Tandem Reactions

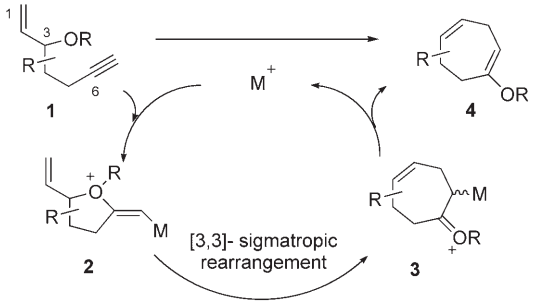
DOI: 10.1002/ange.200705117

Gold(I)-Catalyzed Cycloisomerization of 3-Methoxy-1,6-enynes Featuring Tandem Cyclization and [3,3]-Sigmatropic Rearrangement**

*Hyo J. Bae, Baburaj Baskar, Sang E. An, Jae Y. Cheong, Daniel T. Thangadurai, In-Chul Hwang, and Young H. Rhee**

The transition-metal-catalyzed cycloisomerization of 1,6-enynes is one of the most powerful strategies for the synthesis of highly functionalized carbocyclic compounds.[1] Recent studies on the gold- and platinum-catalyzed cycloisomerizations are particularly noteworthy because of the structural diversity of the products provided by these reactions.[2] Numerous carbocyclic frameworks have been assembled by using structurally simple 1,6-enyne precursors. In many reactions, addition of internal olefins to the metal-activated alkynes has been proposed as the key event.[3]

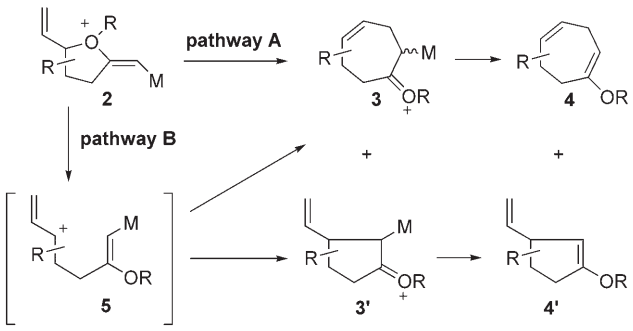
Unlike the structurally simple 1,6-enynes mentioned above, 3-alkoxy-1,6-enynes **1** offer an alternative mode of reaction as depicted in Scheme 1. In this case, the oxygen atom can participate as a competing nucleophile in the addition to the metal-activated alkynes. The resulting cyclic oxonium ion **2** has a structural platform for a [3,3]-sigmatropic rearrangement, which generates cycloheptenyl cation **3**.[4] Elimination of the cationic metal species produces 1-alkoxy-1,4-cycloheptadiene **4** in a catalytic manner.



Scheme 1. Proposed mechanism for the gold(I)-catalyzed cycloisomerization of 3-alkoxy-1,6-enynes.

On the basis of the recent reports on Lewis acid promoted (or catalyzed) Claisen rearrangement of cyclic enol ethers,[5] we envisioned that the involvement of the oxonium ion intermediate **2** could facilitate the key [3,3]-sigmatropic process. Moreover, the enol ether moiety in **4** can be chemoselectively transformed into a variety of other functional groups. Thus, we envisaged that the proposed reaction would provide highly efficient access to cycloheptene frameworks having diverse functional groups, which are important building blocks in a variety of bioactive natural products.[6]

In light of the proposed catalytic cycle, a potentially competing pathway is the metal-catalyzed carboalkoxylation (Scheme 2; pathway B).[7] This alternative pathway would result in a mixture of cycloheptadiene **4** and cyclopentene **4′** formed from allylic cation **5**, whereas the concerted nature of the proposed sigmatropic pathway leads to the selective formation of **4** (Scheme 2; pathway A).[8]



Scheme 2. Sigmatropic rearrangement (pathway A) versus carboalkoxylation (pathway B).

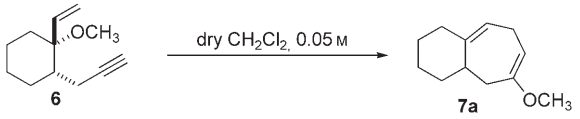
To investigate this mechanistic proposal, we initially examined various platinum and gold complexes by using **6** as the substrate (Table 1). Preliminary investigations using a platinum catalyst (Table 1, entry 1)[7c,d] or neutral [Au{P-(C_6H_5)$_3$}Cl] (Table 1, entry 2) failed to give the desired bicyclic heptadiene **7a**. To our delight, switching to pregenerated cationic gold complex **8a** (5 mol%) in CH_2Cl_2 produced the cycloisomerized product **7a** in 55% yield within 10 minutes at room temperature, and there was no evidence of the formation of carbocyclic five-membered rings (Table 1, entry 3).[9] Notably, employing a more electrophilic catalyst (**8b**)[10] gave **7a** almost instantaneously in 92% yield

[*] H. J. Bae, B. Baskar, S. E. An, J. Y. Cheong, D. T. Thangadurai, Prof. Dr. Y. H. Rhee
Department of Chemistry
POSTECH (Pohang University of Science and Technology)
Pohang, 790-784 (Korea)
Fax: (+82) 54-279-3399
E-mail: yhrhee@postech.ac.kr
Dr. I.-C. Hwang
Department of Chemistry
Center for Superfunctional Molecules
Center for Basic Sciences
POSTECH (Pohang University of Science and Technology) (Korea)

[**] This work was supported by the Korea Science and Engineering Foundation (KOSEF), which is funded by the Korean government (R01-2007-000-10889-0). H.J.B. thanks the BK21 program for a fellowship. We thank Prof. Dr. Kwang S. Kim for the supporting crystal structure analysis.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1: Optimization of the reaction conditions.



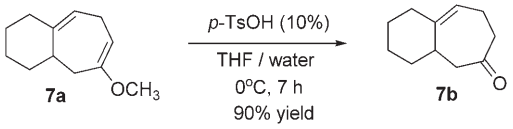
[Au{P(C$_6$H$_5$)$_3$}Cl] / AgSbF$_6$ **8a** [Au{P(C$_6$F$_5$)$_3$}Cl] / AgSbF$_6$ **8b**

Entry	Catalyst [mol%]	Solvent	*T*	*t*	Yield [%][a]
1	$PtCl_2$/CO (5%)	toluene	80°C	6 h	–[b]
2	[Au{P(C$_6$H$_5$)$_3$}Cl]	CH_2Cl_2	RT	1 h	n.r.
3	**8a** (5%)	CH_2Cl_2	RT	10 min	55
4	**8b** (5%)	CH_2Cl_2	RT	2 min	92
5	**8b** (5%)	CH_2Cl_2	−15°C	2 min	95
6	**8b** (1%)	CH_2Cl_2	−15°C	2 min	>99(97[c])
7	**8b** (0.3%)	CH_2Cl_2	−15°C	10 min	95(91[c])
8	**8b** (1%)	CH_3CN	RT	6 h	25[d]

[a] Yield determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. RT = room temperature, n.r. = no reaction. [b] A mixture of unidentified compounds was obtained. [c] Yield of isolated product. [d] A significant amount of **6** was recovered (ca. 60%).

(Table 1, entry 4). Lowering the temperature to −15°C increased the yield with little effect on the rate of the reaction (Table 1, entry 5). Interestingly, reducing the catalyst loading to 1 mol% produced **7a** in almost quantitative yield (Table 1, entry 6). Moreover, purification of this acid-labile compound by silica gel chromatography (deactivated with triethylamine) gave an analytically pure isolated sample of **7a** in 97% yield. Reduction of the catalyst loading to 0.3 mol% resulted in a completed reaction within 10 minutes, albeit with a small decrease in the yield (Table 1, entry 7).[11] Changing the solvent to CH_3CN significantly slowed the formation of **7a** (Table 1, entry 8).

Conversion of **7a** into bicyclic cyclohept-4-en-1-one **7b** was investigated to demonstrate the synthetic utility of the cycloisomerization process. After extensive optimization, we found that using catalytic *p*-TsOH (10 mol%) in aqueous THF furnished **7b** in 90% yield [Eq. (1)].[12]

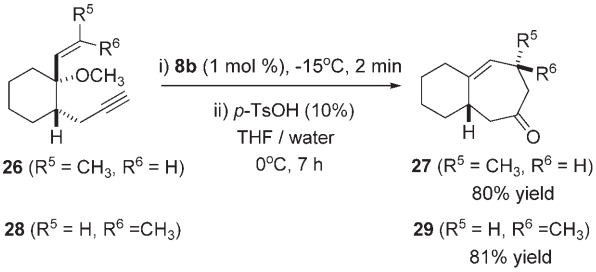


(1)

By using 1–5 mol% of the optimized catalyst shown in Table 1, various 3-methoxy-1,6-enynes were converted into 1-methoxy-1,4-cycloheptadienes in high yields (Table 2). Furthermore, all of the cycloisomerized products obtained were transformed into the corresponding cyclohept-4-en-1-ones by using the optimized conditions [Eq. (1)].[13a] As shown in Table 2, substrates with a cyclopentane framework (**9** and **11**) reacted with comparable efficiency to give cycloheptadienes (**10a** and **12a**) in nearly quantitative yields (Table 2, entries 1 and 2). Gratifyingly, acyclic substrate **13** also furnished the monocyclic product **14a** in high yield (Table 2, entry 3). The cycloisomerization was tolerant of the methyl substitution on the internal position (Table 2, entry 4), as well as on the terminal positions of the vinyl group (Table 2, entries 5 and 6). Interestingly, no significant difference in the yield was observed between the two latter examples.

Remarkably, even substrate **20**, which possesses dimethyl substituents at the terminal vinylic positions, produced ketone **21b** with a quartenary carbon center in good yield after hydration (Table 2, entry 7).[13b,14] Introducing an alkyl substituent on the homopropargylic position had little effect on the yield of the cycloisomerization reaction (Table 2, entry 8). Notably, substrate **24**, bearing a phenyl substituent at the allylic position, also produced cycloheptadiene **25a** in near-quantitative yield (Table 2, entry 9).

The data compiled in Table 2 are consistent with the working hypothesis involving the concerted sigmatropic pathway (Scheme 2, pathway A) because the exclusive formation of cycloheptadienes was observed in all cases, even when the substrate containing a carbocation stabilizing phenyl group (**24**) was employed.[15] To investigate the nature of the rearrangement of the oxonium-ion intermediate **2**, two olefin isomers (**26** and **28**) were tested. The *E* olefin substrate **26** was converted into ketone **27** in 80% yield as a single diastereomer [Eq. (2)],[16] and the structure was unambiguously determined by the X-ray crystallographic analysis (Figure 1).[17] Under identical conditions, *Z* olefin substrate **28** produced the diastereomeric ketone **29** in a comparable yield (81%) without evidence of the formation of **27**.[16] The complete transfer of stereochemical information observed in these experiments confirms the concerted nature of the rearrangement of the oxonium ion intermediate **2** (Scheme 2).



26 (R^5 = CH_3, R^6 = H) **27** (R^5 = CH_3, R^6 = H) 80% yield

28 (R^5 = H, R^6 = CH_3) **29** (R^5 = H, R^6 = CH_3) 81% yield

(2)

In summary, we discovered a highly efficient gold(I)-catalyzed cycloisomerization of 3-methoxy-1,6-enynes that features a tandem cyclization and an unprecedented [3,3]-sigmatropic rearrangement as the key event. Notably, the reaction can be performed under very mild conditions by using a low catalyst loading (maximum turnover number ca. 300). The synthetic potential of the reaction was demonstrated by the facile conversion into the various cyclohept-4-en-1-ones. Extrapolation of this method to the formation of other carbocyclic rings and the application to the total synthesis of bioactive natural products are currently under investigation.

Experimental Section

Cycloisomerization of **6** to **7a**: Methylene chloride (10 mL) was added to a mixture of gold complex [Au{P(C$_6$F$_5$)$_3$}Cl] (5.1 mg,

Table 2: Scope of the gold(I)-catalyzed cycloisomerization of 3-methoxy-1,6-enynes.[a]

Entry	Substrate	Catalyst [mol%]	Product	Yield [%][b]	Ketone	Yield [%][b]
1	**9** $R^1 = H$	1	**10a**	96	**10b**	90
2	**11** $R^1 = CH_3$	5	**12a**	95	**12b**	88
3	**13** $R^2 = H$	1	**14a**	90	**14b**	84
4	**15** $R^2 = CH_3$	1	**16a**	85	**16b**	85
5	**17** $R^3 = CH_3$, $R^4 = H$	1	**18a**	89	**18b**	80
6	**19** $R^3 = H$, $R^4 = CH_3$	1	**18a**	95	**18b**	—
7[e]	**20** $R^3 = CH_3$, $R^4 = CH_3$	2	**21a**	74[c]	**21b**	60[d]
8	**22**	5	**23a**	94	**23b**	90
9	**24**	2	**25a**	97	**25b**	74

[a] Conditions: Substrate (0.05 M), catalyst **8b**, −15 °C, dry CH_2Cl_2. [b] Yield of isolated product for each step. [c] Yield determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard. [d] Yield of isolated product for the two-step conversion. [e] The reaction was performed at room temperature.

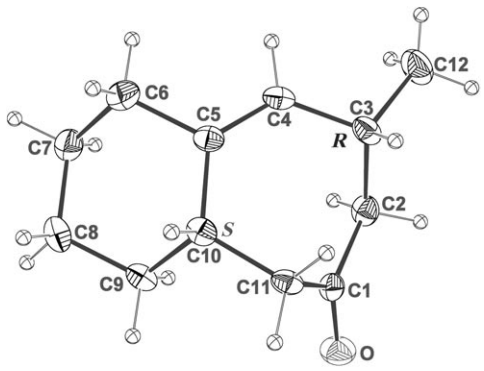


Figure 1. View of the molecular structure of compound **27** with displacement ellipsoids at 30% probability. Selected bond lengths [Å] and angles [°]: O–C1 1.212(3), C4–C5 1.329(4); O-C1-C2 120.0(2), C4-C5-C10 127.0(2).

0.0067 mmol) and $AgSbF_6$ (2.3 mg, 0.0067 mmol), and the reaction mixture was stirred for 10 min. The resulting solution was filtered through a pad of celite and concentrated. The residue was dried under high vacuum for 2 h and then cooled to −15 °C. A solution of **6** (120 mg, 0.67 mmol) in CH_2Cl_2 (13.4 mL, 0.05 M, precooled to −15 °C) was added to this residue to give a colorless solution, which was stirred for 2 min. Triethylamine (1 mL) was added to the solution and it was stirred for 5 min. The resulting reaction mixture was passed through a pad of celite and concentrated. The residual oil was purified by flash chromatography on silica gel (deactivated by triethylamine before use, eluted with pentane/ether = 95:5) to give compound **7a** as a colorless oil (117 mg, 0.65 mmol, 97% yield). $R_f = 0.45$ (pentane/ether = 95:5); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.14$–1.47 (m, 3H), 1.66–1.77 (m, 3H), 1.87–1.95 (m, 1H), 2.04–2.14 (m, 2H), 2.38–2.40 (m, 2H), 2.45–2.57 (m, 2H), 2.64–2.74 (m, 1H), 3.47 (s, 3H), 4.79 (app t, $J = 6.4$ Hz, 1H), 5.45 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 23.6, 27.0, 28.9, 35.7, 37.5, 38.8, 39.2, 54.6, 95.7, 120.3, 143.8, 159.4 ppm; IR: $\tilde{\nu} = 2925$, 2852, 1666, 1155 cm^{-1}; HRMS calcd for $C_{12}H_{18}O$: 178.1358. found: 178.1358.

Conversion of **7a** into **7b**: Water (0.1 mL) and *p*-toluenesulfonic acid (2.3 mg, 0.012 mmol) was added to a solution of **7a** (22 mg, 0.12 mmol) in THF (1 mL) at 0 °C. The reaction mixture was stirred for 7 h at 0 °C and then diluted with ether (20 mL). This solution was washed with a saturated aq $NaHCO_3$ solution (2 × 10 mL), water (10 mL), dried over anhydrous Na_2SO_4, and concentrated. The residual oil was purified by flash chromatography on silica gel (eluted with pentane/ether = 85:15) to give the compound **7b** as a colorless oil (18 mg, 0.11 mmol, 90% yield). The spectral data are in complete agreement with those in the literature.[13a]

Crystal structure analysis: a suitable crystal was mounted onto a specially constructed apparatus[18] with cooling in an inert atmosphere on a Bruker SMART CCD1000 APEX diffractometer and analyzed.[17] After semi-empirical absorption correction by equalization

of like-symmetry reflections (SADABS), structure solution and refinement was carried out with the SHELX programs.[19,20]

Received: November 6, 2007
Revised: January 4, 2008
Published online: February 11, 2008

Keywords: cyclization · gold · homogeneous catalysis · sigmatropic rearrangement

[1] Reviews on transition-metal-catalyzed cycloisomerization of enynes: a) B. M. Trost, F. D. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067; b) G. C. Lloyd-Jones, *Org. Biomol. Chem.* **2003**, *1*, 215; c) C. Bruneau, *Angew. Chem.* **2005**, *117*, 2380; *Angew. Chem. Int. Ed.* **2005**, *44*, 2328; d) S. T. Diver, A. J. Giessert, *Chem. Rev.* **2004**, *104*, 1317.

[2] Recent reviews on the gold- and platinum-catalyzed reactions involving enyne cycloisomerizations: a) A. Fürstner, P. W. Davies, *Angew. Chem.* **2007**, *119*, 3478; *Angew. Chem. Int. Ed.* **2007**, *46*, 3410; b) S. Ma, S. Yu, Z. Gu, *Angew. Chem.* **2006**, *118*, 206; *Angew. Chem. Int. Ed.* **2006**, *45*, 200; c) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271; d) A. S. K. Hashmi, G. J. Hutchings, *Angew. Chem.* **2006**, *118*, 8064; *Angew. Chem. Int. Ed.* **2006**, *45*, 7896; e) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Commun.* **2007**, 333; f) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395.

[3] Catalytic alkyne activation with concomitant nucleophilic trapping: a) P. Y. Toullec, E. Genin, L. Leseurre, J.-P. Genêt, V. Michelet, *Angew. Chem.* **2006**, *118*, 7587; *Angew. Chem. Int. Ed.* **2006**, *45*, 7427; b) S. F. Kirsch, J. T. Binder, B. Crone, A. Duschek, T. T. Haug, C. Liébert, H. Menz, *Angew. Chem.* **2007**, *119*, 2360; *Angew. Chem. Int. Ed.* **2007**, *46*, 2310; c) G. Y. Lin, C. Y. Yang, R.-S. Liu, *J. Org. Chem.* **2007**, *72*, 6753; d) V. Belting, N. Krause, *Org. Lett.* **2006**, *8*, 4489; e) J. Barluenga, A. Diéguez, A. Fernández, F. Rodríguez, F. J. Fañanás, *Angew. Chem.* **2006**, *118*, 2145; *Angew. Chem. Int. Ed.* **2006**, *45*, 2091; f) A. S. K. Hashmi, M. C. Blanco, E. Kurpejović, W. Frey, J. W. Bats, *Adv. Synth. Catal.* **2006**, *348*, 709; g) C. Lim, J.-E. Kang, J.-E. Lee, S. Shin, *Org. Lett.* **2007**, *9*, 3539; h) A. K. Buzas, F. M. Istrate, F. Gagosz, *Angew. Chem.* **2007**, *119*, 1159; *Angew. Chem. Int. Ed.* **2007**, *46*, 1141.

[4] General reviews on the [3,3]-sigmatropic rearrangement of allyl vinyl ethers (Claisen rearrangement): a) A. M. Castro, *Chem. Rev.* **2004**, *104*, 2939; b) F. E. Ziegler, *Chem. Rev.* **1988**, *88*, 1423.

[5] Examples of Lewis acid mediated/catalyzed Claisen rearrangement of cyclic enol ethers: a) C. M. G. Philippo, N. H. Vo, L. A. Paquette, *J. Am. Chem. Soc.* **1991**, *113*, 2762; b) L. A. Paquette, D. Friedrich, R. D. Rogers, *J. Org. Chem.* **1991**, *56*, 3841.

[6] Reviews on the synthesis of natural products containing carbocyclic seven-membered rings: M. A. Battiste, P. M. Pelphrey, D. L Wright, *Chem. Eur. J.* **2006**, *12*, 3438, and references therein.

[7] Recent examples of transition-metal-catalyzed carboalkoxylation of alkynes: a) P. Dube, F. D. Toste, *J. Am. Chem. Soc.* **2006**, *128*, 12062; b) A. Fürstner, P. W. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 15024; c) A. Fürstner, H. Szillat, F. Stelzer, *J. Am. Chem. Soc.* **2000**, *122*, 6785; d) A. Fürstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.* **2001**, *123*, 11863; e) I. Nakamura, T. Sato, Y. Yamamoto, *Angew. Chem.* **2006**, *118*, 4585; *Angew. Chem. Int. Ed.* **2006**, *45*, 4473.

[8] a) Related discussions on the aza-Claisen rearrangement in pyrrole formation: F. M. Istrate, F. Gagosz, *Org. Lett.* **2007**, *9*, 3181; b) For selected examples on other gold-catalyzed Claisen rearrangements: B. D. Sherry, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 15978; N. W. Reich, C.-G. Yang, Z. Shi, C. He, *Synlett* **2006**, 1278; G. E. Veitch, E. Beckmann, B. J. Burke, A. Boyer, S. L. Maslen, S. V. Ley, *Angew. Chem.* **2007**, *119*, 7773; *Angew. Chem. Int. Ed.* **2007**, *46*, 7629; H. Menz, S. F. Kirsch, *Org. Lett.* **2006**, *8*, 4795.

[9] Using in situ generated cationic complexes gave lower yields of the desired products.

[10] J.-E. Kang, H.-B. Kim, J.-W. Lee, S. Shin, *Org. Lett.* **2006**, *8*, 3537.

[11] We found that a pure sample of **7a** decomposes slowly under the reaction conditions with formation of an unidentified mixture of compounds. Thus, the decrease in yield in this case can be explained by the instability of the product **7a**.

[12] We also investigated the one-step preparation of **7b** from **6** by adding various amounts of water to the reaction mixture. In all cases the yield of ketone **7b** was significantly lower (max. 60%).

[13] a) Although cyclohept-4-en-1-ones can be synthesized from the corresponding 1,6-enyne-3-ols by a one-pot cyclization/rearrangement, this thermal rearrangement generally requires forcing conditions. References on this reaction: X. Li, R. E. Kyne, T. V. Ovaska, *J. Org. Chem.* **2007**, *72*, 6624, and also see the references cited therein; b) this type of substitution pattern is known to be resistant to thermal Claisen rearrangement: E. N. Marvell, D. Titterington, *Tetrahedron Lett.* **1980**, *21*, 2123.

[14] Although the cycloisomerized product was not obtained in pure form, generation of the product was undoubtedly confirmed by the analysis of ^{1}H NMR data of the reaction mixture.

[15] Within the limits of detection by ^{1}H NMR and GC methods.

[16] ^{1}H NMR spectrum of the crude reaction mixture from the cycloisomerization also clearly shows the formation of single diastereomer.

[17] Crystallographic data for compound **27**: monoclinic, space group $P2_1/c$, $a = 5.264(2)$, $b = 22.873(8)$, $c = 8.654(3)$ Å, $\beta = 97.418(7)°$, $V = 1033.3(6)$ Å^3, $T = -30$ °C, $Z = 4$, $Mo_{K\alpha}$ radiation, graphite monochromator, scan width 0.3° in ω, 20 s irradiation time per measurement reflections, 2830 measurements, 11733 measured reflections, 2128 independent reflections, 119 parameters, GOF = 1.058, $R_1(I>2\sigma(I)) = 0.0888$, $wR_2 = 0.1680$. CCDC 671143 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

[18] T. Kottke, D. Stalke, *J. Appl. Crystallogr.* **1993**, *26*, 615.

[19] G. Sheldrick, Program for Crystal Structure Solution, Universitaet Goettingen, **1986**.

[20] G. Sheldrick, Program for Crystal Structure Refinement, Universitaet Goettingen, **1993**.

