

Rh-Catalyzed rearrangement of vinylcyclopropane to 1,3-diene units attached to *N*-heterocycles

Franca M. Cordero^{*1}, Carolina Vurchio¹, Stefano Cicchi¹, Armin de Meijere²
and Alberto Brandi^{*1}

Full Research Paper

Open Access

Address:

¹Dipartimento di Chimica "Ugo Schiff", Università degli Studi di Firenze, Via della Lastruccia 13, 50019 Sesto Fiorentino (FI), Italy and ²Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen, Tammannstrasse 2, 37077 Göttingen, Germany

Email:

Franca M. Cordero^{*} - franca.cordero@unifi.it; Carolina Vurchio - carla.vurchio@unifi.it; Stefano Cicchi - stefano.cicchi@unifi.it; Armin de Meijere - ameijer1@gwdg.de; Alberto Brandi^{*} - alberto.brandi@unifi.it

* Corresponding author

Keywords:

nitrogen heterocycles; rearrangement; rhodium; small ring systems; spiro compounds

Beilstein J. Org. Chem. **2011**, *7*, 298–303.

doi:10.3762/bjoc.7.39

Received: 21 December 2010

Accepted: 08 February 2011

Published: 09 March 2011

Associate Editor: M. Rueping

© 2011 Cordero et al; licensee Beilstein-Institut.

License and terms: see end of document.

Abstract

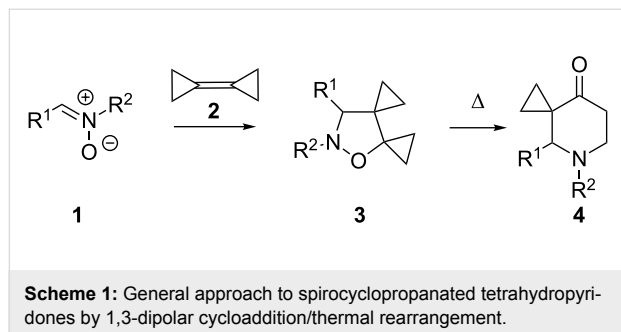
Dienes embedded in quinolizidine and indolizidine structures can be prepared in four steps from cyclic nitrones and bicyclopopylidene. The key intermediates α -spirocyclopropanated *N*-heterocyclic ketones, generated via a domino 1,3-dipolar cycloaddition/thermal rearrangement sequence, were converted by Wittig methylenation to the corresponding vinylcyclopropanes (VCPs), which underwent rearrangement to 1,3-dienes in the presence of the Wilkinson Rh(I) complex under microwave heating. The previously unexplored Rh(I)-catalyzed opening of the VCP moiety embedded in an azapolycyclic system occurs at high temperature (110–130 °C) to afford the corresponding 1,3-dienes in moderate yield (34–53%).

Introduction

The cyclopropyl group endows many natural and synthetic compounds with a broad spectrum of interesting properties, mainly related to its unusual bonding and inherent ring strain [1-3]. This characteristic confers on molecules containing this moiety high reactivity, especially towards ring expansion and ring-opening transformations. The smallest carbocycle can therefore be considered as a peculiar functional group that can promote unique reactivities and synthetic possibilities [4]. The

main obstacle to full exploitation of this chemistry is the difficulty of selectively introducing a cyclopropyl group into a given substrate so that the various specific cyclopropane transformations can be used as a synthetic tool. In recent years we have shown that 1,3-dipolar cycloadditions of nitrones **1** to the highly strained alkene bicyclopopylidene (BCP, **2**) [5-7] afford spirocyclopropanated isoxazolines **3** [8,9] which, on heating, rearrange [10] to yield a large variety of spirocyclopropanated

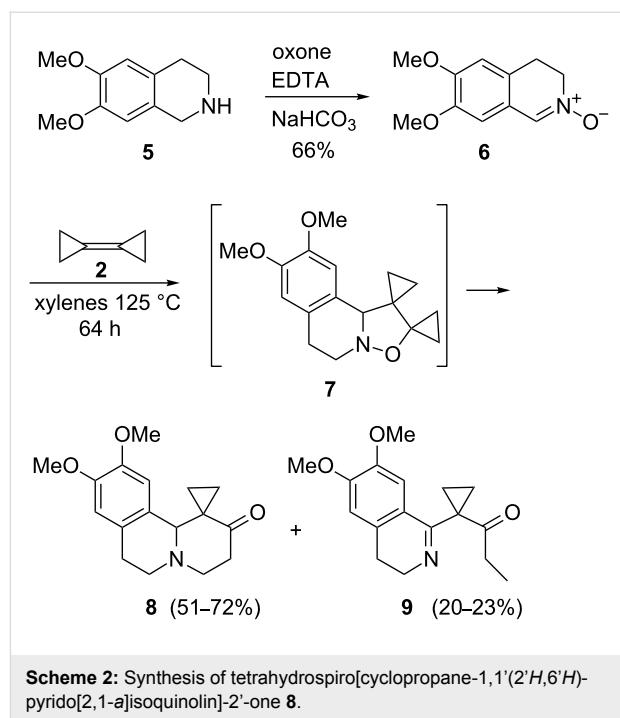
heterocyclic ketones **4** depending on the nature of the starting nitron (Scheme 1) [11–17].



This rather general and convenient access to spirocyclopropane-annulated heterocyclic ketones **4** makes it attractive for the construction of other heterocyclic compounds by selective elaboration of the α -oxocyclopropane functionality, for example, to vinylcyclopropane (VCP) by simple Wittig olefination. The rearrangement of VCPs to cyclopentenones and dienes are well known processes [18–25] that occur thermally or under catalysis by various transition metals including Rh, Ni, Pd, Cu, Cr, Mo, and Fe [26–34]. To date the metal-catalyzed rearrangement of azaheterocyclic VCP has not been reported. In the context of our interest in the VCP chemistry of spirocyclopropane-annulated heterocyclic compounds [35], we started to investigate some metal-catalyzed rearrangements. The first choice was the readily available so-called Wilkinson catalyst $\text{Rh}(\text{PPh}_3)_3\text{Cl}$, because of its documented efficiency in catalyzing the rearrangement [26] and of the possibility to extend its use to other interesting transformations, such as the [5 + 2] cycloadditions of vinylcyclopropanes to alkynes developed by Wender and co-workers [36,37]. It is known, that rhodium-catalyzed rearrangements of unactivated VCPs, without any functional substituent, usually afford dienes. In order to evaluate the influence of the *N*-heterocyclic system on the rearrangement, some model VCPs were generated by Wittig olefination of the α -oxocyclopropane group of functionalized oligocyclic spirocyclopropane-tetrahydropyridones and converted into the corresponding 1,3-dienes by treatment with $\text{Rh}(\text{PPh}_3)_3\text{Cl}$.

Results and Discussion

The tetrahydropyridones employed in this study were prepared according to published procedures with slight modifications. In particular, oxidation of the tetrahydroquinoline **5** with oxone [38] afforded the nitron **6** [39–41] in 66% yield (Scheme 2, see Supporting Information File 1 for full experimental data). Treatment of **6** (1.2–1.7 equiv) with BCP (**2**) in xylenes at 125 °C for 64 h directly afforded the α -oxocyclopropane derivative **8** [13] (51–72% yield) along with a minor amount of the open-chain isomer **9** (20–23% yield).

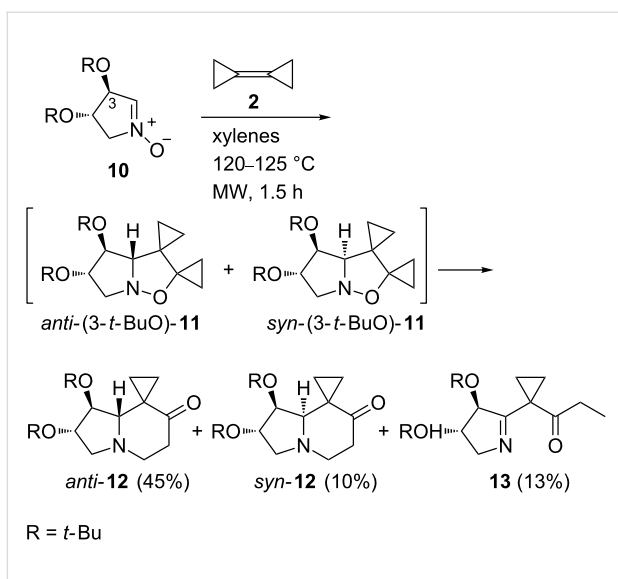


The open-chain isomer **9** is derived from a rarely observed 1,5-hydrogen shift in the cyclopropanated 1,6-diradical intermediate, which in this case is probably facilitated by the enhanced mobility of the benzylic hydrogen and by the formation of the conjugationally stabilized imine **9** [11].

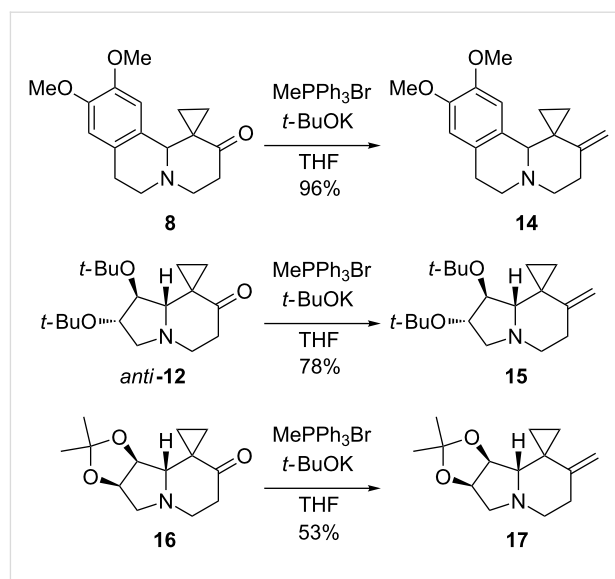
The 1,3-dipolar cycloaddition/thermal rearrangement domino reaction of BCP (**2**) with the enantiopure nitron **10** [42] derived from L-tartaric acid was complete within only 1.5 h at 120–125 °C under microwave (MW) heating and afforded the oxospirocyclopropanes *anti*-**12** and *syn*-**12** in 55% overall yield along with the 1,5-hydrogen shift product **13** (13%) (Scheme 3, see Supporting Information File 1 for full experimental data). The two diastereomeric indolizidinones *anti*-**12** and *syn*-**12** are formed by the thermal rearrangement of the cycloadducts *anti*-(3-*t*-BuO)-**11** and *syn*-(3-*t*-BuO)-**11**, respectively.

Wittig olefination of ketones **8**, *anti*-**12** and **16** [43] with $\text{MePPh}_3\text{Br}/t\text{-BuOK}$ in THF at room temperature gave the VCPs **14**, **15**, and **17** in good yields (53–96%) (Scheme 4, see Supporting Information File 1 for full experimental data). The configuration was retained under the reaction conditions in compounds **15** and **17**, as ascertained by the unique set of ^1H NMR signals in the crude reaction mixture.

The tricyclic compound **14** was then treated with a catalytic amount of $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ (Table 1). In toluene at room temperature no reaction occurred, but on heating under reflux (110 °C) or at 130 °C in a microwave (MW) oven a rearrangement



Scheme 3: Synthesis of 7'-oxohexahydro spiro[cyclopropane-1-8'(5'H)indolizines] **12**.



Scheme 4: Olefination of spirocyclopropanated heterocyclic ketones **8**, **12** and **16**.

occurred leading to a main product assigned as the diene **18** and a mixture of the two diastereomers (*E*)- and (*Z*)-**19**. No trace of the cyclopentene-annelation product was observed in the reaction mixture. In refluxing toluene, the reaction was quite slow and after 15 h in the presence of 5 mol % of catalyst, a considerable amount of starting material still remained. Even after the addition of a second portion of the catalyst and further heating at 110 °C for 18 h, the conversion was incomplete, and

the VCP **14** was recovered in 18% yield after chromatography (Table 1, entry 1). The dienes **18** and **19** were obtained in 35% overall yield (43% yield based on converted **14**). The VCP was completely consumed after 58 h at 110 °C by adding three portions of the catalyst (5 mol % each at 0, 24 and 40 h, respectively) (Table 1, entry 2). In this case, the products were obtained in a lower yield (28%) probably because they partially decomposed upon prolonged heating. The reaction carried out

Table 1: Rearrangement of VCP **14** catalyzed by Rh(PPh₃)₃Cl.

Entry	Rh(I) (%)	Temp. ^a (°C)	Time	Conv. ^b (%)	18/19	Yield ^c (%)
1	5 + 5 ^d	110	15 + 18 h	82	2.5:1	35 (43)
2	5 + 5 + 5 ^e	110	24 + 16 + 18 h	100	1.1:1	28 (28)
3	5	130 (MW)	1 h 30 min	62	4.5:1	46 (74)
4	10	130 (MW)	2 h 20 min	78	1.4:1	59 (75)
5	5 + 5 ^d	130 (MW)	3 + 4 h	100		dec ^f
6 ^g	5 + 5 ^d	160 (MW)	2 + 1 h	72 ^h	3.3:1	nd ⁱ
7 ^j	5	130 (MW)	2 h	55 ^h	3:1	nd ⁱ
8 ^k	10	130 (MW)	5 h 30 min	100	1:1	46 (46)

^aMW: the reaction was carried out in a CEM Discover microwave reactor with IR temperature monitoring. ^bBased on recovered starting material after chromatography. ^cOverall yield after chromatography on SiO₂. The yield based on converted VCP is given in parentheses. ^dThe catalyst was added in two batches (5 mol % each at 0 and 15 h in entry 1, at 0 and 3 h in entry 5, at 0 and 2 h in entry 6). ^eThe catalyst was added in three batches (5 mol % each at 0, 24 and 40 h). ^fDecomposition products. ^gThe reaction was run in xylenes. ^hDetermined by ¹H NMR analysis of the crude reaction mixture. ⁱNot determined. ^j5% AgOTf was added. ^k5% TFE was added.

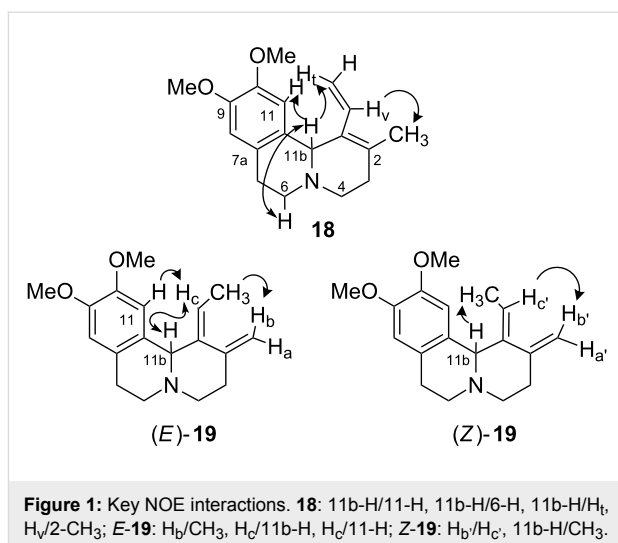
at 130 °C in an MW reactor for shorter times actually gave better yields (Table 1, entries 3 and 4). The best result with a conversion of 78% and 59% yield was achieved by heating a mixture of the VCP **14** and 10 mol % of the catalyst in toluene at 130 °C for 140 min (Table 1, entry 4). When the reaction was allowed to continue until all the starting material was completely consumed led to complete decomposition of the products (Table 1, entry 5). Higher temperatures (160 °C in xylenes) or the addition of AgOTf [44] did neither improve the conversion rate nor the yield of the rearrangement products (Table 1, entries 6 and 7). A slight improvement was achieved by addition of trifluoroethanol (TFE, 5% of the total volume) as a co-solvent [45]. Under these conditions, the conversion of the VCP was complete after 5.5 h at 130 °C, and the dienes **18** and **19** were obtained in a 1:1 ratio in 46% overall yield after chromatography (Table 1, entry 8, see Supporting Information File 1 for full experimental data).

The collected data show that longer reaction times significantly influence the product ratio in favour of the dienes **19** (Table 1). These results are in accord with an isomerization of **18** into **19** under the reaction conditions. However, in the absence of the catalyst, heating of diene **18** under otherwise identical conditions did not induce any isomerization of **18** to **19**, which confirms that Rh also catalyzes the 1,5-hydrogen shift in **18**.

The structure assignment was easily made on the basis of ^1H NMR data. In particular, the diene **18** showed the typical signals of an exocyclic vinyl substituent (δ 7.00 (=CH_v), 5.17 (=CHH_{cis}), 5.17 (=CHH_{trans}) ppm; $J_{trans} = 17.5$, $J_{cis} = 11.3$ Hz). Irradiation of 11b-H (δ 4.76 ppm) produced a positive NOE on the olefinic H_{trans} whereas irradiation of =CH resulted in enhancement of the 2-CH₃ signal (δ 1.87 ppm) suggesting a preferred *s-trans* conformation for the diene moiety in solution (Figure 1).

The ^1H NMR spectra of the dienes **19** showed a quartet in the region of olefinic due to the resonance of the proton H_c coupled with the methyl group (δ 5.29 and 5.96 ppm, $^3J = 6.9\text{--}7.0$ Hz) and two signals due to the methylene protons H_a and H_b (δ 5.06 and 4.75; 4.89 and 4.65 ppm, $^2J = 2.3\text{--}2.1$ Hz).

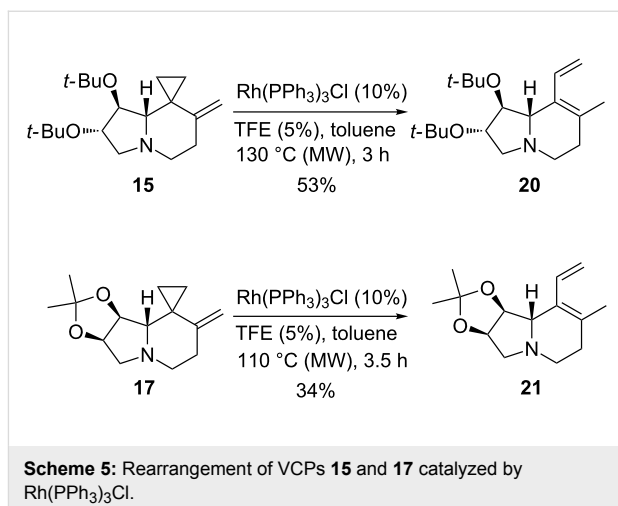
The *E*- and *Z*-configuration of the dienes **19** was determined by NOESY 1D NMR spectroscopy. In the major compound (*E*)-**19**, irradiation of the olefinic H_b (δ 4.75 ppm) gave enhancement of the ethylidene methyl group (δ 1.76 ppm), and irradiation of H_c (δ 5.29 ppm) showed enhancement at 11-H and 11b-H (δ 6.56 and 4.41 ppm). For the isomer (*Z*)-**19**, irradiation of H_c (δ 5.96 ppm) gave enhancement of H_b (δ 4.89 ppm) and an NOE interaction was present between the methyl group and



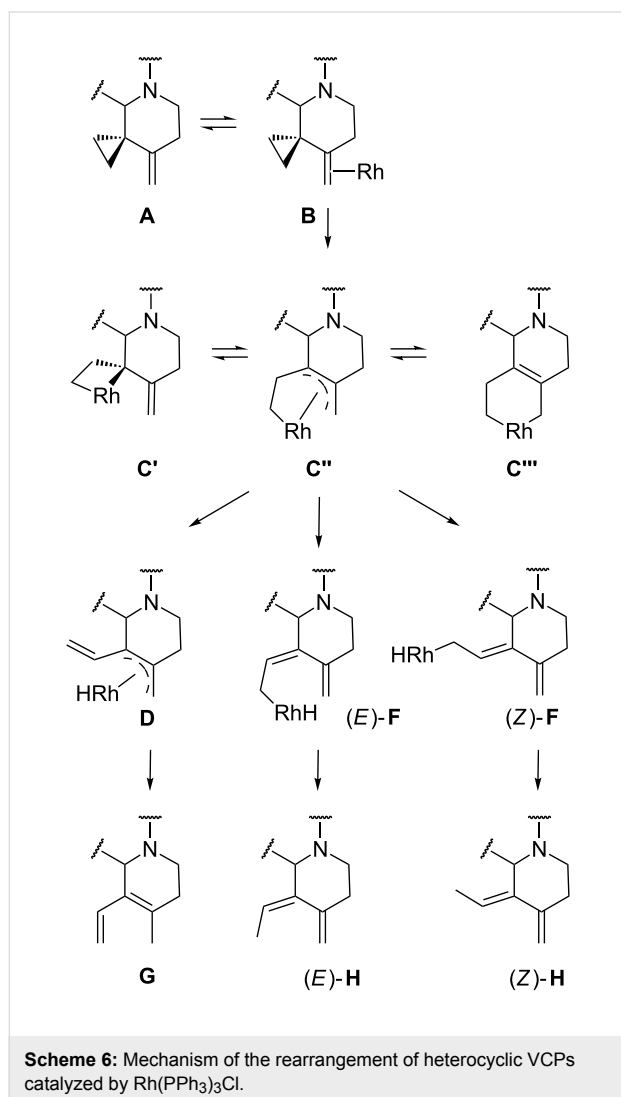
11b-H (δ 5.02 ppm) in agreement with the assigned configuration (Figure 1).

The VCPs **15** and **17** were completely consumed on heating in toluene in a MW oven at 130 °C for 3 h and 110 °C for 3.5 h, respectively, in the presence of Rh(PPh₃)₃Cl (10%) and TFE (5%). In these cases, dienes **20** and **21** were obtained in 53 and 34% yield, respectively, as the sole reaction products (Scheme 5, see Supporting Information File 1 for full experimental data). Their structures were assigned analogously as before. Compounds **20** and **21** were found to be unstable upon standing for prolonged periods, even at low temperatures. This explains the low isolated yields in their syntheses.

Analogously to other Rh(I)-catalyzed VCP rearrangements [46,47], the mechanism of the rearrangement likely involves insertion of the Rh(I) species into the cyclopropane ring of the VCP system, with or without incorporation of the double



bond to form the intermediates **C** which can undergo metal hydride elimination or 1,3-hydride migration to the rhodium to give, respectively, the allyl- and alkylrhodium(III) hydride complexes **D** and **F**. Metal extrusion by reductive elimination leads to the observed dienes and regeneration of the catalyst (Scheme 6).



Conclusion

Azaheterocycles **14**, **15** and **17** containing a spiro-annulated VCP moiety have been synthesized starting from cyclic nitrones and BCP by a three-step two-pot sequence consisting of a 1,3-dipolar cycloaddition, thermal rearrangement and Wittig methylenation. These compounds in the presence of the Wilkinson Rh(I) complex at high temperatures (110–130 °C) under MW heating underwent a slow rearrangement to afford the corresponding azaheterocycles containing 1,3-diene units in moderate yields. The rearrangement produced mixtures of isomeric dienes from benzoquinolizidine **14** and was regioselective

in the case of indolizidines **15** and **17**, showing that the Wilkinson Rh(I) catalyst is also capable of inducing the VCP rearrangement in the presence of strongly nucleophilic azaheterocycles. Accordingly, new functionalised heterocyclic compounds can be produced by the straightforward methodology based on nitrones and bicyclopropylidene.

Supporting Information

Supporting information features experimental procedures and spectroscopic data.

Supporting Information File 1

Experimental part.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-7-39-S1.pdf>]

Acknowledgements

Mr. Reent Michel, a Sokrates-exchange student from the Georg-August-Universität Göttingen (Germany), is acknowledged for his partial contribution to this work. Ente Cassa di Risparmio di Firenze (Florence, Italy) is acknowledged for partial financial support of a fellowship for C. V. Ministry of University and Research (MIUR Rome-Italy) is acknowledged for financial support (PRIN project).

References

- de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 809–826. doi:10.1002/ange.19790911104
- Salaün, J. In *The Chemistry of the Cyclopropyl Group*; Patai, S.; Rappoport, Z., Eds.; Wiley: New York, 1987; pp 809–878.
- Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1–67. doi:10.1007/3-540-48255-5_1
- de Meijere, A., Ed. *Houben-Weyl, Carbocyclic Three-Membered Ring Compounds*; Thieme: Stuttgart, 1997; Vol. E17.
- Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589–636. doi:10.1021/cr940341t
- de Meijere, A.; Kozhushkov, S. I. *Eur. J. Org. Chem.* **2000**, 3809–3822. doi:10.1002/1099-0690(200012)2000:23<3809::AID-EJOC3809>3.0.CO;2-X
- de Meijere, A.; Kozhushkov, S. I. *Chem. Rev.* **2000**, *100*, 93–142. doi:10.1021/cr960153y
- Brandi, A.; Cordero, F. M.; De Sarlo, F.; Goti, A.; Guarna, A. *Synlett* **1993**, 1–8. doi:10.1055/s-1993-22329
- Goti, A.; Cordero, F. M.; Brandi, A. *Top. Curr. Chem.* **1996**, *178*, 1–97. doi:10.1007/3-540-60495-2_1
- Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213–1269. doi:10.1021/cr010005u
- Goti, A.; Anichini, B.; Brandi, A.; Kozhushkov, S. I.; Gratkowski, C.; de Meijere, A. *J. Org. Chem.* **1996**, *61*, 1665–1672. doi:10.1021/jo951838l
- Goti, A.; Anichini, B.; Brandi, A.; de Meijere, A.; Citti, L.; Nevischi, S. *Tetrahedron Lett.* **1995**, *36*, 5811–5814. doi:10.1016/0040-4039(95)01103-0

13. Zorn, C.; Anichini, B.; Goti, A.; Brandi, A.; Kozhushkov, S. I.; de Meijere, A.; Citti, L. *J. Org. Chem.* **1999**, *64*, 7846–7855. doi:10.1021/jo990873f
14. Anichini, B.; Goti, A.; Brandi, A.; Kozhushkov, S. I.; de Meijere, A. *Synlett* **1997**, 25–26. doi:10.1055/s-1997-684
15. Marradi, M.; Brandi, A.; Magull, J.; Schill, H.; de Meijere, A. *Eur. J. Org. Chem.* **2006**, 5485–5494. doi:10.1002/ejoc.200600417
16. Zorn, C.; Goti, A.; Brandi, A.; Johnsen, K.; Noltemeyer, M.; Kozhushkov, S. I.; de Meijere, A. *J. Org. Chem.* **1999**, *64*, 755–763. doi:10.1021/jo981366l
17. Revuelta, J.; Cicchi, S.; Faggi, C.; Kozhushkov, S. I.; de Meijere, A.; Brandi, A. *J. Org. Chem.* **2006**, *71*, 2417–2423. doi:10.1021/jo052564x
18. Neureiter, N. P. *J. Org. Chem.* **1959**, *24*, 2044–2046. doi:10.1021/jo01094a621
19. Overberger, C. G.; Borchert, A. E. *J. Am. Chem. Soc.* **1960**, *82*, 1007–1008. doi:10.1021/ja01489a069
20. Flowers, M. C.; Frey, H. M. *J. Chem. Soc.* **1961**, *82*, 3547–3548.
21. Hudlicky, T.; Becker, D. A.; Fan, R. L.; Kozhushkov, S. I. In *Houben-Weyl*; de Meijere, A., Ed.; Thieme: Stuttgart, 1997; Vol. E17c, pp 2538–2565.
22. Hudlicky, T.; Fan, R. L.; Reed, J. W.; Gadamasetti, K. G. *Org. React.* **1992**, *41*, 1–133. doi:10.1002/0471264180.or041.01
23. Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis-Selectivity, Strategy & Efficiency in Modern Organic Chemistry*; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 899–970.
24. Baldwin, J. E. *Chem. Rev.* **2003**, *103*, 1197–1212. doi:10.1021/cr010020z
25. Wang, S. C.; Tantillo, D. J. *J. Organomet. Chem.* **2006**, *691*, 4386–4392. doi:10.1016/j.jorganchem.2005.12.052
26. Hayashi, M.; Ohmatsu, T.; Meng, Y.-P.; Saigo, K. *Angew. Chem., Int. Ed.* **1998**, *110*, 877–879. doi:10.1002/(SICI)1521-3773(19980403)37:6<837::AID-ANIE837>3.0.CO;2-R
27. Zuo, G.; Louie, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2277–2279. doi:10.1002/anie.200353469
28. Hiroi, K.; Arinaga, Y. *Tetrahedron Lett.* **1994**, *35*, 153–156. doi:10.1016/0040-4039(94)88188-X
29. Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 2871–2874. doi:10.1016/S0040-4039(00)88436-1
30. Davies, H. M. L.; Hu, B. *J. Org. Chem.* **1992**, *57*, 3186–3190. doi:10.1021/jo00037a041
31. Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020–5027. doi:10.1021/jo01313a003
32. Buchert, M.; Reissig, H.-U. *Liebigs Ann.* **1996**, 2007–2013. doi:10.1002/jlac.199619961210
33. Davies, H. M. L.; Hu, B. *Tetrahedron Lett.* **1992**, *33*, 453–456.
34. Doyle, M. P.; van Leusen, D. *J. Org. Chem.* **1982**, *47*, 5326–5339. doi:10.1021/jo00148a020
35. Brandi, A.; Cicchi, S.; Brandl, M.; Kozhushkov, S. I.; de Meijere, A. *Synlett* **2001**, 433–435. doi:10.1055/s-2001-11396
Example for a study of the thermal VCP to cyclopentene rearrangement in such compounds.
36. Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720–4721. doi:10.1021/ja00121a036
37. Wegner, H. A.; de Meijere, A.; Wender, P. A. *J. Am. Chem. Soc.* **2005**, *127*, 6530–6531. doi:10.1021/ja043671w
38. Sánchez-Izquierdo, F.; Blanco, P.; Busqué, F.; Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Parella, T. *Org. Lett.* **2007**, *9*, 1769–1772. doi:10.1021/ol070486p
39. Brandi, A.; Garro, S.; Guarna, A.; Goti, A.; Cordero, F.; De Sarlo, F. *J. Org. Chem.* **1988**, *53*, 2430–2434. doi:10.1021/jo00246a008
40. Yamazaki, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 877–883. doi:10.1246/bcsj.70.877
41. Zhao, B.-X.; Yu, Y.; Eguchi, S. *Org. Prep. Proced. Int.* **1997**, *29*, 185–194. doi:10.1080/00304949709355182
42. Cicchi, S.; Corsi, M.; Goti, A. *J. Org. Chem.* **1999**, *64*, 7243–7245. doi:10.1021/jo990417r
43. Revuelta, J.; Cicchi, S.; de Meijere, A.; Brandi, A. *Eur. J. Org. Chem.* **2008**, 1085–1091. doi:10.1002/ejoc.200700912
44. Wender, P. A.; Dyckman, A. *J. Org. Lett.* **1999**, *1*, 2089–2092. doi:10.1021/ol991171f
45. Wender, P. A.; Barzilay, C. M.; Dyckman, A. *J. Am. Chem. Soc.* **2001**, *123*, 179–180. doi:10.1021/ja0021159
46. Salomon, R. G.; Salomon, M. F.; Kachinski, J. L. C. *J. Am. Chem. Soc.* **1977**, *99*, 1043–1054. doi:10.1021/ja00446a012
47. Salomon, M. F.; Salomon, R. G. *J. Chem. Soc., Chem. Commun.* **1976**, 89–90. doi:10.1039/C39760000089

License and Terms

This is an Open Access article under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/2.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

The license is subject to the *Beilstein Journal of Organic Chemistry* terms and conditions: (<http://www.beilstein-journals.org/bjoc>)

The definitive version of this article is the electronic one which can be found at:
[doi:10.3762/bjoc.7.39](https://doi.org/10.3762/bjoc.7.39)