

Electronic Supplementary Information

Reversibility in the boron-mediated ketone–ketone aldol reaction

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General Experimental

NMR spectra were recorded at either 273, 278 or 300 K using a Bruker Avance DRX400 NMR spectrometer. Residual benzene (δ_{H} 7.16), chloroform (δ_{H} 7.26), and ether (δ_{H} 3.44, 1.07) were used as internal references for ^1H NMR spectra measured in these solvents. The data is reported as chemical shift (δ_{H} ppm), relative integral, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J Hz) and assignment. Solvent peaks for benzene (δ_{C} 128.1), and chloroform (δ_{C} 77.0) were used as internal references for ^{13}C NMR spectra measured in these solvents. Chloroform-*d* was de-acidified before use by passing it through a column of basic alumina. Assignment of proton signals was assisted by COSY, NOESY, ^1H – ^{13}C HSQC and HMBC experiments when necessary; assignment of carbon signals was assisted by DEPT and ^1H – ^{13}C HSQC experiments. IR spectra were recorded on a Shimadzu FTIR-8400 S spectrometer as thin films on NaCl plates, unless otherwise stated. Mass spectra were recorded by the Mass Spectrometry Unit of the School of Chemistry, University of Sydney, and high resolution mass spectra were recorded by the Mass Spectrometry Unit of the Research School of Chemistry, Australian National University. Melting points were measured on a Gallenkamp variable heat apparatus, or a Reichert melting point stage and are uncorrected. Reactions were conducted under a positive pressure of dry

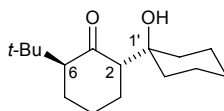
nitrogen or argon. Diethyl ether was dried and distilled from sodium/benzophenone. All liquid reagents were purified by distillation. Analytical TLC was performed with Merck silica plates, precoated with silica gel 60 F254 (0.2 mm). Flash chromatography employed either Merck Kieselgel 60 (230–400 mesh), Labchem 922 (200–325 mesh), or Scharlau 60 (230–400 mesh) silica gel.

Experimental Procedures and Characterization Data

General Procedure for the boron-mediated ketone–ketone aldol reaction

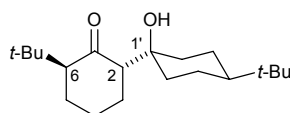
To a solution of Chx_2BCl (1.1 mmol, 1.1 eq.) in Et_2O (3–4 mL) at 0 °C was added Et_3N (1.3 mmol, 1.3 eq.) dropwise, followed by the donor ketone (1 mmol, 1 eq.) and the resulting mixture was stirred for 1 h. The acceptor ketone (1.1 to 3 eq.) was added and the mixture left in a refrigerator at 5 °C for 20–70 hours. A pre-mixed solution of 6:1 MeOH (6 mL) and pH 7 buffer (1 mL) was added at 0 °C followed by a pre-mixed solution of 2:1 MeOH (2 mL) and 30% H_2O_2 (1 mL), and the mixture was warmed to r.t.. After stirring vigorously for 2 hours at r.t. the mixture was diluted with Et_2O and H_2O , and the aqueous portion was extracted with Et_2O ($\times 3$). The combined organic extracts were washed with sat. NaHCO_3 (15 mL), and brine (15 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Crude products were purified using flash chromatography (silica).

trans-2-(1'-hydroxycyclohexyl)-6-*tert*-butylcyclohexanone (**5**)



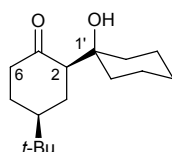
Following the general procedure, the acceptor ketone, cyclohexanone (3 mmol, 3 eq.) was added, and the reaction mixture was left at 5 °C for 70 h. The crude oil was purified by flash chromatography (10:90 $\rightarrow$ 20:80 EtOAc/hexanes) to afford the aldol adduct **5** (242 mg, 91%) as a colourless oil: **R_f** 0.42 (20:80 EtOAc/hexanes); **IR** (thin film) 3502, 2935, 2864, 1690, 1448, 1364, 1356, 1340, 1294, 1261, 1227, 1182, 1121, 1090, 1036 cm^{-1} ; **¹H NMR** (400 MHz, C_6D_6) δ 3.68 (1H, s, OH), 2.29 (1H, dd, $J = 9.3, 9.5$ Hz, 2-CH), 1.95 (1H, dd, $J = 9.3, 11.0$ Hz, 6-CH), 1.91–1.54 (7H, m), 1.45–1.23 (6H, m), 1.18–0.98 (3H, m), 0.90 (9H, s, $\text{C}(\text{CH}_3)_3$); **¹³C NMR** (100.6 MHz, C_6D_6) δ 220.1, 72.0, 61.0, 55.4, 37.6, 34.8, 33.4, 28.4, 26.6, 25.4, 24.3, 22.5, 22.1, 21.3; **HRMS** (+ESI) Calc. for $\text{C}_{16}\text{H}_{28}\text{O}_2\text{Na}$ $[\text{M} + \text{Na}]^+$: 275.1982, found: 275.1983.

***trans*-2-(*cis*-1'-hydroxy-4'-*tert*-butylcyclohexyl)-6-*tert*-butylcyclohexanone (6)**



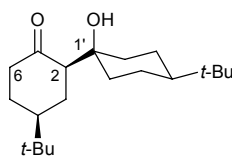
Following the general procedure, the acceptor ketone, 4-*tert*-butylcyclohexanone (1.3 mmol, 1.3 eq.) was added, and the reaction mixture was left at 5 °C for 20 h. The crude oil was purified by flash chromatography (10:90 EtOAc/hexanes) to afford the aldol adduct **6** (288 mg, 94%) as a colourless solid: **m.p.** 60.0–62.0 °C **R_f** 0.48 (20:80 EtOAc/hexanes); **IR** (thin film) 3508, 2949, 2910, 2868, 1691, 1477, 1468, 1448, 1393, 1366, 1234, 1227, 1190, 1144, 1130, 1016 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 3.47 (1H, s, OH), 2.40 (1H, dd, *J* = 9.8, 11.0 Hz, 2-CH), 2.04 (1H, dd, *J* = 8.3, 9.1 Hz, 6-CH), 2.06–1.71 (7H, m), 1.52–1.31 (5H, m), 1.17 (1H, ddd, *J* = 4.9, 13.0, 13.2 Hz), 1.04 (1H, dddd, *J* = 1.5, 4.2, 13.0, 13.7 Hz), 0.97–0.79 (1H, m), 0.95 (9H, s, C(CH₃)₃), 0.82 (9H, s, C(CH₃)₃); **¹³C NMR** (100.6 MHz, CDCl₃) δ 221.3, 71.1, 61.0, 55.8, 47.9, 37.1, 34.3, 33.3, 32.3, 28.1, 27.5, 25.2, 24.2, 22.1, 21.9, 20.7; **HRMS** (+ESI) Calc. for C₂₀H₃₆O₂Na [M + Na]⁺: 331.2608, found: 331.2605.

***cis*-2-(1'-hydroxycyclohexyl)-4-*tert*-butylcyclohexanone (8)**



Following the general procedure, the acceptor ketone, cyclohexanone (3 mmol, 3 eq.) was added slowly over a period of 15–20 minutes to avoid the formation of by-product **9**. The reaction was left at 5 °C for 20 h, and the crude oil was purified by flash chromatography (12:88 → 15:85 EtOAc/hexanes) to yield the aldol adduct **8** (229 mg, 92%) as a colourless solid: **m.p.** 83.5–85.5 °C; **R_f** 0.48 (20:80 EtOAc/hexanes); **IR** (thin film) 3516, 2945, 2866, 1693, 1479, 1470, 1462, 1447, 1435, 1394, 1367, 1356, 1348, 1338, 1319, 1273, 1227, 1180, 1144, 1163, 1099, 1078, 1043 cm⁻¹; **¹H NMR** (400 MHz, CDCl₃) δ 3.66 (1H, s, OH), 2.36 (1H, dd, *J* = 5.1, 13.3 Hz, 2-CH), 2.31 (2H, m), 2.19–2.13 (1H, m), 2.09–2.02 (1H, m), 1.74–1.09 (13H, m), 0.88 (9H, s, C(CH₃)₃); **¹³C NMR** (100.6 MHz, CDCl₃) δ 216.6, 72.0, 57.9, 47.1, 42.9, 36.0, 33.2, 32.5, 29.8, 28.8, 27.6, 25.8, 21.6, 21.3; **HRMS** (+ESI) Calc. for C₁₆H₂₈O₂Na [M + Na]⁺: 275.1982, found: 275.1987.

cis-2-(1'-hydroxy-4'-tert-butylcyclohexyl)-4-tert-butylcyclohexanone (9)

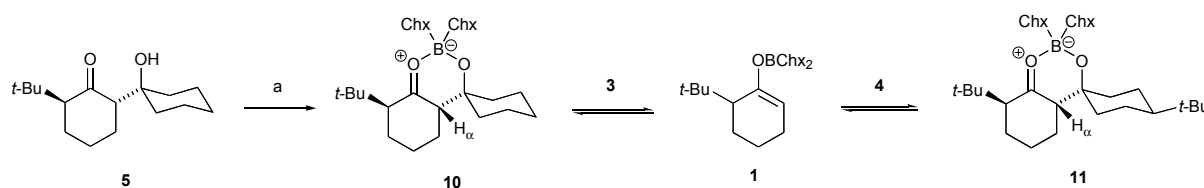


Following the general procedure, which was scaled up by a factor of 2, 4-*tert*-butylcyclohexanone (4.2 mmol, 2.1 eq.) was added to a solution of Chx_2BCl and Et_3N in Et_2O at 0 °C, and the reaction was left at 5 °C for 20 h. The crude oil was purified by flash chromatography (10:90 $\rightarrow$ 13:87 EtOAc/hexanes) to yield the aldol adduct **9** (598 mg, 97%), as a colourless solid: **m.p.** 100–101 °C; **R_f** 0.53 (20:80 EtOAc/hexanes); **IR** (thin film) 3518, 2953, 2910, 2868, 1697, 1477, 1470, 1448, 1394, 1366, 1317, 1231, 1146, 1014 cm^{-1} ; **¹H NMR** (400 MHz, CDCl_3) δ 3.57 (1H, s, OH), 2.32–2.27 (3H, m, 2- CH + 6- CH_2), 2.18–2.12 (1H, m), 2.07–2.00 (1H, m), 1.82 (1H, dq, J = 3.4, 13.0 Hz), 1.74 (1H, dq, J = 2.9, 13.0 Hz), 1.55–1.23 (8H, m), 1.55 (1H, ddd, J = 4.7, 13.0, 13.5 Hz), 0.91–0.83 (1H, m), 0.87 (9H, s, $\text{C}(\text{CH}_3)_3$), 0.81 (9H, s, $\text{C}(\text{CH}_3)_3$); **¹³C NMR** (100.6 MHz, CDCl_3) δ 216.5, 71.5, 58.9, 47.8, 47.0, 42.8, 36.1, 33.3, 32.5, 32.3, 30.0, 28.7, 27.6, 27.5, 22.0, 21.9; **HRMS** (+ESI) Calc. for $\text{C}_{20}\text{H}_{36}\text{O}_2\text{Na}$ $[\text{M} + \text{Na}]^+$: 331.2608, found: 331.2610.

General Procedure for ¹H NMR experiments

To a solution of Chx_2BCl (0.28 mmol, 1.1 eq.) in d_{10} -diethyl ether (1 mL), in a thoroughly dried Young's nmr tube fitted with a suba seal, under argon at 0 °C, was added Et_3N (0.33 mmol, 1.3 eq.) dropwise. 2-*tert*-butylcyclohexanone (0.25 mmol, 1 eq.) was added, and the resulting mixture was left at 0 °C for 1 h. After compacting the precipitate using an nmr tube centrifuge, a ¹H NMR spectrum of the resulting boron enolate, at $T = 273\text{ K}$ was acquired. The first acceptor ketone, cyclohexanone or 4-*tert*-butylcyclohexanone (0.28 mmol, 1.1 eq.) was added and the sample was centrifuged again. A ¹H NMR time course study was carried out over 14 h at $T = 278\text{ K}$. The second acceptor ketone (0.5 mmol, 2 eq.) was added, and ¹H NMR spectra were recorded at either $T = 278$ or 300 K as indicated, at regular time intervals.

Additional ^1H NMR experiments

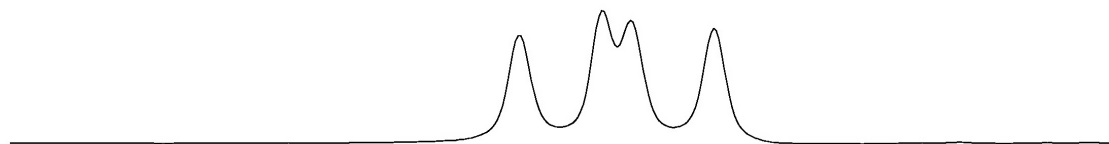


Scheme S1 Reagents and Conditions: a. Chx₂BCl, Et₃N, Et₂O, 0 °C, 1 h.

Experimental Procedure

To a solution of Chx₂BCl (0.67 mmol, 1.1 eq.) in *d*₁₀-diethyl ether (0.7 mL), in a thoroughly dried Young's nmr tube fitted with a suba seal, under argon at 0 °C, was added Et₃N (0.79 mmol, 1.3 eq.) dropwise. Aldol product **5** (0.61 mmol, 1 eq.) was added, and the resulting mixture was left at 0 °C for 1 h. After compacting the precipitate using an nmr tube centrifuge, the supernatant was transferred to another Young's nmr tube via cannula, and a ^1H NMR spectrum of the reformed boron aldolate was acquired (*T* = 278 K). 4-*tert*-butylcyclohexanone (1.83 mmol, 3 eq.) was added, and ^1H NMR spectra were recorded at regular time intervals (*T* = 278 K).

a) *t* = 0



b) *t* = 16 h



c) *t* = 30 h

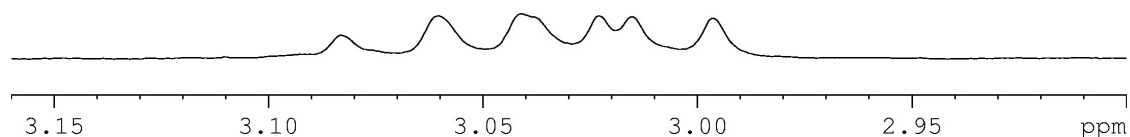


Fig. S1 ^1H NMR spectra (400 MHz, *d*₁₀-diethyl ether, 300 K). (a) Reformed boron aldolate **10**; (b) 16 h after addition of **4**; (c) 30 h after addition of **4**.

Single Crystal X-ray Diffraction Structure Determination Details for 6

A colorless block like crystal was attached with Exxon Paratone N, to a short length of fibre supported on a thin piece of copper wire inserted in a copper mounting pin. The crystal was quenched in a cold nitrogen gas stream from an Oxford Cryosystems Cryostream. A Bruker CCD-1000 area detector diffractometer employing graphite monochromated MoK α radiation generated from a fine-focus sealed tube was used for the data collection. Cell constants were obtained from a least squares refinement against 8700 reflections located between 4.61 and 56.55° 2 θ . Data were collected at 150(2) Kelvin with ω scans to 56.64° 2 θ . The data integration and reduction were undertaken with SAINT and XPREP,¹ and subsequent computations were carried out with the XP SHELXTL-Plus² graphical user interface. The intensities of 207 standard reflections recollected at the end of the experiment did not change significantly during the data collection. An empirical absorption correction determined with SADABS³ was applied to the data.

The structure was solved in the space group $P2_1/c$ (#14) by direct methods with SHELXS-97,⁴ and extended and refined with SHELXL-97.⁴ The non-hydrogen atoms in the asymmetric unit were modeled with anisotropic displacement parameters. Of the 36 hydrogen atoms included in the model, one was located and modeled with isotropic displacement parameters, and a riding atom model was used for the remainder. There is an intramolecular hydrogen bond interaction between the hydroxyl and carbonyl residues. An ORTEP^{5,6} depiction of the molecule with 50% displacement ellipsoids is provided in Figure S2.

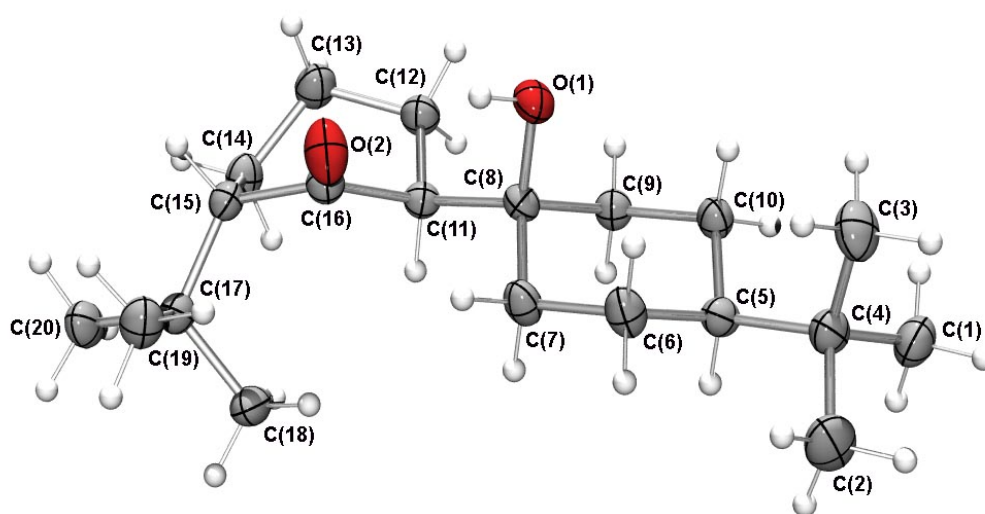


Fig. S2 ORTEP^{5,6} depiction of 6, with 50% displacement ellipsoids.

Formula $C_{20}H_{36}O_2$, M 308.49, Monoclinic, space group $P2_1/c(\#14)$, a 13.179(1), b 12.282(1), c 12.063(1) Å, β 104.982(1), V 1886.2(3) Å³, D_c 1.086 g cm⁻³, Z 4, crystal size 0.45 by 0.45 by 0.43 mm, colour colourless, habit block, temperature 150(2) Kelvin, $\lambda(\text{MoK}\alpha)$ 0.71073 Å, $\mu(\text{MoK}\alpha)$ 0.067 mm⁻¹, $T(\text{SADABS})_{\text{min,max}}$ 0.928, 0.972, $2\theta_{\text{max}}$ 56.64, hkl range -16 17, -15 15, -15 15, N 18394, N_{ind} 4483 (R_{merge} 0.0203), N_{obs} 3692 ($I > 2\sigma(I)$), N_{var} 208, residuals* $R1(F)$ 0.0411, $wR2(F^2)$ 0.1230, $\text{GoF}(\text{all})$ 1.041, $\Delta\rho_{\text{min,max}}$ -0.165, 0.367 e⁻ Å⁻³.

* $R1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$ for $F_o > 2\sigma(F_o)$; $wR2 = (\Sigma w(F_o^2 - F_c^2)^2 / \Sigma (wF_c^2)^2)^{1/2}$ all reflections
 $w = 1 / [\sigma^2(F_o^2) + (0.0686P)^2 + 0.3458P]$ where $P = (F_o^2 + 2F_c^2) / 3$

Table S1. Hydrogen Bond Geometry

Donor	Hydrogen	Acceptor	D-H(Å)	H-A(Å)	D-A(Å)	DHA Angle(°)
O(1)	H(1)	O(2)	0.842(15)	2.065(15)	2.7550(12)	138.9(13)

Single Crystal X-ray Diffraction Structure Determination Details for 9

A colourless prismatic crystal was attached with Exxon Paratone N, to a short length of fibre supported on a thin piece of copper wire inserted in a copper mounting pin. The crystal was quenched in a cold nitrogen gas stream from an Oxford Cryosystems Cryostream. An APEXII-FR591 diffractometer employing graphite monochromated MoK α radiation generated from a rotating anode was used for the data collection. Cell constants were obtained from a least squares refinement against 6953 reflections located between 5 and 55° 2 θ . Data were collected at 150(2) Kelvin with ω + ϕ scans to 58° 2 θ . The data integration and reduction were undertaken with SAINT and XPREP¹, and subsequent computations were carried out with the WinGX⁶ and XTAL⁷ graphical user interfaces.

The structure was solved in the space group $P2_1/n$ (#14) by direct methods with SIR97,⁸ and extended and refined with SHELXL-97.⁴ The asymmetric unit contains two crystallographically independent molecules. The non-hydrogen atoms were modelled with anisotropic displacement parameters, and a riding atom model with group displacement parameters was used for the hydrogen atoms. There is an intramolecular hydrogen bond interaction between the hydroxyl and carbonyl residues of each molecule. An ORTEP^{5,6} depiction of the molecule with 50% displacement ellipsoids is provided in Figure S2.

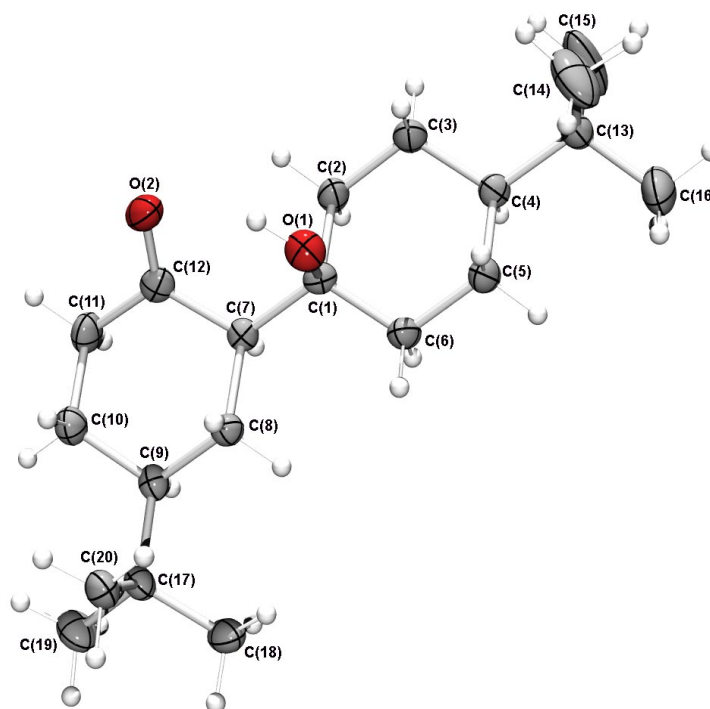


Fig. S3 ORTEP^{5,6} depiction of **9**. One of two crystallographically independent molecules in the asymmetric unit (50% displacement ellipsoids).

Formula $C_{20}H_{36}O_2$, M 308.49, monoclinic, space group $P2_1/n$ (#14), a 11.9035(3), b 12.7978(4), c 24.8807(7) Å, β 96.953(1), V 3762.42(18) Å³, D_c 1.089 g cm⁻³, Z 8, crystal size 0.200 by 0.179 by 0.122 mm, colour colourless, habit prism, temperature 150(2) Kelvin, λ (MoK α) 0.71073 Å, μ (MoK α) 0.068 mm⁻¹, $2\theta_{max}$ 58.24, hkl range -16 15, -17 17, -34 34, N 80737, N_{ind} 10076(R_{merge} 0.0696), N_{obs} 5389($I > 2\sigma(I)$), N_{var} 411, residuals* $R1(F)$ 0.0447, $wR2(F^2)$ 0.0848, GoF(all) 1.242, $\Delta\rho_{min,max}$ -0.273, 0.264 e⁻ Å⁻³.

* $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ for $F_o > 2\sigma(F_o)$; $wR2 = (\Sigma w(F_o^2 - F_c^2)^2/\Sigma(wF_c^2)^2)^{1/2}$ all reflections
 $w=1/[\sigma^2(F_o^2)+(0.02P)^2]$ where $P=(F_o^2+2F_c^2)/3$

Table S2. Hydrogen Bond Geometry for structure **9**

Donor	Hydrogen	Acceptor	D-H(Å)	H-A(Å)	D-A(Å)	DHA Angle(°)
O(1)	H(1)	O(2)	0.84	2.14	2.7858(11)	134.1
O(3)	H(3)	O(4)	0.84	2.09	2.7470(12)	135.0

References

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- 4) G. M. Sheldrick, *SHELX97 Programs for Crystal Structure Analysis*. University of Göttingen. Institut für Anorganische Chemie der Universität, Tammanstrasse 4, D-3400 Göttingen, Germany, 1998.
- 5) ORTEP3 for Windows: L. J. Farrugia, *J. Appl. Cryst.* 1997, **30**, 565.
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