

N-2-Phenylaziridinyl Imines: Fragmentation and C–C-Bond Formation

A. Stephen K. Hashmi

Frankfurt am Main, Institut für Organische Chemie der Johann Wolfgang Goethe-Universität

Received Mai 26th, 1999

Keywords: Carbenes, Hydrazones, Radical Reactions, Aziridines, Fragmentations

Contents

1. Principles
2. Synthesis of the N-2-Phenylaziridinyl Imines
3. Eschenmoser Fragmentations and Related Reactions
4. Generation of Carbenes and Rearrangement to Olefins
5. Bamford-Stevens and Shapiro Reactions
6. Radical Reactions
7. Miscellaneous
8. Future Prospects

An efficient synthesis of 1-amino-2-phenylaziridine **1** was developed by Eschenmoser [1] in 1968. This opened an easy access to the corresponding N-2-phenylaziridinyl imines **2** and enabled chemists to investigate the manifold and synthetically useful reactions of **2**. Since the beginning of the nineties, especially the group of Sunggak Kim [2–12] has provided a major contribution to the development of new reactions with this class of compounds. Recently, the first applications in the key-steps of total syntheses demonstrated the versatility of these reactions, one of the latest example is Keck's [13] synthesis of (+)-7-deoxypancratistatin.

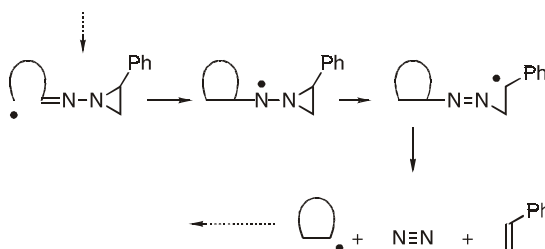


1. Principles

There are two different modes of reaction which have been utilized in organic synthesis. The first one is a fragmentation of the strained **2** upon heating or irradiation with UV-light. It leads to a carbene, styrene **3** and nitrogen. This carbene then undergoes the subsequent intramolecular reactions described below (section 3–5). So overall the carbene can be generated from a ketone in a two-step sequence and – different from the classical Bamford-Stevens reactions applying tosylhydrazones – is set free under *neutral* conditions.



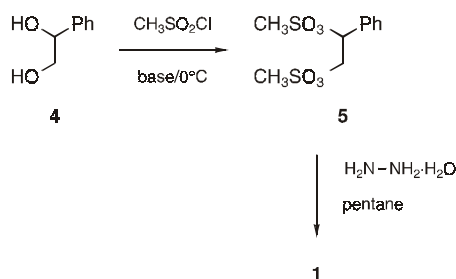
Secondly, the imino-group of **2** is a good intramolecular radical acceptor. Then a fragmentation that again sets free styrene and nitrogen, will generate another radical-center at the very same carbon atom that accepted the radical before. Thus this carbon atom is a radical acceptor and donor and two new bonds to that carbon atom will be formed during the reaction (section 6).



In this context the N-2,3-diphenylaziridinyl imines were also investigated [14], but in the reactions developed in the recent years in most cases **2** was used. **1** contains one stereogenic center and is used as a racemate. Therefore, the imines formed from chiral ketones are mixtures of diastereomers. But this is not a serious problem, the additional stereocenter is lost again during the fragmentation reaction.

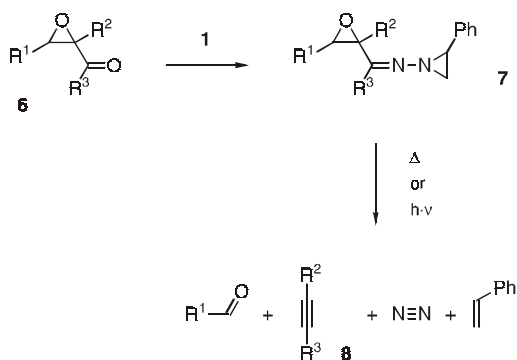
2. Synthesis of the N-2-Phenylaziridinyl Imines

The preparation of **1** was first reported by Eschenmoser [1], subsequent improvements [14] led to a patent [15] and a well defined experimental procedure in Organic Synthesis [16–18]. The sequence started from the commercially available styrene glycol (1-phenyl-1,2-ethandiol) **4** which was transferred into the dimesylate **5**. The reaction of **5** with hydrazine delivered **1** which formed **2** with carbonyl compounds under standard conditions [17]. There exists one report on the explosion of 1-amino-2-phenylaziridinium acetate at room temperature [5], but the pentane solution of **1** that one obtains during the synthesis can directly be used for the reaction with the carbonyl compound, so this problem will be avoided.

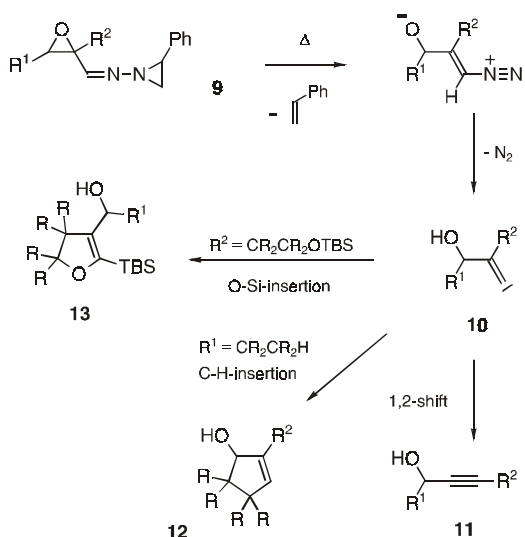


3. Eschenmoser Fragmentations and Related Reactions

The fragmentation of imines like **7** derived from epoxyketones **6** has initially been developed for the synthesis of macrocyclic ketones like exaltone and muscone [19]. Soon it was recognized that this was a quite general synthetic pathway for alkynes **8**.



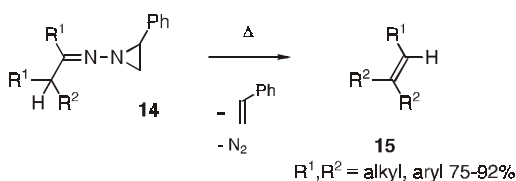
In this context the first synthetic applications of **2** (respectively **6**) were investigated [1, 14], several related conversions in the synthesis of nine-membered cyclooctines [20], of pheromones [21] and of vitamin B₁₂ [22, 23] have been reported.



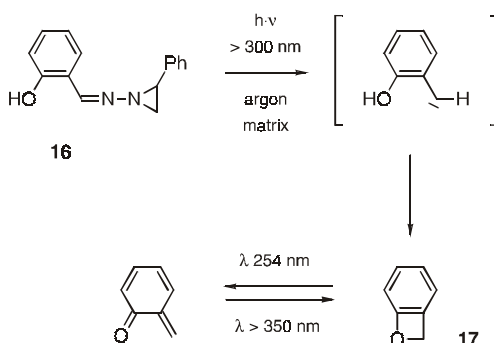
Recently, S. Kim *et al.* have observed that the α,β -epoxy-*N*-aziridiny aldimines **9** do not show the fragmentation by C–C-bond breaking. Upon heating they formed alkylidene carbenes **10** that either led to propargylic alcohols **11** by 1,2-migration or formed five-membered carbo- (**12**) and heterocycles (**13**) by insertion reactions [8, 9].

4. Generation of Carbenes and Rearrangement to Olefins

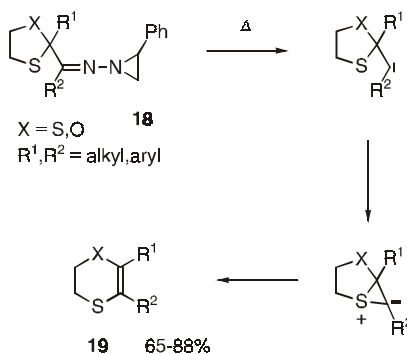
Upon heating, **14** was able to deliver trisubstituted olefins **15** under neutral conditions in good yields [24].



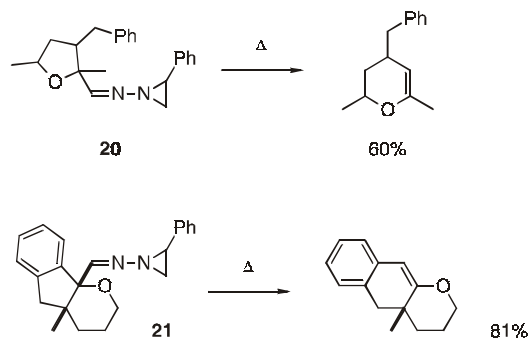
This principle has been utilized in the investigation of the first example of an interconverting carbene–bridgehead alkene pair, the equilibrium between homocub-1(9)-ene and homocub-9-ylidene [25]. Benzoxetene **17** was prepared by photolysis of the precursor **16** in an argon-matrix at 10 K [26].



If, like in **18**, thioethers were placed next to the carbene, heterocycles **19** have been obtained as the products of a ring expansion [11].

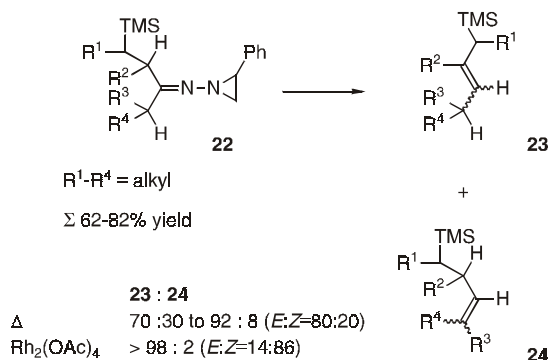


Similar ring expansions could be achieved with cyclic ethers like **20**, in other cases (substrates like **21**) the ether remained untouched and the carbene inserted into the neighboring C–C-bond [10].

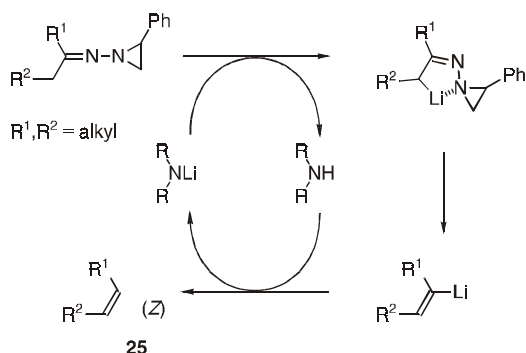


5. Bamford-Stevens and Shapiro Reactions

A silicon-directed version of the Bamford–Stevens reaction was described in the literature, the product selectivity of the double-bond formation (allylsilanes **23** : homoallylsilanes **24**) in thermal reactions of **22** ranges between 70:30 and 92:8. In the presence of $\text{Rh}(\text{OAc})_4$ it was improved to 98:2 or better, interestingly under these conditions the *E*:*Z* ratio was inverted: instead of about *E*:*Z* = 80:20 a ratio of about 14:86 is observed [27].



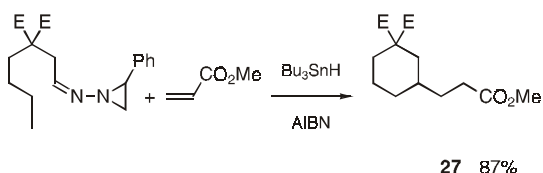
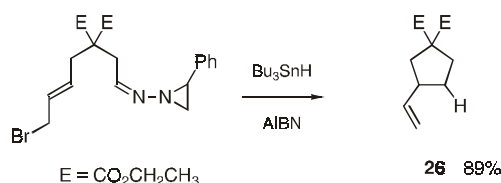
2 could also be applied in Shapiro reactions. One example was reported in the studies on the stereoselective synthesis of juvabione [28], a catalytic Shapiro reaction is also known,



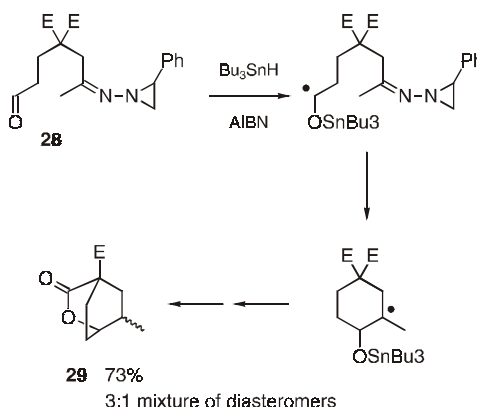
the olefins **25** were formed with high *Z*-selectivity (at least 96% *Z*, in most cases even >99% *Z*) [29].

6. Radical Reactions

In the last years Kim has demonstrated that aziridinyl imines are radical acceptors that will regenerate a radical center at the former imine carbon atom. Thus two consecutive bond formations at the same carbon were possible in a one-pot procedure. In the first examples the formation of five- (like **26**) and six-membered rings (like **27**) was demonstrated [4, 5].



Carbonyl groups have been shown to react faster with the tributyltin radical than the aziridinyl imines in most cases, **28** thus leads to the lactone **29** [2].

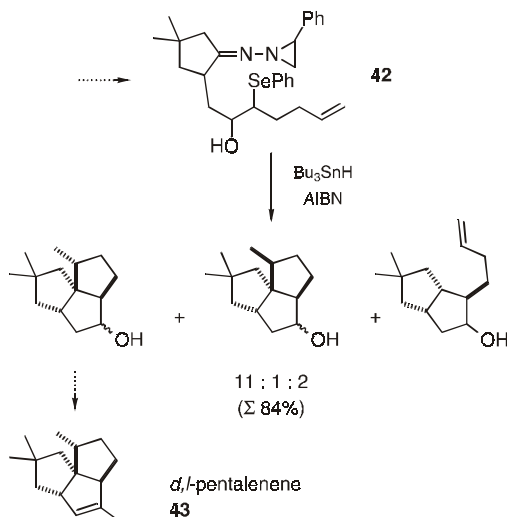
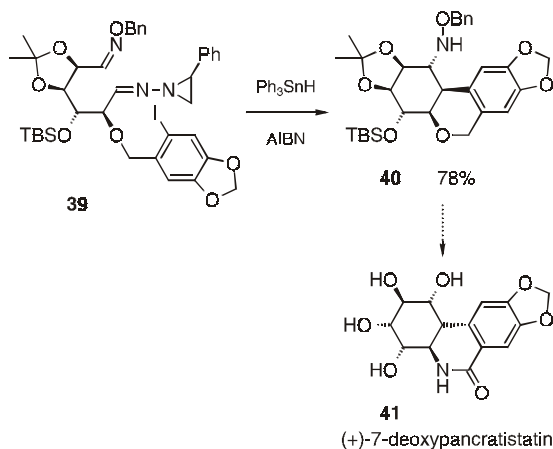
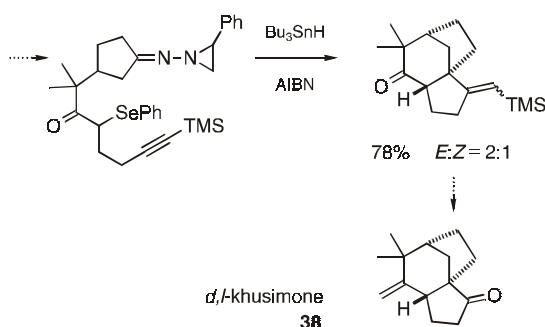
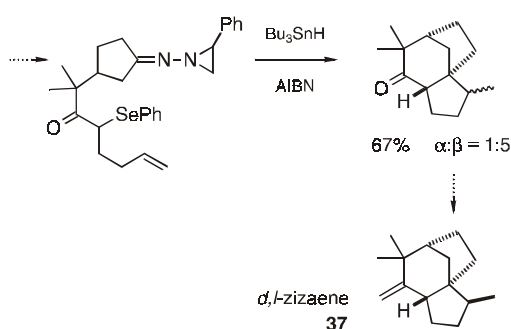
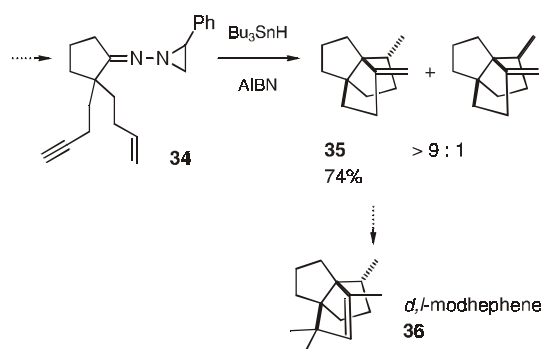
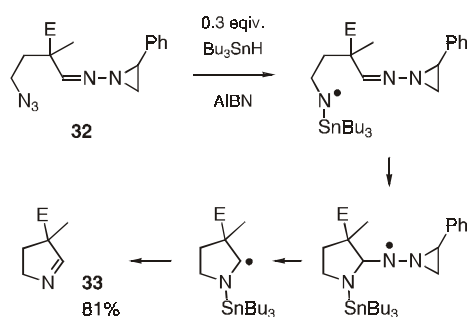
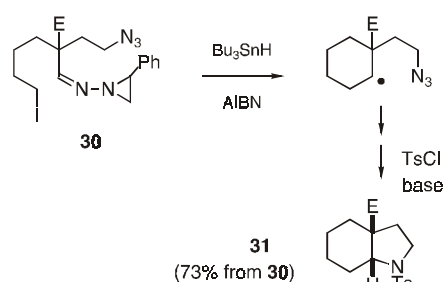


In combination with the radical cyclization of alkyl azides, a new route to nitrogen-heterocycles was developed [7]. **30** delivers only the *cis*-fused **31**, with substrates like **32** the tributyltin radical is set free again, and **33** was isolated.

Polycyclic systems like [3.3.3]propellanes can also be prepared from simple, open-chained precursors. This principle was applied in the transformation of **34** to **35** in the course of a formal total synthesis of DL-modhephene **36** [6].

Other examples are found in the syntheses of DL-zizaene **37** and DL-khusimone **38** [3].

A quite impressive application in total synthesis was the key-step in the synthesis of (+)-7-deoxypancratistatin **41** [13].



40 was prepared from **39**, the diastereoselectivity of this reaction forming two rings was very high – the authors could only detect **40** but none of the other three diastereomers conceivable in this reaction creating two new stereogenic centers in a chiral and enantiomerically pure molecule.

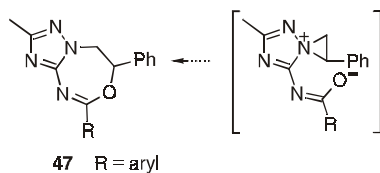
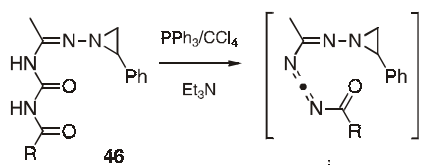
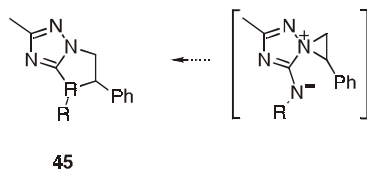
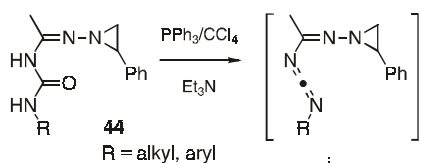
Recently, Kim demonstrated that precursor **42** can be utilized in the synthesis of DL-pentalene **43** [12].

7. Miscellaneous

Not always a fragmentation was observed. In the reaction of the substrates **44** and **46**, the 1,2,4-triazole fused heterocycles **45** and **47** were obtained [30].

8. Future Prospects

This short contribution covers all relevant types of transformations of the 2-phenylaziridinyl imines known so far. If one takes into account the relatively small number of scientists involved up to now in combination with the recent and very successful applications, one can easily imagine that in the near future many more applications will be reported. For example the utilization of other radical acceptors with hete-



roatoms probably opens new synthetic pathways to highly functionalized molecules.

References

- [1] D. Felix, J. Schreiber, K. Piers, U. Horn, A. Eschenmoser, *Helv. Chim. Acta* **1968**, *51*, 1461
- [2] S. Kim, I. S. Kee, *Tetrahedron Lett.* **1993**, *34*, 4213
- [3] S. Kim, J. H. Cheong, *Synlett* **1997**, 947
- [4] S. Kim, J. H. Cheong, K. S. Yoon, *Tetrahedron Lett.* **1995**, *36*, 6069
- [5] S. Kim, I. S. Kee, S. Lee, *J. Am. Chem. Soc.* **1991**, *113*, 9882
- [6] H.-Y. Lee, D.-I. Kim, S. Kim, *J. Chem. Soc., Chem. Commun.* **1996**, 1539
- [7] S. Kim, G. H. Joe, J. Y. Do, *J. Am. Chem. Soc.* **1994**, *116*, 5521
- [8] S. Kim, C. M. Cho, *Tetrahedron Lett.* **1995**, *36*, 4845
- [9] S. Kim, C. M. Cho, *Tetrahedron Lett.* **1994**, *35*, 8405
- [10] S. Kim, J.-Y. Yoon, C. M. Cho, *J. Chem. Soc., Chem. Commun.* **1996**, 909
- [11] S. Kim, C. M. Cho, *Heterocycles* **1994**, *38*, 1971
- [12] S. Kim, J. H. Cheong, J. Yoo, *Synlett* **1998**, 981
- [13] G. E. Keck, T. T. Wager, S. F. McHardy, *J. Org. Chem.* **1998**, *63*, 9164
- [14] A. Eschenmoser, *Helv. Chim. Acta* **1972**, *55*, 1276
- [15] A. Eschenmoser, *Ger. Offen.* 1951103, **1971**; *Chem. Abstr.* **1971**, *75*, 63132p
- [16] R. K. Müller, R. Joos, D. Felix, J. Schreiber, C. Wintner, A. Eschenmoser, *Org. Synth.* **1973**, *53*, 191
- [17] The imines are easily prepared in analogy to procedure for the corresponding 1,2-diphenylaziridinyl derivative: D. Felix, C. Wintner, A. Eschenmoser, *Org. Synth.* **1976**, *55*, 52
- [18] R. K. Müller, R. Joos, D. Felix, J. Schreiber, C. Wintner, A. Eschenmoser, *Org. Synth.* **1976**, *55*, 114
- [19] A. Eschenmoser, D. Felix, G. Ohloff, *Helv. Chim. Acta* **1967**, *50*, 708
- [20] M. Hanack, W. Spang, *Chem. Ber.* **1980**, *113*, 2015
- [21] M. Stoll, I. Flament, *Helv. Chim. Acta* **1969**, *52*, 1996
- [22] R. V. Stevens, R. E. Cherpeck, B. L. Harrison, J. Lai, R. Lapalme, *J. Am. Chem. Soc.* **1976**, *98*, 6314
- [23] R. V. Stevens, J. H. Chang, R. Lapalme, S. Schow, M. G. Schlageter, R. Shapiro, H. N. Weller, *J. Am. Chem. Soc.* **1983**, *105*, 7719
- [24] F. Mohamadi, D. B. Collum, *Tetrahedron Lett.* **1984**, *25*, 271
- [25] N. Chen, M. Jones, W. R. White, M. S. Platz, *J. Am. Chem. Soc.* **1991**, *113*, 4981
- [26] H. Tomioka, T. Matsushita, *Chem. Lett.* **1997**, 399
- [27] T. K. Sarkar, B. K. Ghorai, *J. Chem. Soc., Chem. Commun.* **1992**, 1184
- [28] D. A. Evans, J. V. Nelson, *J. Am. Chem. Soc.* **1980**, *102*, 774
- [29] K. Maruoka, M. Oishi, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 2289
- [30] K.-J. Lee, S.-U. Kang, *Tetrahedron Lett.* **1995**, *36*, 2815

Address for correspondence:

Dr. A. S. K. Hashmi

Johann Wolfgang Goethe-Universität Frankfurt

Institut für Organische Chemie

Marie-Curie-Str. 11

D-60439 Frankfurt am Main

Fax: Internat. code (0) 69 - 798 29464

E-mail: hashmi@chemie.uni-frankfurt.de