattay, *Tetrahedron* **1997**, *53*, 14297; S. Bergmeier, S. L. Fundy, P. P. Seth, *Tetrahedron* **1999**, *55*, 8025; K. Bellos, H. Stamm, *J. Org. Chem.* **1998**, *63*, 7749, and references therein.

[5] R. Huisgen, *Angew. Chem.* **1963**, *75*, 605; *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 633.

[6] In preliminary experiments the reaction of **1** with (*E*)-hex-3-ene or (*E*)-oct-4-ene worked well giving a mixture of all four possible diastereomeric cycloadducts of the corresponding *N*-tosyl-3-phenyl-4,5-diethyl- or -dipropylpyrrolidines in 43 and 36% yield, respectively. But these adducts could not be separated by column chromatography and their relative ratios were not equally distributed.

[7] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-142893 (**4a**) and -142894 (**3a**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[8] D. R. Adams, S. P. Bhatnagar, *Synthesis* **1977**, 661.

[9] S. Shatzmiller, E. Shalom, E. Bahar, *J. Chem. Soc. Chem. Commun.* **1984**, 1522; A. S. Caille, L. Trimble, C. Berthelette, C. K Lau, *Synlett* **1996**, 669.

[10] D. Munro, C. Newman, *Tetrahedron Lett.* **2000**, *41*, 1483.

[11] M. Ikeda, M. Hamada, Y. Takashi, K. Matsui, T. Sato, H. Ishibashi, *J. Chem. Soc. Perkin Trans. 1* **1991**, 1949.

  1433-7851/00/3924-4617 $ 17.50+.50/0