Nitrogen Heterocycles

DOI: 10.1002/anie.201101326

Synthesis with Perfect Atom Economy: Generation of Diazo Ketones by 1,3-Dipolar Cycloaddition of Nitrous Oxide at Cyclic Alkynes under Mild Conditions**

Klaus Banert and Oliver Plefka*

In memory of Adolf Krebs

Nitrous oxide is well-known as cheap nontoxic gas utilized not only in medicine and food technology but also as oxidizing reagent,[1,2] for example, in the transformation of benzene derivatives into phenols[1,3] and in the epoxidation of olefins.[4] In some other selective oxidation processes, such as the synthesis of cyclohexanone from cyclohexene and nitrous oxide,[5] a 1,3-dipolar cycloaddition at alkenes **1a** to generate short-lived 4,5-dihydro-1,2,3-oxadiazoles **2a** was postulated to explain the final products **5a** (Scheme 1).[6] Intermediates **2a** and **3a** are also plausible when Wagner–Meerwein rearrangement to yield **6a** or cleavage into **7a** and **8a** followed by formation of cyclopropane **9a** via the corresponding carbene was observed.[5a,7] In the case of alkynes **1b**, treatment with nitrous oxide should lead to 1,2,3-oxadiazoles **2b** and diazo carbonyl compound **3b**.[8] Under the reaction conditions, most probably, ketenes **4b** were produced by Wolff rearrangement and isolated as dimers or trapped by nucleophilic addition of water, alcohols, or amines.[9] All these results indicated that nitrous oxide acted in cycloaddition reactions as a 1,3-dipole of the diazonium betaine type, based on Huisgen's classification.[10] This mechanistic interpretation was also supported by quantum chemical calculations.[7e,11] However, the very low reactivity of nitrous oxide, which required drastic, potentially dangerous, and technically demanding reaction conditions,[5a,7a,9] did not allow nitrogen-containing products, such as **2**, **3**, or **8a**, to be detected.

Herein, we show that the addition of nitrous oxide at cyclic alkynes to generate diazo ketones is possible under mild conditions. By using these processes in the range −25 °C to ambient temperature, the first sequential products containing all three atoms of nitrous oxide are be prepared.

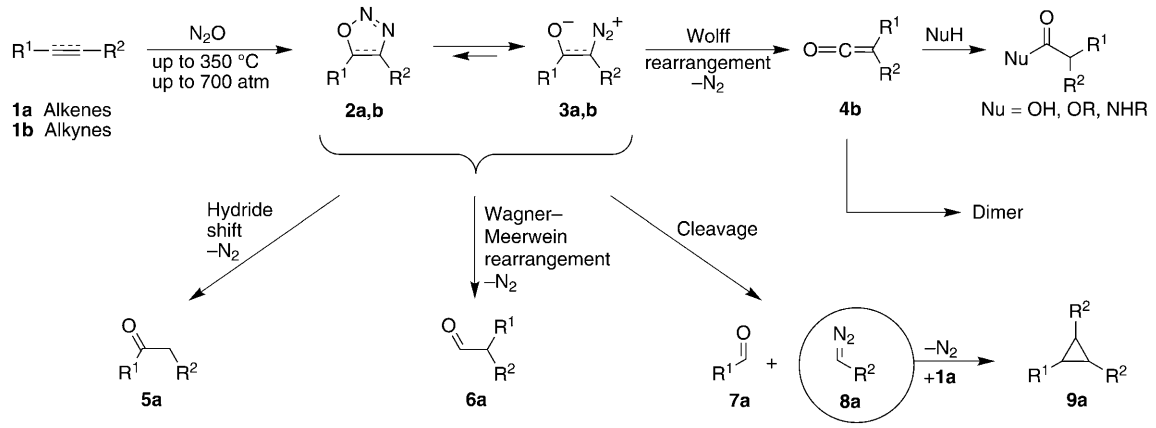
A slow reaction leading to ester **12**[12] in 77 % yield was observed when we treated a solution of the cycloalkyne **10**[13] in methanol with nitrous oxide (50 bar)[14] at room temperature (Scheme 2). We assume that diazo ketone **11** was formed by strain-promoted 1,3-dipolar cycloaddition and subsequent ring opening of the corresponding 1,2,3-oxadiazole. However, the intermediate **11** clearly underwent a rapid Wolff rearrangement to produce the ring-contracted ketene, which was trapped by the nucleophilic addition of methanol to afford **12**. Thus, we were not able to detect **11** directly. Surprisingly, the stability of **11** seems to be lower than that of **20a**, which is in contrast to the properties of other cyclic α-diazo ketones with adjacent benzo units.[15] The cycloheptyne derivative **13**, first synthesized by Krebs et al.,[16] proved to be even more reactive. Substrate **13** was consumed within less than 60 min if subjected to an excess of nitrous oxide (50 bar) in chloroform at ambient temperature. When this transformation was performed at −25 °C, the diazo compound **14** was obtained in 95 % yield and could be analyzed at the same temperature by ^{1}H and ^{13}C NMR spectroscopy for the first time. If the solution of **14** was warmed to room temperature, the known ketene **15**,[16b,17] diketone **16**,[16,17] and the rearrangement product **17**[16b,17] were formed rapidly as the main products.[18] Previously, diazo ketone **14** was generated only in situ owing to its low stability, which was explained by the conformation of the seven-membered ring that excludes resonance stabilization because the diazo and carbonyl functions are orthogonal to one another.[17,19]

When cyclooctyne (**18a**)[20] or cycloocten-5-yne (**18b**)[21] were treated with nitrous oxide in the presence of nucleophiles NuH, the reaction sequences did not stop at diazo ketones **20** and did not precede via ketenes of type **4b** (Scheme 3).[22] Instead we obtained the stable products **19**, which clearly include two molecules of **18**, all three atoms of nitrous oxide, and the nucleophile NuH. Most probably, after cycloaddition of nitrous oxide and ring opening, the corresponding diazo compounds **20** very rapidly[23] underwent another 1,3-dipolar cycloaddition to bring about short-lived 3*H*-pyrazoles **21** that isomerized to the aromatic heterocycles **22** by 1,5-acyl migration.[24] Finally, nucleophilic attack should lead from **22** to esters and amides of type **19**. Polycyclic 1-acyl-1*H*-pyrazoles react easily with alcohols or amines to yield the corresponding acylated products,[25] and some of them are highly sensitive to hydrolysis.[24] Nevertheless we isolated the

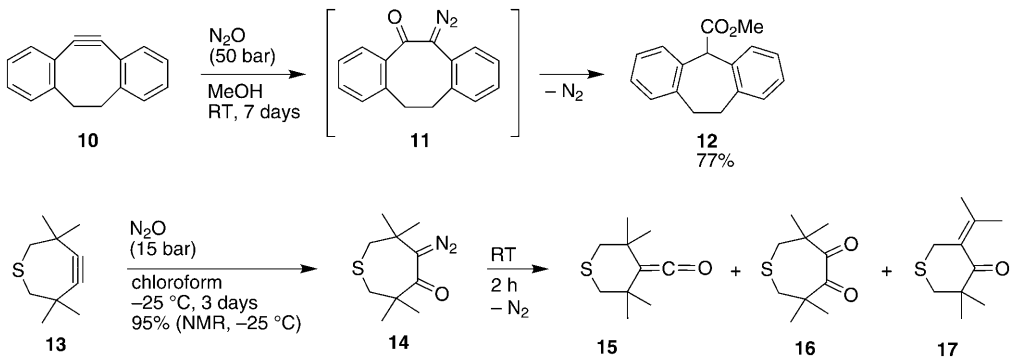
[*] Prof. Dr. K. Banert, O. Plefka
Chemnitz University of Technology, Organic Chemistry
Strasse der Nationen 62, 09111 Chemnitz (Germany)
Fax: (+49) 371-531-21229
E-mail: klaus.banert@chemie.tu-chemnitz.de
Homepage: http://www.tu-chemnitz.de/chemie/org/indexe.html

[**] We gratefully acknowledge financial support from the Deutsche Forschungsgemeinschaft (BA 903/10-3). O.P. thanks the Studentenwerk Chemnitz–Zwickau for a fellowship of the Freistaat Sachsen. We are grateful to Dr. M. Hagedorn for experimental support and assistance with the manuscript. Prof. A. Krebs and Prof. H. Detert gave us highly useful tips for the synthesis of cycloalkynes. We thank Prof. M. Oestreich for support with the MS experiments. Strained Rings, Part 2; for Part 1, see: M. Al-Omari, K. Banert, M. Hagedorn, *Angew. Chem.* **2006**, *118*, 315–317; *Angew. Chem. Int. Ed.* **2006**, *45*, 309–311.

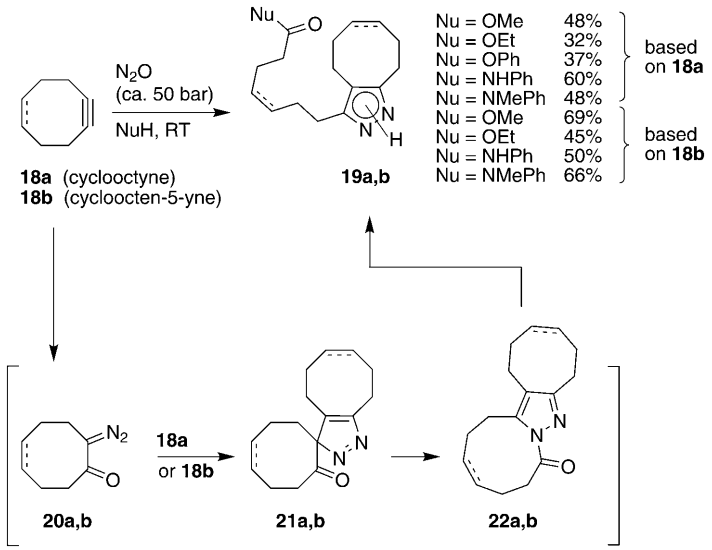
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201101326.



Scheme 1. Postulated 1,3-dipolar cycloaddition of nitrous oxide at alkenes **1a** or alkynes **1b** and the corresponding secondary reactions.



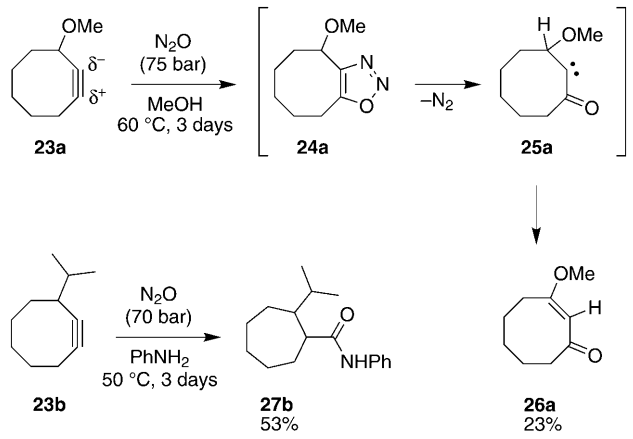
Scheme 2. Reactions of cycloalkynes **10** and **13** with nitrous oxide.



Scheme 3. Cascade reactions of cycloalkynes **18** with nitrous oxide.

tricyclic compound **22a** after treatment of **18a** with nitrous oxide (50 bar) in solvents such as dichloromethane, chloroform, or tetrachloromethane, at ambient temperature. The same 1-acyl-1*H*-pyrazole was also formed when **18a** was subjected to **20a**[26] in chloroform. However, after contact with moisture, for example, in an attempt at purification by chromatography, **22a** was hydrolyzed to the corresponding 7-(pyrazol-3-yl)heptanoic acid.

We assumed that the first step in the formation of diazo ketones, such as **20**, is rate-determining and that the rate of this cycloaddition process to generate 1,2,3-oxadiazoles can be strongly influenced by substituents in position 3 of **18a**. Thus, we treated the cycloalkynes **23a**[27,28] and **23b**[29] with nitrous oxide in the presence of nucleophiles, such as methanol and aniline (Scheme 4). Both substrates **23** are significantly less reactive than the parent compound **18a**. However, the reactivity of **23a**, bearing a weak acceptor substituent (CHOMe) at the triple bond, is less than that of **23b** which has the more bulky isopropyl group. This outcome indicates that sterically demanding as well as electron-withdrawing substituents decrease the rate of the cycloaddition step. This effect of electron-withdrawing substituents, observable in the case of acceptor-substituted alkynes, was predicted by quantum chemical calculations.[11b,d] The diazo ketone, resulting from cycloaddition of nitrous oxide at **23b** followed by ring opening, underwent Wolff rearrangement via the corresponding ketene, and led to the expected amide **27b**, which does not give any information on the regiochemistry of the first step. Surprisingly, **23a** did not yield a ring-contracted ester, and **26a** was formed instead. In a control experiment with **23a** in methanol (air, 55 bar, 60 °C), generation of **26a** without nitrous oxide was ruled out. Thus, we suggest that **26a** was produced from **23a** via the heterocycle **24a** and the carbene **25a**, which isomerized to **26a** by hydrogen shift. The regiochemistry of the postulated cycloaddition reaction **23a**→**24a** seems to be compatible with



Scheme 4. Reactions of substituted cyclooctynes **23** with nitrous oxide.

quantum chemical calculations.[11i] However, these calculations include π-electron-withdrawing substituted alkynes instead of acetylenes with substituents showing an electron-accepting inductive effect.

In summary, we have found convincing evidence that treatment of alkynes with nitrous oxide precedes via 1,3-dipolar cycloaddition and subsequent ring opening to give diazo ketones, which can be analyzed in one special case or utilized in cascade reactions to synthesize pyrazole derivatives with perfect atom economy.

Received: February 22, 2011
Published online: May 25, 2011

Keywords: cascade reactions · nitrogen heterocycles · reaction mechanisms · rearrangements · strained compounds

[1] Review: A. V. Leont'ev, O. A. Fomicheva, M. V. Proskurnina, N. S. Zefirov, *Russ. Chem. Rev.* **2001**, *70*, 91 – 104, and references therein.

[2] a) J. Ettedgui, R. Neumann, *J. Am. Chem. Soc.* **2009**, *131*, 4 – 5; b) H. Matsumoto, S. Tanabe, K. Okitsu, Y. Hayashi, S. L. Suib, *J. Phys. Chem. A* **2001**, *105*, 5304 – 5308; c) P. Kuśtrowski, L. Chmielarz, R. Dziembaj, P. Cool, E. F. Vansant, *J. Phys. Chem. A* **2005**, *109*, 330 – 336; d) S. Poh, R. Hernandez, M. Inagaki, P. G. Jessop, *Org. Lett.* **1999**, *1*, 583 – 585; e) F. Rondinelli, N. Russo, M. Toscano, *Inorg. Chem.* **2007**, *46*, 7489 – 7493; f) F. Rondinelli, N. Russo, M. Toscano, *J. Chem. Theory Comput.* **2008**, *4*, 1886 – 1890; g) K. Pacultová, L. Obalová, F. Kovanda, K. Jirátová, *Catal. Today* **2008**, *137*, 385 – 389; h) J. R. Bleeke, R. Behm, Y.-F. Xie, T. W. Clayton, Jr., K. D. Robinson, *J. Am. Chem. Soc.* **1994**, *116*, 4093 – 4094; i) N. D. Harrold, R. Waterman, G. L. Hillhouse, T. R. Cundari, *J. Am. Chem. Soc.* **2009**, *131*, 12872 – 12873.

[3] a) G. I. Panov, A. S. Kharitonov, V. I. Sobolev, *Appl. Catal. A* **1993**, *98*, 1 – 20; b) V. I. Sobolev, A. S. Kharitonov, Ye. A. Paukshtis, G. I. Panov, *J. Mol. Catal.* **1993**, *84*, 117 – 124; c) G. I. Panov, A. K. Uriarte, M. A. Rodkin, V. I. Sobolev, *Catal. Today* **1998**, *41*, 365 – 385; d) H. Xin, A. Koekkoek, Q. Yang, R. van Santen, C. Li, E. J. M. Hensen, *Chem. Commun.* **2009**, 7590 – 7592.

[4] a) R. Ben-Daniel, L. Weiner, R. Neumann, *J. Am. Chem. Soc.* **2002**, *124*, 8788 – 8789; b) T. Thömmes, I. Gräf, A. Reitzmann, B. Kraushaar-Czarnetzki, *Ind. Eng. Chem. Res.* **2010**, *49*, 2624 – 2637; c) X. Wang, Q. Zhang, S. Yang, Y. Wang, *J. Phys. Chem. B* **2005**, *109*, 23500 – 23508; d) T. Yamada, K. Hashimoto, Y. Kitaichi, K. Suzuki, T. Ikeno, *Chem. Lett.* **2001**, 268 – 269; e) H. Tanaka, K. Hashimoto, K. Suzuki, Y. Kitaichi, M. Sato, T. Ikeno, T. Yamada, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1905 – 1914; f) E. K. Beloglazkina, A. G. Majouga, A. A. Moiseeva, N. V. Zyk, N. S. Zefirov, *Mendeleev Commun.* **2009**, *19*, 69 – 71.

[5] a) F. S. Bridson-Jones, G. D. Buckley, L. H. Cross, A. P. Driver, *J. Chem. Soc.* **1951**, 2999 – 3008; b) G. I. Panov, K. A. Dubkov, E. V. Starokon, V. N. Parmon, *React. Kinet. Catal. Lett.* **2002**, *76*, 401 – 406.

[6] K. A. Dubkov, G. I. Panov, E. V. Starokon, V. N. Parmon, *React. Kinet. Catal. Lett.* **2002**, *77*, 197 – 205.

[7] a) F. S. Bridson-Jones, G. D. Buckley, *J. Chem. Soc.* **1951**, 3009 – 3016; b) E. V. Starokon, K. A. Dubkov, D. E. Babushkin, V. N. Parmon, G. I. Panov, *Adv. Synth. Catal.* **2004**, *346*, 268 – 274; c) E. V. Starokon, K. A. Dubkov, V. N. Parmon, G. I. Panov, *React. Kinet. Catal. Lett.* **2005**, *84*, 383 – 388; d) S. V. Semikolenov, K. A. Dubkov, E. V. Starokon, D. E. Babushkin, G. I. Panov, *Russ. Chem. Bull. Int. Ed.* **2005**, *54*, 948 – 956; e) I. Hermans, B. Moens, J. Peeters, P. Jacobs, B. Sels, *Phys. Chem. Chem. Phys.* **2007**, *9*, 4269 – 4274.

[8] For the equilibrium of α-diazo carbonyl compounds and 1,2,3-oxadiazoles, see: a) M. T. Nguyen, A. F. Hegarty, J. Elguero, *Angew. Chem.* **1985**, *97*, 704 – 705; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 713 – 715; b) W. M. F. Fabian, V. A. Bakulev, C. O. Kappe, *J. Org. Chem.* **1998**, *63*, 5801 – 5805; c) R. Schulz, A. Schweig, *Angew. Chem.* **1984**, *96*, 494 – 495; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 509 – 511; d) A. Blocher, K.-P. Zeller, *Angew. Chem.* **1991**, *103*, 1489 – 1490; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1476 – 1477.

[9] G. D. Buckley, W. J. Levy, *J. Chem. Soc.* **1951**, 3016 – 3018.

[10] R. Huisgen, *Angew. Chem.* **1963**, *75*, 604 – 637; *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565 – 598.

[11] a) V. I. Avdeev, S. P. Ruzankin, G. M. Zhidomirov, *Chem. Commun.* **2003**, 42 – 43; b) K. N. Houk, J. Sims, C. R. Watts, L. J. Luskus, *J. Am. Chem. Soc.* **1973**, *95*, 7301 – 7315; c) M.-D. Su, H.-Y. Liao, W.-S. Chung, S.-Y. Chu, *J. Org. Chem.* **1999**, *64*, 6710 – 6716; d) K. N. Houk, *J. Am. Chem. Soc.* **1972**, *94*, 8953 – 8955; e) D. H. Ess, K. N. Houk, *J. Phys. Chem. A* **2005**, *109*, 9542 – 9553; f) S. Grimme, C. Mück-Lichtenfeld, E.-U. Würthwein, A. W. Ehlers, T. P. M. Goumans, K. Lammertsma, *J. Phys. Chem. A* **2006**, *110*, 2583 – 2586; g) D. H. Ess, K. N. Houk, *J. Am. Chem. Soc.* **2008**, *130*, 10187 – 10198; h) L. T. Nguyen, F. De Proft, V. L. Dao, M. T. Nguyen, P. Geerlings, *J. Phys. Org. Chem.* **2003**, *16*, 615 – 625; i) L. T. Nguyen, F. De Proft, A. K. Chandra, T. Uchimaru, M. T. Nguyen, P. Geerlings, *J. Org. Chem.* **2001**, *66*, 6096 – 6103; j) B. Braida, C. Walter, B. Engels, P. C. Hiberty, *J. Am. Chem. Soc.* **2010**, *132*, 7631 – 7637.

[12] For the synthesis of **12** without using **10** or **11**, see: a) M. A. Davis, F. Herr, R. A. Thomas, M.-P. Charest, *J. Med. Chem.* **1967**, *10*, 627 – 635; b) J. Platzek, G. Snatzke, *Tetrahedron* **1987**, *43*, 4947 – 4968.

[13] a) H. Meier, H. Gugel, *Synthesis* **1976**, 338 – 339; b) C. S. McKay, J. Moran, J. P. Pezacki, *Chem. Commun.* **2010**, *46*, 931 – 933.

[14] A bottle with nitrous oxide for medical use (50 bar, ca. 0.21 Euro per mole) was utilized.

[15] a) R. L. Danheiser, A. L. Helgason, *J. Am. Chem. Soc.* **1994**, *116*, 9471 – 9479; b) H. Tomioka, A. Okuno, T. Sugiyama, S. Murata, *J. Org. Chem.* **1995**, *60*, 2344 – 2352; c) W. Kirmse, *Eur. J. Org. Chem.* **2002**, 2193 – 2256.

[16] a) A. Krebs, H. Kimling, *Tetrahedron Lett.* **1970**, *11*, 761 – 764; b) A. Krebs, H. Kimling, *Justus Liebigs Ann. Chem.* **1974**, 2074 – 2084.

[17] A. de Groot, J. A. Boerma, J. de Valk, H. Wynberg, *J. Org. Chem.* **1968**, *33*, 4025 – 4029.

[18] For details, see the Supporting Information.
[19] V. V. Popik, V. A. Nikolaev, *J. Chem. Soc. Perkin Trans. 2* **1993**, 1791 – 1793.
[20] L. F. Tietze, T. Eicher, *Reaktionen und Synthesen im organisch-chemischen Praktikum und Forschungslaboratorium*, 2nd ed., Thieme, Stuttgart, **1991**, p. 40.
[21] a) H. Petersen, H. Meier, *Chem. Ber.* **1980**, *113*, 2383 – 2397; b) M. Schmitt, Dissertation, Universität Mainz, **1992**.
[22] For the thermal decomposition of **20a**, see: P. W. Concannon, J. Ciabattoni, *J. Am. Chem. Soc.* **1973**, *95*, 3284 – 3289.
[23] Clearly, diazo ketone **20**, generated from **18** and nitrous oxide, added **18** very rapidly so that the Wolff rearrangement of **20** could not compete. On the other hand, attempts to trap the intermediate **20** by electron-deficient alkynes, such as dimethyl acetylenedicarboxylate (see Ref. [24]) or dicyanoacetylene (to avoid addition of **18**) were unsuccessful.
[24] For similar rearrangement reactions of 3-acyl-3*H*-pyrazoles to produce 1-acyl-1*H*-pyrazoles, see: M. Martin, M. Regitz, *Justus Liebigs Ann. Chem.* **1974**, 1702 – 1708.
[25] a) R. F. Smith, F. K. Kirchner, *J. Org. Chem.* **1958**, *23*, 621; b) A. L. Johnson, P. B. Sweetser, *J. Org. Chem.* **1976**, *41*, 110 – 114; c) J. Bermudez, C. S. Fake, G. F. Joiner, K. A. Joiner, F. D. King, W. D. Miner, G. J. Sanger, *J. Med. Chem.* **1990**, *33*, 1924 – 1929; d) P. G. Baraldi, L. Garuti, M. Roberti, *Synthesis* **1994**, 1437 – 1440; e) H. Harada, T. Morie, Y. Hirokawa, S. Kato, *Chem. Pharm. Bull.* **1996**, *44*, 2205 – 2212; f) P. G. Baraldi, B. Cacciari, R. Romagnoli, G. Spalluto, *Synthesis* **1999**, 453 – 458.
[26] a) M. Regitz, F. Menz, J. Rüter, *Tetrahedron Lett.* **1967**, *8*, 739 – 742; b) M. Regitz, J. Rüter, *Chem. Ber.* **1968**, *101*, 1263 – 1270.
[27] a) C. B. Reese, A. Shaw, *J. Chem. Soc. Chem. Commun.* **1970**, 1172 – 1173; b) T. Gerres, A. Heesing, *Chem. Ber.* **1992**, *125*, 1431 – 1437.
[28] We prepared **23a** from 3-methoxycyclooctene by addition of bromine and subsequent treatment with potassium *tert*-butoxide and then treatment with lithium diisopropylamide, see the Supporting Information.
[29] The unknown **23b** was synthesized from 3-bromocyclooctene by addition of bromine and subsequent treatment with potassium *tert*-butoxide. The resulting dibromides were treated with isopropylmagnesium bromide and then with lithium diisopropylamide, see the Supporting Information.

