
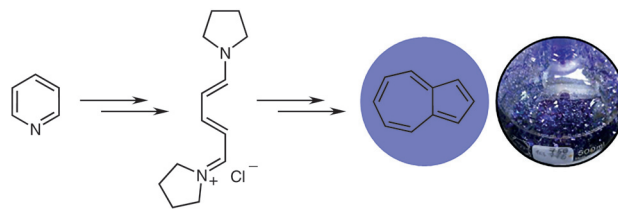


A Convenient Synthesis of Azulene

Heinz Langhals* 
Moritz Eberspächer

LMU University of Munich, Department of Chemistry,
Butenandtstr. 13, 81377 Munich, Germany
Langhals@lrz.uni-muenchen.de

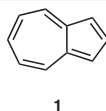


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Abstract. An improved and scalable synthesis of azulene has been developed by the application of pyrrolidine as a reagent and continuous steam distillation and extraction for workup. Applications for the coloration of perfluorinated media and silicones were demonstrated.

Key words arenes, azulene, annulenes, carbocycles, natural products, ring closure

Azulene (**1**; Figure 1),¹ a hydrocarbon with unusual properties,² is of interest in many fields. Its deep blue color is caused by an appreciable bathochromic absorption of this simple C₁₀H₈ compound, and its fluorescence of the second electronically excited state is one of the most prominent examples of the exceptions of Kasha's rule.³ The unusually efficient interaction with solvents and polymeric media allows the coloration of media that are usually difficult to stain, such as perfluorinated hydrocarbons and ethers, silicon oil, and even PTFE.⁴ Moreover, the chamomile-derived azulene finds many applications in cosmetics.⁵ Finally, **1** is useful for basic chemical education⁶ both for learning about aromaticity and for simple chemical experiments⁷ with minimal equipment, because the compound is considered to be nonhazardous;^{8,9} indeed the material has internationally approved certification for skin applications.



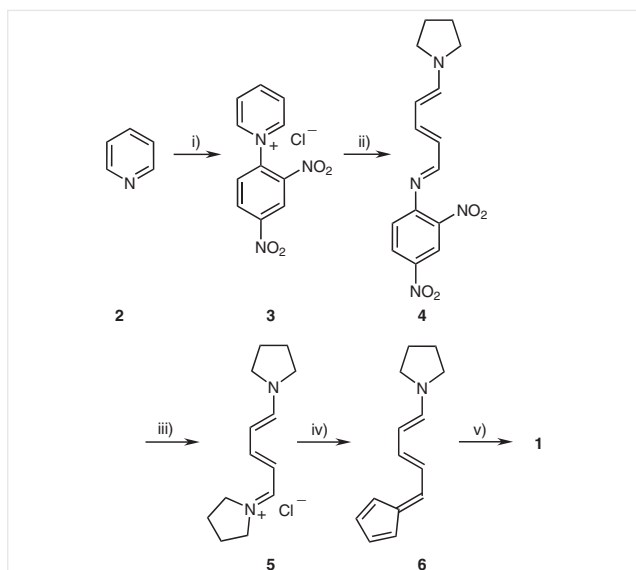
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Figure 1

Several syntheses of azulene (**1**) have been published¹⁰ such as aromatization of hydro derivatives^{2c,11} (for more recent developments see ref.¹²). A popular approach is the concept developed by Ziegler and Hafner, starting with cyclopentadiene and annellating the seven membered ring, with the required five carbon atoms being obtained from ring-opening of pyridine.¹³ A secondary amine is required to support the latter reaction, and *N*-methylaniline was initially applied; however, this material is difficult to remove from the final product. Later, a significantly more reliable preparation applying dimethylamine was elaborated for organic synthesis.¹⁴ However, the necessary preparation of an anhydrous solution of gaseous dimethylamine in pyridine and the final evolution of gaseous dimethylamine makes handling complex; furthermore, decomposition of azulene under the reaction conditions remains a problem and causes a quantity-dependent inverse scaling of yields. Better results were obtained through the use of benzidine¹⁵ as a medium for the reaction; however, this is problematic for applications of **1** in cosmetics and basic chemical research because of possible residual contaminations. As a consequence, none of the syntheses are completely satisfactory.

Here, we report an improvement of the synthesis that is suitable for scaling up, and that involves simplified processing in which the handling of the problematic benzidine is avoided. We started the synthesis with the ring opening of pyridine (**2**) by means of 2,4-dinitrochlorobenzene to obtain Zincke salt **3**. Subsequent reaction with pyrrolidine¹⁶ gave **4** and further reaction gave König's salt **5**.¹⁷ Solvolysis to give Zincke aldehyde and in situ base-induced condensation with cyclopentadiene allowed the preparation of the hitherto unknown **6**, from which a subsequent rearrangement and thermal elimination of pyrrolidine formed azulene (**1**). The sequence, which is summarized in Scheme 1, may be carried out either stepwise or, more conveniently, in one pot. The comparably sluggish reaction of **6** and the

decomposition of the accumulated azulene can limit the syntheses according to Ziegler and Hafner's route; moreover, the collection of the finally formed **1** by extraction with a Soxhlet apparatus proved to be very tedious. Better results and a yield of 39% of isolated material (42% after extended the reaction time of 14 d) was obtained when steam distillation was used to remove the formed **1** continuously from the reaction mixture. However, large volumes of distillate were obtained and handling and collection of **1** by extraction was laborious.



Scheme 1 Synthesis of azulene (**1**). Reagents and conditions: (i) 2,4-dinitrochlorobenzene (ii) pyrrolidine (– HCl); (iii) pyrrolidine, HCl; (iv) cyclopentadiene, sodium methanolate; (v) thermal rearrangement and elimination of pyrrolidine.

More convenient handling was facilitated by combining steam distillation and extraction in the continuously operating apparatus¹⁸ shown in Figure 2. This arrangement allows the preparation of azulene in varying quantities without the yields scaling with the batch size. The purity of **1** thus obtained is higher than that obtained by using standard procedures, and traces of by-products can be removed by simple chromatographic methods. The purity of **1** proved to be of importance for the stability; pure material could be stored at room temperature in air for more than two years without any evidence for the reported decomposition.²

The secondary amine applied as a reagent actually plays the role of a catalyst because of its recovery after the reaction. Structural influences on the efficiency are expected to be complex because it is involved in four steps of the one-pot synthesis: Firstly the addition to the pyridinium salt to form **4** and analogues; then a second attack to form König's salts such as **5**, the exchange by the C–H acid cyclopentadiene to form **6**, and finally the elimination in the last step

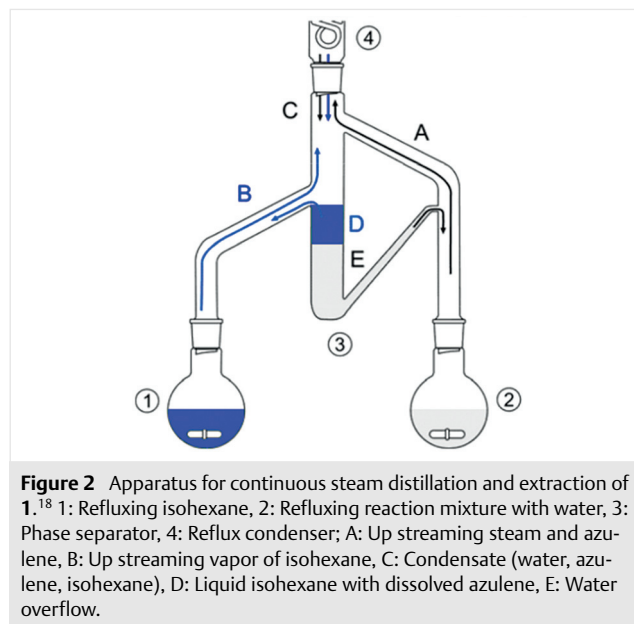


Figure 2 Apparatus for continuous steam distillation and extraction of **1**.¹⁸ 1: Refluxing isohehexane, 2: Refluxing reaction mixture with water, 3: Phase separator, 4: Reflux condenser; A: Up streaming steam and azulene, B: Up streaming vapor of isohehexane, C: Condensate (water, azulene, isohehexane), D: Liquid isohehexane with dissolved azulene, E: Water overflow.

of the synthesis of **1**. As a consequence, various electronic and steric influences are expected on the overall yield of **1**. The application of diethylamine was taken as a reference and gave 13% yield under these conditions (Table 1, entry 1). A reduction in the steric effects upon ring closure with azetidione lowered the yield slightly to 10% (entry 2); this may due to lower steric effects in elimination and electronic effects of this strained amine. The optimum was found for the five-membered ring in pyrrolidine (40%; entry 3). A further ring expansion to the six-membered ring in piperidine lowered the yield (entry 4), for which steric effects in the initial steps may be important. A further reduction in the yield when using morpholine indicates the importance of electronic effects in this six-membered cyclic amine (3%; entry 5). A strong increase in steric bulk such as in diisopropylamine, blocks the reaction completely (entry 6); in this case, only a weak intermediary red coloration indicated the formation of some König's salt. Finally, 2,2,6,6-tetramethylpiperidine (entry 7) gave no product or coloration; one can suppose that the reaction conditions are not harsh enough for the application of this amine (compare the recommended¹⁵ application of the problematic melt benzdine).

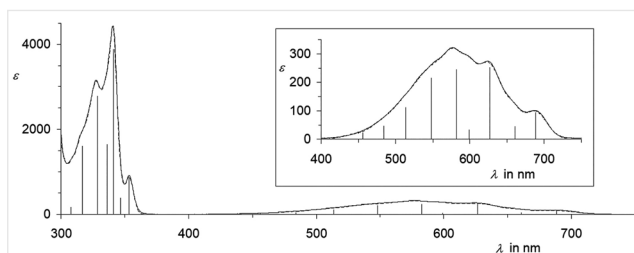
Azulene (**1**) is isolated in large dark-blue plates and forms deep-blue solutions in solvents such as chloroform, for which the UV/Vis spectrum is shown in Figure 3 (for spectra in hydrocarbons see, for example, ref.¹⁹). The characteristic, structured absorption could be split into individual Gaussian bands²⁰ according to Equation 1 for which the wavelength-dependent molar absorptivity $\epsilon_{(\lambda)}$ in the UV/Vis spectrum is precisely described by a sum of n Gaussian functions. $\epsilon_{\max(i)}$ denotes the intensities of the individual Gaussian bands i , $\lambda_{\max(i)}$ their positions, and $\sigma(i)$ their half

Table 1 Overall Yields of Isolated **1** by Continuous Extraction Relative to 2,4-Dinitrochlorobenzene Depending on the Applied Secondary Amine^a

Entry	Amine	Isolated 1 (%)
1	diethylamine	13
2	azetidine	10
3	pyrrolidine	40 (42 ^b)
4	piperidine	20 ^c
5	morpholine	3 ^c
6	diisopropylamine ^d	–
7	2,2,6,6-tetramethylpiperidine	–

^a Reaction time 6 d.^b Reaction time 14 d.^c Simple extraction.^d Intermediary light-red color as indicator for the formation of a König's salt.

widths. The factor 100 in the exponent simplifies the inter-conversion between wavelengths λ in nm and wavenumbers of the σ values in kK (10000 cm^{-1}).

**Figure 3** UV/Vis absorption spectrum of **1** in chloroform (solid line) and simulated spectrum based on a Gaussian analysis (dashed curve, mainly covered by the experimental spectrum). Bars: Positions and intensities of the individual Gaussian bands. Insert: Details of the bathochromic region.

$$\epsilon_{(\lambda)} = \sum_{i=0}^n \epsilon_{\max(i)} e^{-100 \left(\frac{1}{\lambda} - \frac{1}{\lambda_{\max(i)}} \right)^2 / 2\sigma_{(i)}^2}$$

Equation 1

The UV/Vis spectrum of azulene in chloroform (solid curve in Figure 3) could be simulated (dashed curve in Figure 3, mainly covered by the experimental spectrum) with high precision by using Equation 2 and the parameters given in Table 2: Residual $R = 0.9\%$ for 300 to 800 nm.

$$(R = \sqrt{\int [\epsilon(\lambda)_{\text{calcd.}} - \epsilon(\lambda)_{\text{exp.}}]^2 d\lambda / \int [\epsilon(\lambda)_{\text{exp.}}]^2 d\lambda})$$

Equation 2 Residual concerning experimental data and simulation

A very similar pattern of Gaussian bands was found in the visible ($\lambda > 400\text{ nm}$) and in the UV ($\lambda < 400\text{ nm}$); however, with about ten times higher absorptivity for the latter (see Figure 3 and Table 2).

Table 2 Gaussian Analysis of UV/Vis Spectra of **1** in Chloroform (300–800 nm) Indicating the Individual Bands i

i	$\lambda_{\max(i)}$ ^a	$\epsilon_{\max(i)}$ ^b	$2\sigma^2(i)$ ^c
1	688.6	95.4	0.202
2	660.6	45.1	0.087
3	626.6	252.7	0.504
4	599.2	33.4	0.074
5	582.3	245.7	0.532
6	548.0	215.1	0.848
7	513.8	111.9	0.819
8	484.1	46.2	0.803
9	456.0	22.5	2.665
10	353.3	895.4	0.155
11	346.7	393	0.05
12	341.3	3890.4	0.122
13	335.9	1658	0.123
14	328.4	2781	0.48
15	316.7	1608.0	0.714
16	307.9	164	0.089
17	273.3	8769	6.457

^a Position of the individual Gaussian band i ; see Equation 1.^b Absorptivity of the individual bands.^c Widths of the individual bands.

Azulene exhibits an unusually high solubility in organic solvents; surprisingly, solvents that are typically difficult to color such as silicone oil and even perfluorinated aliphatic and aromatic hydrocarbons, for example perfluorodecalin, as well as ethers, could be colored deeply blue by addition of **1** (see Figure 4 and Table 3). The coloration of the latter is important for applications in eye surgery.⁸ Moreover, the generally high solubility of **1** allows its application in micellar structures⁷ in water-based cosmetics.

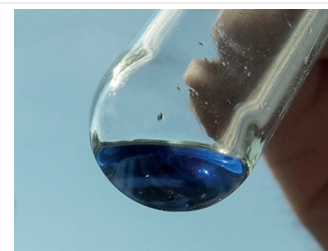
**Figure 4** Coloration of perfluorodecalin by **1**

Table 3 Solubility of **1** in Perfluorinated Hydrocarbons and Silicone Oil Based on UV/Vis Spectroscopic Measurements^a

Solvent	Solubility of 1 (mmol·L ⁻¹)
Perfluorohexane (CAS Reg. No. 355-42-0)	2.7
Perfluoromethylcyclohexane (CAS Reg. No. 355-02-2)	3.4
Perfluorodecalin (CAS Reg. No. 306-94-5)	3.6
Perfluoro-2-methyl-2-pentene (CAS Reg. No. 1584-03-8)	5.7
Perfluorotributylamine (CAS Reg. No. 311-89-7)	2.6
Hexafluorobenzene (CAS Reg. No. 392-56-3)	650
Poly-1,1,2,3,3,3-hexafluoropropylene oxide (CAS Reg. No. 69991-67-9; HT110, b.p. 110 °C, M _n 580)	3.1
Silicone oil (Baysilon Grüssing 250 °C; Wacker silicone oil AK 100, n = 70, M _n 5000)	110

^a Molar absorptivity of **1**: ϵ (340.6 nm) = 4446 L·mol⁻¹·cm⁻¹, ϵ (578.4 nm) = 323 L·mol⁻¹·cm⁻¹.

To conclude, azulene (**1**) could be efficiently prepared by Ziegler and Hafner's route, wherein the use of pyrrolidine as the required intermediary secondary amine allowed a simple procedure. The obtained yields were similar and were unaffected by batch size. Workup by continuous close-loop steam distillation with an interlinked extraction makes synthesis of **1** more convenient, even in larger scales, and is thus well accessible. The UV/Vis spectra of **1** could be simulated with high precision by using a series of Gaussian functions. Applications of **1** in cosmetics and for the coloration of silicone oil and of perfluorinated organic compounds including those applied in eye surgery are of technical interest.

Azulene (**1**)

1-Chloro-2,4-dinitrobenzene (20.3 g, 100 mmol) and anhydrous pyridine (120 mL) under nitrogen atmosphere were heated with stirring at 90 °C for 4 h (formation of a voluminous precipitate, initially colorless, then turning from yellow to finally brown), cooled to 0 °C, then slowly treated dropwise with pyrrolidine (18.1 mL, 220 mmol, clearing and turning to red) and stirred at r.t. for 16 h. The red solution was then treated with freshly (!) distilled cyclopentadiene (8.68 mL, 105 mmol) and then a solution of sodium methoxide in methanol [freshly prepared from sodium (2.30 g, 100 mmol) and MeOH (40.0 mL)] was added dropwise. The reaction mixture was then stirred at r.t. for 16 h, then concentrated by distillation with the application of a Vigreux column (30 cm, bath 130 °C) until 95 °C of the distillate, and subsequently allowed to cool to r.t. The distillate was treated with anhydrous pyridine (200 mL), then heated to reflux for 6 d (bath 135 °C), and allowed to cool to r.t. After addition of distilled water (200 mL), the reaction flask was attached to a phase separator according to Fig-

ure 2, equipped with distilled water (300 mL) and isohexane (300 mL), heated to reflux (bath 125 °C) so that steam distillation and phase separation proceeded simultaneously and steam distilled and extracted until colorless condensation of isohexane (1–2 days). The deep-blue phase of isohexane was washed with 2 M aqueous HCl (3 × 100 mL), distilled water, then dried with Na₂SO₄, evaporated, purified by column separation (basic alumina, activity II, isohexane, first intensely blue band), filtrated through a D5 glass filter and evaporated.

Yield: 4.4 g (36%); bluish black leaflets; mp 99–100 °C (Lit.²¹ 99–100 °C); R_f = 0.67 (Al₂O₃ neutral, isohexane).

IR (ATR): 3075.8 (vw), 2958.5 (vw), 2923.8 (w), 2853.8 (vw), 1816.3 (w), 1641.8 (br), 1569.9 (w), 1530.5 (w), 1475.8 (m), 1452.3 (w), 1437.8 (w), 1389.2 (w), 1296.0 (w), 1260.8 (vw), 1204.3 (m), 1151.9 (vw), 1051.7 (w), 1012.2 (w), 984.2 (w), 965.0 (m), 952.1 (m), 897.3 (w), 823.6 (w), 792.2 (w), 755.0 (vs), 725.3 (s), 674.3 (m) cm⁻¹.

¹H NMR (600 MHz, CDCl₃, 27 °C, TMS): δ = 7.18 (t, ³J_{H-H} = 9.8 Hz, 2 H, CH_{Ar}), 7.41 (d, ³J_{H-H} = 3.7 Hz, 2 H, CH_{Ar}), 7.60 (t, ³J_{H-H} = 9.9 Hz, 1 H, CH_{Ar}), 7.92 (t, ³J_{H-H} = 3.7 Hz, 1 H, CH_{Ar}), 8.36 (d, ³J_{H-H} = 9.1 Hz, 2 H, CH_{Ar}).

UV/vis (CHCl₃): λ_{\max} (ϵ_{rel}) = 327.40 (0.71), 340.60 (1.00), 353.20 (0.21), 579.20 (0.08) nm.

MS (DEI⁺/70 eV): m/z (%) = 129.1 (7) [M⁺ + H], 128.1 (100) [M⁺], 127.0 (16) [M⁺ - H], 126.0 (7) [M⁺ - 2H], 102.0 (10), 84.9 (1), 82.9 (2), 81.9 (1), 78.0 (1), 76.0 (2), 75.0 (3), 74.0 (4), 63.0 (3), 51.0 (1), 50.0 (2), 50.0 (2), 50.0 (2), 43.0 (1).

HRMS (DEI-C1 + C EI Full ms [39.50–440.50]): m/z calcd for C₁₀H₈: 128.0626; found: 128.0626, Δ = 0.0 mmu.

Anal. Calcd for C₁₀H₈: C, 93.71; H, 6.29. Found: C, 93.03; H, 6.24.

References

- (1) (a) Sherndal, A. E. *J. Am. Chem. Soc.* **1915**, *37*, 167. (b) Sherndal, A. E. *J. Am. Chem. Soc.* **1915**, *37*, 1537.
- (2) Reviews: (a) Tobe, Y. *Chem. Rec.* **2015**, *15*, 86. (b) Saito, K.; Kawamata, J.; Ito, S. *Mirai Zairyo* **2008**, *8*, 32; *Chem. Abstr.* **2008**, *150*, 514793. (c) Gordon, M. *Chem. Rev.* **1952**, *50*, 127.
- (3) (a) Binsch, G.; Heilbronner, E.; Jankov, R.; Schmidt, D. *Chem. Phys. Lett.* **1967**, *1*, 135. (b) Beer, M.; Longuet-Higgins, H. C. *J. Chem. Phys.* **1955**, *23*, 1390.
- (4) Langhals, H.; Eberspächer, M. Ger. Offen DE 102012019843.4, **2012**; *Chem. Abstr.* **2014**, *160*, 691028
- (5) Della Loggia, R.; Carle, R.; Sosa, S.; Tubaro, A. *Planta Med.* **1990**, *56*, 657.
- (6) (a) Brieger, G. *J. Chem. Educ.* **1992**, *69*, A262. (b) Lemal, D. M.; Goldman, G. D. *J. Chem. Educ.* **1988**, *65*, 923.
- (7) Langhals, H.; Eberspächer, M.; Hofer, A. *J. Chem. Educ.* **2015**, *92*, 1725.
- (8) Kobuch, K.; Menz, D. H.; Hoerauf, H.; Dresch, J. H.; Gabel, V.-P. *Graefe's Arch. Clin. Exp. Ophthalmol.* **2001**, *239*, 635; DOI: 10.1007/s004170100330.
- (9) Teufel, R. *Int. J. Toxicol.* **1999**, *18*, 03 27.
- (10) (a) Copland, D.; Leaver, D.; Menzies, W. B. *Tetrahedron Lett.* **1977**, *639*. (b) Mukherjee, D.; Dunn, L. C.; Houk, K. N. *J. Am. Chem. Soc.* **1979**, *101*, 251. (c) Gupta, Y. N.; Mani, S. R.; Houk, K. N. *Tetrahedron Lett.* **1982**, *23*, 495.
- (11) Treibs, W.; Kirchhof, W.; Ziegenbein, W. *Fortschr. Chem. Forsch.* **1955**, *3*, 334.

- (12) (a) Carret, S.; Blanc, A.; Coquerel, Y.; Berthod, M.; Greene, A. E.; Deprés, J.-P. *Angew. Chem. Int. Ed.* **2005**, *44*, 5130. (b) Crombie, A. L.; Kane, J. L.; Shea, K. M.; Danheiser, R. L. *J. Org. Chem.* **2004**, *69*, 8652. (c) Usui, K.; Tanoue, K.; Yamamoto, K.; Shimizu, T.; Suemune, H. *Org. Lett.* **2014**, *16*, 4662.
- (13) (a) Ziegler, K.; Hafner, K. *Angew. Chem.* **1955**, *67*, 101. (b) Ziegler, K. *Angew. Chem.* **1955**, *67*, 101. (c) Hafner, K. *Angew. Chem.* **1955**, *67*, 101. (d) Rosler, H.; König, W. *Naturwissenschaften* **1955**, *42*, 211.
- (14) Hafner, K.; Meinhardt, K.-P. *Org. Synth.* **1984**, *62*, 134.
- (15) Hafner, K. *Justus Liebigs Ann. Chem.* **1957**, *606*, 79.
- (16) Wilson, R. M.; Gardner, E. J.; Squire, R. E. *J. Chem. Educ.* **1973**, *50*, 94.
- (17) (a) Nolte, K. D.; Daehne, S. *J. Prakt. Chem.* **1976**, *318*, 643. (b) Hünig, S.; Baron, W. *Chem. Ber.* **1957**, *90*, 403.
- (18) Hünig, S.; Kreitmeier, P.; Märkl, G.; Sauer, J. *Arbeitsmethoden in der Organischen Chemie, 1. Auflage*; Lehmanns Media: Berlin, **2006**, 111–112.
- (19) (a) Wagner, B. D.; Tittelbach-Helmrich, D.; Steer, R. P. *J. Phys. Chem.* **1992**, *96*, 7904. (b) Torii, H.; Tasumi, M. *Spectrochim. Acta, Part A* **1989**, *45*, 1173. (c) Olszowski, A.; Ruziewicz, Z.; Chojnacki, H. *J. Mol. Struct.* **1975**, *28*, 5.
- (20) (a) Langhals, H. *Anal. Bioanal. Chem.* **2002**, *374*, 573. (b) Langhals, H. *Spectrochim. Acta, Part A* **2000**, *56*, 2207.
- (21) Tietze, L.-F.; Eicher, T.; Diederichsen, U.; Speicher, A. *Reactions and Syntheses in the Organic Chemistry Laboratory*, 1st ed.; Wiley-VCH: Weinheim, **2007**, 170.