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[2+2] Photocycloaddition of 3-Alkenyloxy-2-cycloalkenones: Enantioselective Lewis Acid Catalysis and Ring Expansion**

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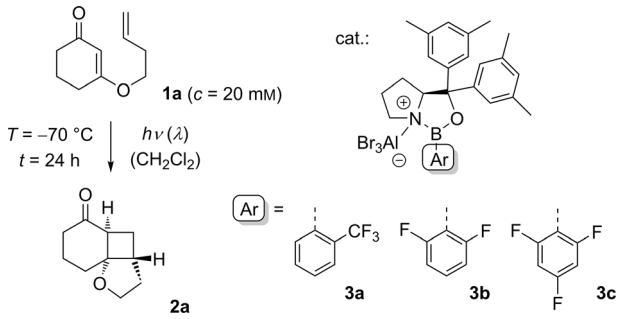
Abstract: *By application of substoichiometric amounts (50 mol%) of a chiral Lewis acid, the intramolecular [2+2] photocycloaddition of the title compounds was achieved with high enantioselectivity (up to 94% ee). Upon cleavage of the cyclobutane ring the resulting tricyclic products underwent ring-expansion reactions under acidic conditions and formed anellated seven- or eight-membered-ring systems without racemization. The ring expansion could be combined with a diastereoselective reduction (triethylsilane) or allylation (allyltrimethylsilane) upon BF_3 catalysis (48–87% yield).*

The ring strain of cyclopropanes and cyclobutanes can be exploited to conduct ring-expansion reactions in di- and tricyclic ring systems.[1] In particular, by cleavage of a carbon–carbon bond, seven- and eight-membered carbocycles can be generated, which are difficult to obtain by conventional methods, and which are recurring elements in numerous natural products.[2] In the context of [2+2] photocycloaddition reactions, ring expansions have been performed by a radical fragmentation[3,4] or preferably by a retro-aldol reaction (de Mayo reaction)[5] or a retro-Mannich reaction.[6] Any stereogenic center that is located at the cleaved bond is—at least temporarily—lost, while the configuration of other stereogenic centers in the molecular framework is retained. Against this backdrop, the enantioselective photochemical generation of cyclobutanes poses a significant challenge, which in the past was very often solved by auxiliary-controlled methods[7] or by the application of stoichiometric chiral templates.[8] In recent times, there have been initial hints that catalytic enantioselective [2+2] photocycloaddition variants[9] can also be used for this purpose.[10,11] Herein we demonstrate that chiral Lewis acids can be employed to perform enantioselective [2+2] photocycloaddition reactions of 2-cycloalkenones. In addition, the cyclobutanes generated in this reaction were found to undergo ring-opening and ring-expansion reactions, which have so far received little attention.

In the beginning of our investigations, the goal was to demonstrate that the previously discovered enantioselective Lewis acid catalyzed photocycloaddition of enones, which was first described for dihydropyridones,[10d] is generally applicable, and we commenced this study with 3-but-3-enyloxy-2-cyclohexenone (**1a**). The intramolecular [2+2] photocycloaddition of this compound has been reported[12] and leads to the racemic photocycloaddition product *rac*-**2a**. Its enantiomers can be readily separated by GC analysis on a chiral stationary phase. The Lewis acid **3a**,[10b,d] which we used for previous enantioselective [2+2] photocycloaddition reactions, gave only moderate enantioselectivities (Table 1, entry 1). An extended optimization of the aryl substituent of the oxazaborolidine skeleton **3** (see Supporting Information) delivered significantly better results with Lewis acids **3b** (entry 2) and **3c** (entry 3).

Table 1: Examples from the optimization of reaction conditions for the enantioselective intramolecular [2+2] photocycloaddition of 2-cyclohexenone **1a** in the presence of chiral Lewis acids **3**.



Entry[a]	Cat.	Loading[b] [mol%]	λ[c] [nm]	Power[d] [W]	Conv.[e] [%]	*ee*[f] [%]
1	**3a**	50	300	36	80	46
2	**3b**	50	300	36	89	75
3	**3c**	50	300	36	67	80
4	–	–	300	36	79	–
5	**3c**	50	300	84	98	56
6	**3c**	40	300	36	42	80
7	**3c**	30	300	36	25	74
8[g]	**3c**	50	366	128	52	80
9[g]	**3c**	50	300	36	99	80

[a] All reactions were performed in CH_2Cl_2 as the solvent with a substrate concentration of 20 mM and at a temperature of −70°C (Duran glass). [b] Amount of the chiral Lewis acid used for the reaction. [c] Emission maximum[13] of the fluorescence lamps. [d] Overall power of the fluorescence lamps. [e] The conversion was determined by GC analysis. [f] The enantiomeric excess (*ee*) was calculated from the ratio of enantiomers as determined by GC analysis on a chiral stationary phase. [g] The solution was irradiated for 48 h.

Fluorescence lamps with an emission maximum at $\lambda = 300$ nm[13] were used in these experiments as the irradiation

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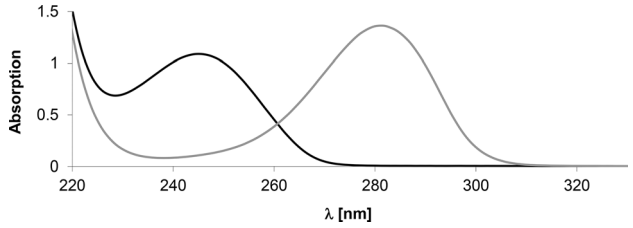


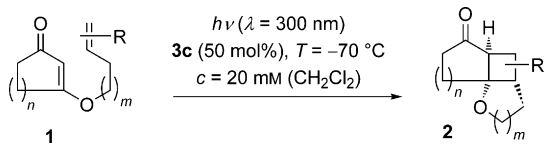
Figure 1. UV/Vis spectrum of compound **1a** in CH_2Cl_2 as solvent ($c = 0.5$ mM) without Lewis acid (black line) and after addition of 10 equivalents of $EtAlCl_2$ (gray line).

source. The choice of wavelength was based on the observation that cyclohexenone **1a** shows an absorption maximum in its UV/Vis spectrum at 245 nm ($\varepsilon = 21\,790\ M^{-1}cm^{-1}$) which was shifted to 281 nm ($\varepsilon = 27\,270\ M^{-1}cm^{-1}$) upon complexation by a Lewis acid (Figure 1). The effect of the Lewis acid is based on the fact that the complex shows a significant absorption in a wavelength range, in which the uncomplexed substrate only shows very weak absorption.[10d] However, in the absence of any Lewis acid this weak absorption—in this case the nπ* band at $\lambda = 299$ nm ($\varepsilon = 90\ M^{-1}cm^{-1}$)—is sufficient to induce a relatively fast [2+2] photocycloaddition reaction (Table 1, entry 4).

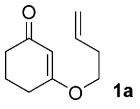
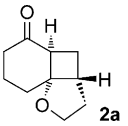
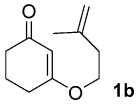
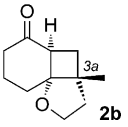
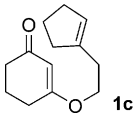
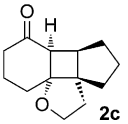
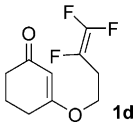
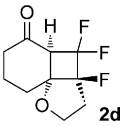
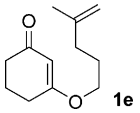
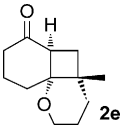
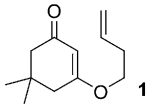
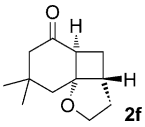
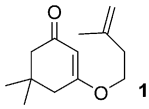
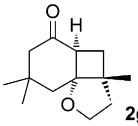
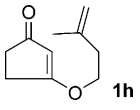
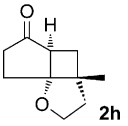
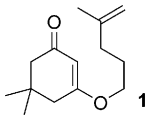
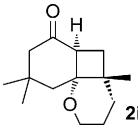
The photon flux was regulated by the power (number of lamps) of the irradiation source. The photoreaction was complete after shorter irradiation times at higher photon flux (entry 5), but the enantioselectivity decreased due to the racemic background reaction (vide supra).[10d] To our delight, catalyst **3c** still delivered high enantioselectivities (entry 6) at a catalyst loading of 40 mol%, however at lower conversion. With 30 mol% catalyst, both the conversion and the enantioselectivity decreased (entry 7). Fluorescence lamps with a red-shifted emission[13] led to a similar result as the 300 nm lamps concerning the enantioselectivity. However, even at a higher irradiation power the conversion remained low (entry 8). The reaction **1a**→**2a** could be completed at low photon flux after longer irradiation times without loss of enantioselectivity (entry 9).

Under the reaction conditions of entry 9 in Table 1, photocycloaddition product **2a** could be isolated in 90% yield and with 80% *ee* (Table 2, entry 1). Further cycloalkenones **1** reacted equally efficiently under optimized reaction conditions[14] and in several cases (entries 2, 5–9) with significantly higher enantioselectivities. Only sterically demanding (entry 3) and electron-deficient olefins (entry 4) led to slightly lower selectivities. In analogy to the bathochromic shift upon addition of $EtAlCl_2$, we assume that the substrates are complexed by the chiral Lewis acid, resulting in the same photophysical effect: The high absorption coefficient of the Lewis acid/substrate complex at $\lambda \approx 300$ nm suppresses the background reaction of the substrate, and the [2+2] photocycloaddition reaction occurs exclusively in the presence of the chiral Lewis acid. The absolute configuration of the photoproducts was assigned based on the face differentation suggested for chiral oxazaborolidines, which has been previously verified not only in thermal[15] but also in photochemical reactions.[10b,d]

Table 2: Yields and enantioselectivities for the intramolecular [2+2] photocycloaddition of the 2-cycloalkenones **1**.



1 → **2**

Entry	Substrate[a]	Power[b] [W]	t[c] [h]	Product	Yield[d] [%]	ee[e] [%]
1	 **1a**	36	48	 **2a**	90	80
2	 **1b**	84	24	 **2b**	93[f]	82
3	 **1c**	84	48	 **2c**	93[g]	75
4	 **1d**	54	48	 **2d**	91	76
5	 **1e**	84	48	 **2e**	81	86
6	 **1f**	48	24	 **2f**	94[h]	86
7	 **1g**	72	48	 **2g**	69	87
8	 **1h**	84	48	 **2h**	86[i]	82
9	 **1i**	84	48	 **2i**	93	94

[a] All reactions were performed with 0.1 mmol of starting material in a Rayonet reactor with fluorescence lamps (6 W power output each; emission maximum at $\lambda = 300$ nm)[13] as the light source. [b] Overall power of the fluorescence lamps used. [c] Irradiation time. [d] Yield of isolated product. [e] The enantiomeric excess (*ee*) was calculated from the ratio of enantiomers as determined by GC analysis on a chiral stationary phase. [f] The reaction was additionally performed on a larger scale (0.6 mmol) (81% yield, 85% *ee*). [g] Based on conversion (55%). [h] Based on conversion (72%). [i] Based on conversion (29%).

After completion of the photoreaction, a base (NEt_3) was routinely added to the reaction mixture at −70 °C, since ring-opening products seemed to be formed when the solution was

warmed to room temperature in the presence of the chiral Lewis acid **3c**. In fact, it has been reported for the reaction **1f**→**2f** that such a ring-opening reaction can occur, which leads to an achiral compound after elimination of a proton.[14b,16] This elimination cannot take place in product **2b** (Table 2, entry 2), which bears a methyl group instead of a proton in position C3a of the hexahydro-2*H*-benzo-[1,4]cyclobuta[1,2-b]furan framework. Consequently, upon treatment of compound **2b** with a Brønsted acid (1N HCl in CH_2Cl_2), the chiral tricyclic compound **4b** was isolated in very good yield (Figure 2). The product is the acetal of the

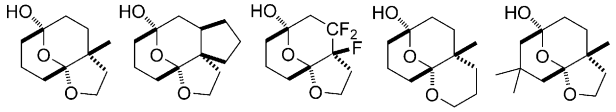
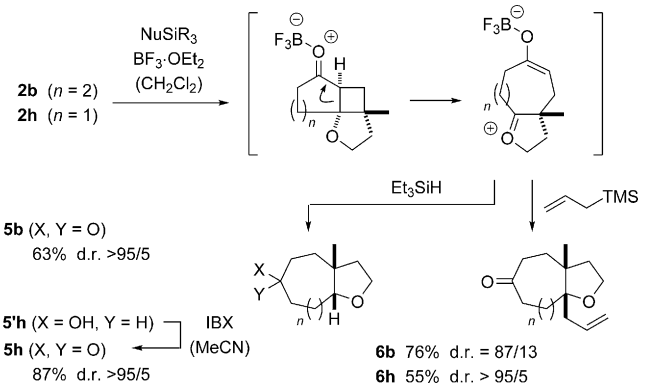


Figure 2. Products **4** and yields of the acid-catalyzed ring opening (HCl in CH_2Cl_2) of cyclobutanes **2** formed in the intramolecular [2+2] photocycloaddition reaction.

corresponding 1,5-cyclooctadione, which in turn is the product of a cyclobutane ring expansion (vide infra). The ring-opening reaction is generally applicable and in the same fashion products **4c**, **4d**, **4e**, and **4g** were obtained.

The assignment of the relative configuration was not trivial for compounds **4**, since the signals in the ^{1}H NMR spectra overlapped significantly. Although cyclobutane **2d** was—presumably due to the electron-withdrawing fluoro substituents—more difficult to hydrolyze than the other cyclobutanes and delivered only relatively low yields, product **4d** turned out to be useful because distinct NOE assignments could be made in this case (see the Supporting Information). The formation of the tricyclic compounds **4** occurs diastereoselectively with retention of the stereogenic center at position C3a formed in the course of the [2+2] photocycloaddition reaction. For compounds **4d** (76% *ee*) and **4e** (86% *ee*), it was explicitly proven that the enantiomeric excess remained unchanged relative to that of the starting materials **2d** and **2e**.

The ring expansion can be explained by the intermediacy of an onium ion. It is formed from the [2+2] photocycloaddition products by activation of the carbonyl group with a Lewis or Brønsted acid and fragmentation of the central carbon–carbon bond (Scheme 1).[17] Since we hoped that this intermediate could be trapped in a subsequent intermolecular reaction,[18] products **2b** and **2h** were treated with a Lewis acid and a silyl nucleophile ($NuSiR_3$). In the case of the eight-membered ring, cyclooctanone **5b** was obtained with Et_3SiH as hydride source, whereas over-reduction occurred in the case of compound **2h** under the same reaction conditions. However, the intermediary alcohol **5h′** was readily oxidized (IBX = 2-iodoxybenzoic acid), affording the desired cycloheptanone **5h**. The reaction proceeded with perfect diastereoselectivity, which is expected due to better shielding at the concave bottom face of the carbocycle.[19] In the same way, allyltrimethylsilane could be used to perform a diastereoselective carbon–carbon bond-formation reaction. Product **6b**



Scheme 1. Diastereoselective BF_3-catalyzed ring opening of the photocycloaddition products **2b** und **2h** to deliver cyclooctanones **5b** and **6b** and cycloheptanones **5h** and **6h**.

was obtained in 76% yield (d.r. = 87/13) and product **6h** was even obtained in diastereomerically pure form (d.r. > 95/5).

In summary, for the first time representatives of the most important substrate class for [2+2] photocycloaddition reactions (2-cycloalkenones) were reacted in an enantioselective, intramolecular variant of the reaction. Thus, this study confirms that enantioselective reaction control by the selective excitation of a Lewis acid/substrate complex is generally applicable. So far, this principle has only been applied to 5,6-dihydro-4-pyridones as substrates.[10d] Furthermore, the products obtained in the present study open up new pathways to interesting molecular frameworks. In this context, the octahydrocyclohepta[*b*]furan framework (compounds **5h**, **6h**) seems to be of particular relevance.[20]

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[1] Reviews: a) H. N. C. Wong, M.-Y. Hon, C.-W. Tse, Y.-C. Yip, *Chem. Rev.* **1989**, *89*, 165–198; b) P. Dowd, W. Zhang, *Chem. Rev.* **1993**, *93*, 2091–2115; c) J. C. Namyslo, D. E. Kaufmann, *Chem. Rev.* **2003**, *103*, 1485–1537; d) C. A. Carson, M. A. Kerr, *Chem. Soc. Rev.* **2009**, *38*, 3051–3060.

[2] Reviews: a) G. Mehta, V. Singh, *Chem. Rev.* **1999**, *99*, 881–930; b) J. W. Blunt, B. R. Copp, M. H. G. Munro, P. T. Northcote, M. R. Prinsep, *Nat. Prod. Rep.* **2005**, *22*, 15–61; Beispiele: c) N. A. Petasis, M. A. Petane, *Tetrahedron* **1992**, *48*, 5757–5821; d) M. A. Battiste, P. M. Delphrey, D. C. Wright, *Chem. Eur. J.* **2006**, *12*, 3438–3447.

[3] Reviews on fragmentation reactions and their synthetic application: a) W. Oppolzer, *Acc. Chem. Res.* **1982**, *15*, 135–141; b) J. D. Winkler, C. M. Bowen, F. Liotta, *Chem. Rev.* **1995**, *95*, 2003–2020; c) J. Iriondo-Alberdi, M. F. Greaney, *Eur. J. Org. Chem.* **2007**, 4801–4815; d) N. Hoffmann, *Chem. Rev.* **2008**, *108*, 1052–1103; e) T. Bach, J. P. Hehn, *Angew. Chem. Int. Ed.* **2011**, *50*, 1000–1045; *Angew. Chem.* **2011**, *123*, 1032–1077.

[4] Examples of radical fragmentations: a) G. L. Lange, C. Gottardo, *J. Org. Chem.* **1995**, *60*, 2183–2187; b) M. T. Crimmins, S. Huang, L. E. Guise-Zawacki, *Tetrahedron Lett.* **1996**, *37*, 6519–6522; c) M. T. Crimmins, Z. Wang, L. A. McKerlie, *J. Am. Chem.*

Soc. **1998**, *120*, 1747 – 1756; d) G. L. Lange, L. Furlan, M. C. MacKinnon, *Tetrahedron Lett.* **1998**, *39*, 5489 – 5492; e) J. P. Hehn, E. Herdtweck, T. Bach, *Org. Lett.* **2011**, *13*, 1892 – 1895.

[5] Reviews: a) H. Hikino, P. de Mayo, *J. Am. Chem. Soc.* **1964**, *86*, 3582 – 3583; b) P. de Mayo, *Acc. Chem. Res.* **1971**, *4*, 41 – 47; c) W. Oppolzer, T. Godel, *J. Am. Chem. Soc.* **1978**, *100*, 2583 – 2584.

[6] Examples of the [2+2] photocycloaddition/retro-Mannich sequence: a) J. D. Winkler, C. L. Muller, R. D. Scott, *J. Am. Chem. Soc.* **1988**, *110*, 4831 – 4832; b) J. D. Winkler, P. M. Hershberger, *J. Am. Chem. Soc.* **1989**, *111*, 4852 – 4856; c) J. D. Winkler, R. D. Scott, P. G. Williard, *J. Am. Chem. Soc.* **1990**, *112*, 8971 – 8975; d) J. D. Winkler, J. M. Axten, *J. Am. Chem. Soc.* **1998**, *120*, 6425 – 6426.

[7] Examples: a) L. M. Tolbert, M. B. Ali, *J. Am. Chem. Soc.* **1982**, *104*, 1742 – 1744; b) A. I. Meyers, S. A. Fleming, *J. Am. Chem. Soc.* **1986**, *108*, 306 – 307; c) M. Demuth, A. Palomer, H.-D. Sluma, A. K. Dey, C. Krüger, M.-H. Tsay, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1117 – 1119; *Angew. Chem.* **1986**, *98*, 1093 – 1095; d) C. Chen, V. Chang, X. Cai, E. Duesler, P. S. Mariano, *J. Am. Chem. Soc.* **2001**, *123*, 6433 – 6434; e) H. Saito, T. Mori, T. Wada, Y. Inoue, *J. Am. Chem. Soc.* **2004**, *126*, 1900 – 1906.

[8] Examples: a) T. Bach, H. Bergmann, K. Harms, *Angew. Chem. Int. Ed.* **2000**, *39*, 2302 – 2304; *Angew. Chem.* **2000**, *112*, 2391 – 2393; b) T. Bach, H. Bergmann, *J. Am. Chem. Soc.* **2000**, *122*, 11525 – 11526; c) A. Furutani, K. Katayama, Y. Uesima, M. Ogura, Y. Tobe, H. Kurosawa, K. Tsutsumi, T. Morimoto, K. Kakiuchi, *Chirality* **2006**, *18*, 217 – 221; d) D. Albrecht, F. Vogt, T. Bach, *Chem. Eur. J.* **2010**, *16*, 4284 – 4296; e) S. C. Coote, T. Bach, *J. Am. Chem. Soc.* **2013**, *135*, 14948 – 14951.

[9] Reviews: a) M. T. Crimmins, T. L. Reinhold, *Org. React.* **1993**, *44*, 297 – 588; b) J. Mattay, R. Conrads, R. Hoffmann in *Methoden der Organischen Chemie (Houben-Weyl) 4th ed.*, Vol. E 21c (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart **1995**, pp. 3085 – 3132; c) P. Margaretha in *Molecular and Supramolecular Photochemistry, Vol. 12* (Eds.: A. G. Griesbeck, J. Mattay), Marcel Dekker, New York, **2005**, pp. 211 – 237; d) J. P. Hehn, C. Müller, T. Bach in *Handbook of Synthetic Photochemistry* (Eds.: A. Albini, M. Fagnoni), Wiley-VCH, Weinheim, **2009**, pp. 171 – 215.

[10] a) C. Müller, A. Bauer, T. Bach, *Angew. Chem. Int. Ed.* **2009**, *48*, 6640 – 6642; *Angew. Chem.* **2009**, *121*, 6767 – 6769; b) H. Guo, E. Herdtweck, T. Bach, *Angew. Chem. Int. Ed.* **2010**, *49*, 7782 – 7785; *Angew. Chem.* **2010**, *122*, 7948 – 7951; c) C. Müller, A. Bauer, M. M. Maturi, M. C. Cuquerella, M. A. Miranda, T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 16689 – 16697; d) R. Brimioulle, T. Bach, *Science* **2013**, *342*, 840 – 843; e) R. Alonso, T. Bach, *Angew. Chem. Int. Ed.* **2014**, *53*, 4368 – 4371; *Angew. Chem.* **2014**, *126*, 4457 – 4460; f) J. Du, K. L. Skubi, D. M. Schultz, T. P. Yoon, *Science* **2014**, *344*, 392 – 396; g) N. Vallavoju, S. Selvakumar, S. Jockusch, M. P. Sibi, J. Sivaguru, *Angew. Chem. Int. Ed.* **2014**, *53*, 5604 – 5608; *Angew. Chem.* **2014**, *126*, 5710 – 5714; h) M. M. Maturi, T. Bach, *Angew. Chem. Int. Ed.* **2014**, *53*, 7661 – 7664; *Angew. Chem.* **2014**, *126*, 7793 – 7796.

[11] Short overview: R. Neier, *Science* **2014**, *344*, 368 – 369.

[12] a) M. C. Pirrung, N. J. G. Webster, *J. Org. Chem.* **1987**, *52*, 3603 – 3613; b) J. Mattay, A. Banning, E. W. Bischof, A. Heidbreder, J. Runsink, *Chem. Ber.* **1992**, *125*, 2119 – 2127.

[13] Emission spectra: M. M. Maturi, M. Wenninger, R. Alonso, A. Bauer, A. Pöthig, E. Riedle, T. Bach, *Chem. Eur. J.* **2013**, *19*, 7461 – 7472.

[14] Apart from **2a** two further products are known; a) **2d**: D. A. Fort, T. J. Woltering, M. Nettekoven, H. Knust, T. Bach, *Angew. Chem. Int. Ed.* **2012**, *51*, 10169 – 10172; *Angew. Chem.* **2012**, *124*, 10316 – 10319; b) **2f**: Y. Tamura, H. Ishibashi, Y. Kita, M. Ikeda, *J. Chem. Soc. Chem. Commun.* **1973**, 101 – 102.

[15] a) D. H. Ryu, E. J. Corey, *J. Am. Chem. Soc.* **2003**, *125*, 6388 – 6390; b) E. J. Corey, *Angew. Chem. Int. Ed.* **2009**, *48*, 2100 – 2117; *Angew. Chem.* **2009**, *121*, 2134 – 2151; c) R. C. Johnston, P. H.-Y. Cheong, *Org. Biomol. Chem.* **2013**, *11*, 5057 – 5064.

[16] For an alternative pathway for the ring opening of the cycloaddition products, see: a) E. W. Bischof, J. Mattay, *Tetrahedron Lett.* **1990**, *31*, 7137 – 7140; b) J. Cossy, P. Aclinou, V. Bellosta, N. Furet, J. Baranne-Lafont, D. Sparfel, C. Souchaud, *Tetrahedron Lett.* **1991**, *32*, 1315 – 1316; c) W. D. Shipe, E. J. Sorensen, *J. Am. Chem. Soc.* **2006**, *128*, 7025 – 7035.

[17] For related ring-opening reactions of thermally generated cyclobutanes, see: S. Yamago, A. Takeichi, E. Nakamura, *J. Am. Chem. Soc.* **1994**, *116*, 1123 – 1124.

[18] Examples from cyclopropane chemistry: a) M. Yu, B. L. Pagenkopf, *Org. Lett.* **2003**, *5*, 4639 – 4640; b) S. J. Gharpure, M. K. Shukla, U. Vijayasree, *Org. Lett.* **2009**, *11*, 5466 – 5469. Review: c) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151 – 1196; d) M. A. Cavitt, L. H. Phun, S. France, *Chem. Soc. Rev.* **2014**, *43*, 804 – 818.

[19] a) H. O. House, G. S. Nomura, D. VanDerveer, J. E. Wissinger, *J. Org. Chem.* **1986**, *51*, 2408 – 2416; b) C. Mehta, N. Krishnamurthy, S. R. Karra, *J. Am. Chem. Soc.* **1991**, *113*, 5765 – 5775.

[20] A literature search revealed more than 2500 natural products exhibiting the octahydrocyclohepta[*b*]furan framework.

