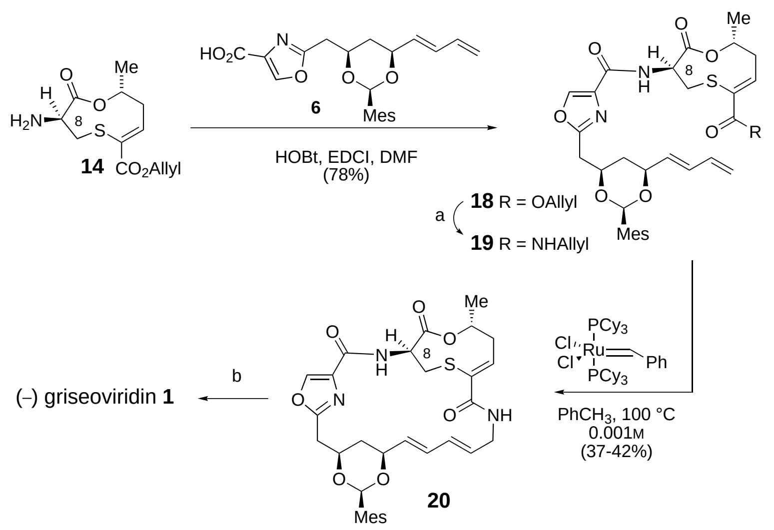

Scheme 3. Synthesis of griseoviridin (**1**). a) [Pd(PPh$_3$)$_4$], pyrrolidine; allyl amine, HOBt, EDCI, DMF, 82 %; b) PPTS, acetone/H$_2$O, 68 %. HOBt = 1-hydroxy-1*H*-benzotriazole, EDCI = *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide, PPTS = pyridinium-*p*-toluenesulfonate.

eomer in 68 % yield. The entire sequence was performed in 24 linear steps from (*S*)-malic acid. The material thus obtained was shown to be identical in all respects to natural griseoviridin[20] (^{1}H, ^{13}C NMR, $[\alpha]_D$, etc.).

The sequence leading to C-8 *epi*-griseoviridin[21] was performed in exactly the same manner and led to a product, in comparable yields, that was distinctly different from natural griseoviridin in its spectroscopic properties. Attempts to ascertain whether ene–thiol lactone **5** could be interconverted to its C-8 epimer proved fruitless due to decomposition when strong bases were employed. Further, attempts to incorporate deuterium into the C-8 position of **5** also failed. In summary, griseoviridin and its C-8 epimer have been synthesized for the first time employing a novel ring-closing metathesis which involved a highly diasteroselective triene to diene macrocyclic ring formation.

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[21] A sample of the heretofore unknown C-8 *epi*-griseoviridin has been submitted for antibacterial screening (Aventis) and found to be only very poorly active (courtesy of Dr.S. Dutka-Malen).

A Structural Model for the Galactose Oxidase Active Site which Shows Counteranion-Dependent Phenoxyl Radical Formation by Disproportionation**

Yuichi Shimazaki, Stefan Huth, Akira Odani, and Osamu Yamauchi*

Galactose oxidase (GO) contains one copper ion at its active site and performs a two-electron oxidation of primary alcohols to aldehydes, coupled with a reduction of O$_2$ to

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[*] Prof. Dr. O. Yamauchi, Y. Shimazaki, S. Huth,[+] Dr. A. Odani
Department of Chemistry
Graduate School of Science and Research Center for Materials Science
Nagoya University, Nagoya 464-8602 (Japan)
Fax: (+81) 52-789-2953
E-mail: b42215a@nucc.cc.nagoya-u.ac.jp

[+] On leave of absence from the University of Bremen

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H_2O_2.[1] Structural studies of the inactive form of GO have revealed that there exist two distinct tyrosine residues in the active site, one of which is a cysteine-modified phenol moiety of tyrosine 272 (Y_{272}) coordinated to the copper center as an equatorial ligand, while the other is a phenol group of tyrosine 495 (Y_{495}) bound at an apical position.[2] The Cu^{II} ion and a phenoxyl radical together effect the two-electron oxidation reaction.[3] The proposed mechanism of catalysis involves a cycle of the Cu^{I}–phenol and Cu^{II}–phenoxyl radical states; no Cu^{II}–phenolate form has been detected during catalysis.[1, 2, 4]

Recent synthetic studies afforded well-characterized mononuclear Cu^{II}–phenoxyl radical species, which provided further insights into the reactivity of the GO active site.[5] Tripodal ligands introduced by Karlin[6] have been developed for use as GO model ligands in a number of studies.[5c, f, h, 7, 8] Model complexes of ligands with two or more phenol moieties have also been synthesized by several groups.[5b, d, e, f, k–m] However, modeling of the coordination structure and roles of the two coordinated phenol moieties with monomeric Cu^{II} complexes has not yet been fully achieved, and dimerization of the complexes often occurs.[5f,h, 7, 8] We report here the synthesis and characterization of a novel mononuclear Cu^{II} complex of a tetradentate tripodal ligand, which is similar to that prepared by Pierre et al.,[5f] with two phenol moieties and two *tert*-butyl groups introduced. The coordination structure has been found to closely resemble that of the inactive GO form.[2] Preliminary studies showed that, while $Cu(OAc)_2$ gives a stable GO-mimicking complex with two phenol moieties coordinated, the $CuCl_2$ and $Cu(ClO_4)_2$ ligand systems react differently and the latter spontaneously gives the phenoxyl radical species by disproportionation.

N-(2-pyridylmethyl)-*N*,*N*-bis(2′-hydroxy-3′,5′-di-*tert*-butylbenzyl)amine (H_2L) was treated with $Cu(OAc)_2 \cdot 2H_2O$ in CH_2Cl_2/CH_3CN in air at room temperature to give $[Cu(HL)(OAc)] \cdot H_2O$ (**1**) as brown crystals (Scheme 1). X-ray crystal structure analysis revealed that **1** contains two phenol moieties coordinated to Cu^{II} in different ways (Figure 1), and the unit cell consists of two crystallographically independent complex molecules.[9] The Cu^{II} center is in a distorted square-pyramidal geometry formed by a phenolate oxygen, a pyridine nitrogen, a tertiary amine nitrogen, and an acetate oxygen in the coordination plane with a protonated phenol oxygen at an axial position with an average Cu–O bond length of 2.40 Å.

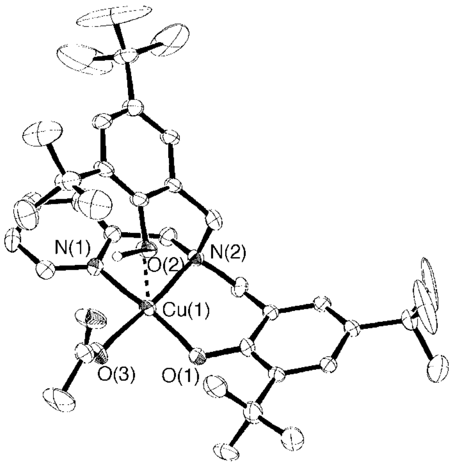
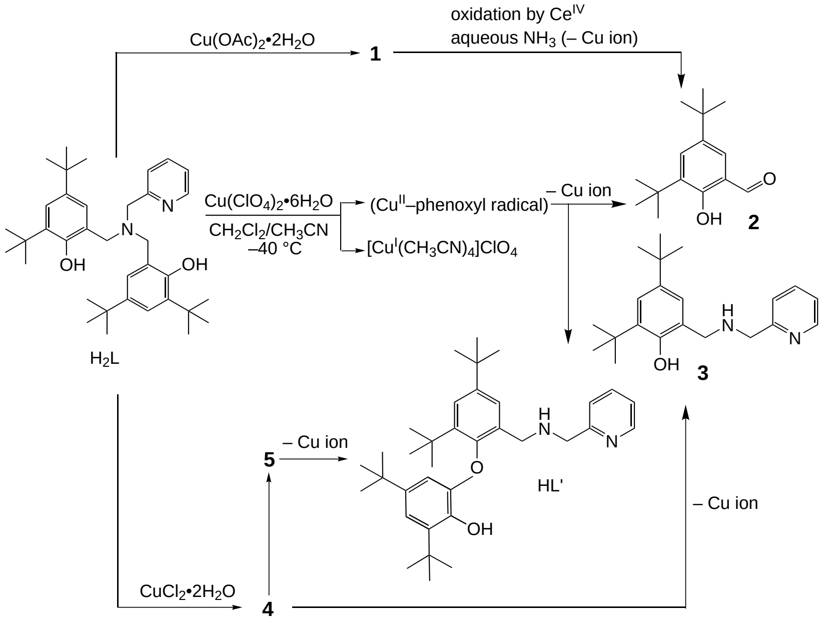


Figure 1. ORTEP view of [Cu(HL)(OAc)] **1** (drawn with the thermal ellipsoids at the 30% probability level) and atomic labeling scheme. Selected bond lengths [Å] and angles [°]: Cu(1)–N(1) 2.001(6), Cu(1)–N(2) 2.043(5), Cu(1)–O(1) 1.883(4), Cu(1)–O(2) 2.418(5), Cu(1)–O(3) 1.957(5); N(1)-Cu(1)-N(2) 83.2(2), N(1)-Cu(1)-O(1) 159.6(2), N(1)-Cu(1)-O(2) 90.5(2), N(2)-Cu(1)-O(2) 86.6(2), N(1)-Cu(1)-O(3) 93.1(2), O(1)-Cu(1)-O(2) 109.6(2), O(1)-Cu(1)-O(3) 88.5(2).



Scheme 1. Reaction scheme for Cu^{II}–H_2L system which shows the dependence on the counterion.

The brown solution of **1** exhibited the phenolate–Cu^{II} charge transfer band at 470 nm ($\varepsilon = 1300$), which disappeared upon oxidation with Ce^{IV} in CH_2Cl_2/CH_3CN at low temperature (−40 °C), but formation of the phenoxyl radical could not be detected. Decomposition products **2** and **3** were isolated from the reaction mixture, both in 15% yield (Scheme 1). Cyclic voltammetry in CH_2Cl_2 with tetrabutylammonium perchlorate revealed an irreversible oxidation at 0.62 V against Ag/AgCl (scan rate = 100 mV s^{-1}). Complex **1** was found to be inactive for oxidation of ethanol.

On the other hand, $Cu(ClO_4)_2 \cdot 6H_2O$ underwent a reaction with H_2L in CH_2Cl_2/CH_3CN, to rapidly form a deep green color. After exposure to air at room temperature, the deep green reaction mixture turned colorless, and yielded colorless crystals of $[Cu(CH_3CN)_4]ClO_4$ (yield of the first crop, 35%; subsequent small crops were also obtained). The deep green intermediate solution at −40 °C exhibited an absorption band centered at 403 nm ($\varepsilon = 2000$) with a shoulder and at 654 nm ($\varepsilon = 400$); no X-band EPR signals were observed, which is consistent with a Cu^{II}–phenoxyl radical species as these are known to give typical absorption peaks, for example, at 410 ($\varepsilon = 4000$), 422 ($\varepsilon = 3800$), and 672 nm ($\varepsilon = 1000$).[5d] The radical species was also detected under an inert gas atmosphere, and colorless crystals of $[Cu(CH_3CN)_4]ClO_4$ were isolated, showing that the radical formation is not due to oxidation by dioxygen. The deep green reaction intermediate was short lived relative to some of the reported oxidized species,[5] decaying by a first order process at $-20\,°C$ with $k = (9.3 \pm 0.2) \times 10^{-4}\,s^{-1}$ (UV–Visible monitoring). No such reactions were observed for a solution containing methanol, which gave the dimeric complex Cu_2L_2 as brown powder upon addition of triethylamine.[5f] Decomposition products **2** and **3** (yields less than 10%) were also detected in the colorless reaction mixture of the $Cu(ClO_4)_2$–H_2L system (Scheme 1). As they are identical with those from complex **1**, we may infer that similar reactions have occurred in both systems.

When $CuCl_2 \cdot 2\,H_2O$ was used in place of $Cu(ClO_4)_2 \cdot 6\,H_2O$, it underwent a reaction with H_2L in CH_2Cl_2/CH_3CN/hexane in air to give $[Cu(H_2L)Cl_2]$ (**4**) as green crystals, where the Cu^{II} ion binds two nitrogen atoms and two chloride ions in the coordination plane and the two phenol hydroxyl groups are protonated, one is also weakly coordinated (Cu–O(1) 2.677(7) Å; Figure 2). Addition of triethylamine to **4** afforded the same dimeric complex as obtained from the $Cu(ClO_4)_2$–H_2L system.[5f] In connection with this, Cu^{II}–tripodal ligand complexes with an N_3O chromophore have been isolated with different anions.[8] By analogy with $CuCl_2$, $Cu(ClO_4)_2$ most probably initially forms a protonated complex such as **4**, and since the perchlorate ions can dissociate easily from Cu^{II} even when they are bound, Cu_2L_2 should be more rapidly formed in the $Cu(ClO_4)_2$–H_2L system than from **4**. Upon standing at room temperature for a few weeks, **4** gave **2**, **3**, and complex **5** which coordinates a new product HL′ (Figure 3); this was also detected in a small amount in the $Cu(ClO_4)_2$–H_2L system. These results indicate that the Cu^{II}–phenoxyl radical in this system was produced together with $[Cu(CH_3CN)_4]ClO_4$ as a result of a disproportionation reaction,[10] which may take place by rapid dimer formation from **4** where the phenol moieties are unbound or only weakly bound.

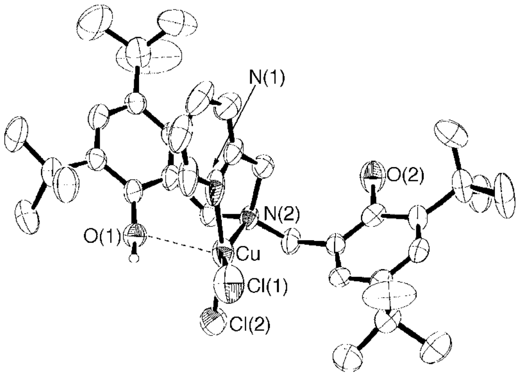


Figure 2. ORTEP view of $[Cu(H_2L)Cl_2]$ **4** (drawn with the thermal ellipsoids at the 30% probability level) and atomic labeling scheme. Selected bond lengths [Å] and angles [°]: Cu–N(1) 1.955(9), Cu–N(2) 2.099(7), Cu–Cl(1) 2.254(4), Cu–Cl(2) 2.230(3), Cu–O(1) 2.677(7); N(1)-Cu-N(2) 82.3(5), N(1)-Cu-Cl(1) 94.3(4), Cl(1)-Cu-Cl(2) 93.7(2), N(1)-Cu-O(1) 80.5(3), N(2)-Cu-O(1) 87.5(3).

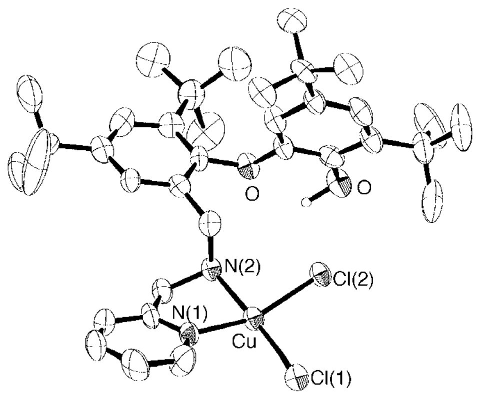


Figure 3. ORTEP view of $[Cu(HL')Cl_2]$ **5** (drawn with the thermal ellipsoids at the 30% probability level) and atomic labeling scheme. Selected bond lengths [Å] and angles [°]: Cu–N(1) 2.002(8), Cu–N(2) 2.024(8), Cu–Cl(1) 2.266(3), Cu–Cl(2) 2.268(3); N(1)-Cu-N(2) 80.2(3), N(1)-Cu-Cl(1) 96.2(3), N(1)-Cu-Cl(2) 158.0(3), N(2)-Cu-Cl(1) 176.2(2), N(2)-Cu-Cl(2) 89.1(2), Cl(1)-Cu-Cl(2) 94.0(1).

In conclusion, we obtained a new GO model Cu^{II} complex **1** of a tripodal ligand H_2L, where the two side-chain phenol moieties coordinated at an equatorial and an axial position in the phenolate and the phenol form, respectively. Different counteranions of the metal sources not only caused a large structural difference in the complexes relative to that reported earlier[8] but also affected the reactivity of the complexes, which increases as the order of anion basicity decreases: $CH_3COO^- > Cl^- > ClO_4^-$.[11] In the $Cu(ClO_4)_2$–H_2L system, spontaneous formation of a phenoxyl radical species and $[Cu(CH_3CN)_4]ClO_4$ due to disproportionation has been observed. To the best of our knowledge, this is the first observation of Cu^{II}–phenoxyl radical formation by disproportionation of Cu^{II} complexes.

Experimental Section

Synthesis of *N*-(2-pyridylmethyl)-*N*,*N*-bis(2′-hydroxy-3′,5′-di-*tert*-butylbenzyl)amine (H_2L): 2,4-di-*tert*-butylphenol (4.12 g, 20 mmol) and paraformaldehyde (0.60 g, 20 mmol) were added to a solution of 2-pyridylmethylamine (1.08 g, 10 mmol) in ethanol (100 mL). The reaction mixture was refluxed for two days to give a white powder which, after isolation, was recrystallized from ethyl acetate to yield 2.01 g (56.3%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$ (s, 18H; $(CH_3)_3C$), 1.40 (s, 18H; $(CH_3)_3C$), 3.80 (s, 4H; phenol-CH_2), 3.84 (s, 2H; py-CH_2), 6.93 (d, 2H; phenol-H), 7.13 (d, 1H; py-H), 7.22 (d, 2H; phenol-H), 7.27 (m, 1H; py-H), 7.69 (td, 1H; py-H), 8.69 (d, 1H; py-H), 10.55 (br s, 2H; phenol-OH).

Synthesis of **1**: The complex was prepared from H_2L and $Cu(OAc)_2 \cdot 2H_2O$ in CH_2Cl_2/CH_3CN (1:1) to give brown crystals. Elemental analysis (%) calcd for $C_{38}H_{57}N_2O_5Cu$: C 66.59, H 8.38, N 4.09; found: C 66.13, H 8.450, N 4.08.

Synthesis of the dimer Cu_2L_2: H_2L (0.545 g, 1.0 mmol) was dissolved in CH_2Cl_2 (10 mL) which contained a few drops of triethylamine and was added to a solution of $Cu(ClO_4)_2 \cdot 6H_2O$ (0.370 g, 1.0 mmol) in methanol (10 mL), which caused a brown powder to separate immediately. This was collected and dried. Elemental analysis (%) calcd for $C_{72}H_{100}N_4O_4Cu_2$: C 71.31, H 8.31, N 4.62; found: C 70.99; H 8.153; N 4.619.

Synthesis of **4**: Small green crystals were obtained from a solution of H_2L and $CuCl_2 \cdot 2\,H_2O$ in CH_2Cl_2/CH_3CN/hexane (1/1/1). Elemental analysis (%) calcd for $C_{36}H_{52}N_2O_2CuCl_2$: C 63.66, H 7.72, N 4.12; found: C 63.29, H 7.596, N 4.07.

Typical recovery of reaction products:[12] compound **4** (0.350 g, 0.514 mmol) was dissolved in CH_3OH/CH_3CN (1:1) and kept standing for a few weeks at room temperature. The green crystals which separated from the reaction mixture were collected, and the brown filtrate was evaporated in vacuo. The residue was dissolved in concentrated aqueous NH_3 (10 mL) and extracted with $CHCl_3$ (4 × 10 mL). The combined organic fractions were washed with concentrated aqueous NaCl (3 × 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to leave a brown oil. Compounds **2** and **3** were separated by column chromatography, and their structures and yields were determined by ^1H NMR. The structure of ligand HL′ in **5** was determined by X-ray analysis of **5** and by ^1H NMR after removal of Cu^{II} as described above. Compound **2**: Yield, 15%; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.33$ (s, 9H; $(CH_3)_3C$), 1.43 (s, 9H; $(CH_3)_3C$), 7.34 (d, 1H; phenol-H), 7.59 (d, 1H; phenol-H), 9.87 (s, 1H; phenol-OH), 11.64 (s, 1H; CHO). Compound **3**: Yield, 15%; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.28$ (s, 9H; $(CH_3)_3C$), 1.43 (s, 9H; $(CH_3)_3C$), 3.93 (s, 2H; CH_2), 3.98 (s, 2H; CH_2), 6.84 (d, 2H; phenol-H), 7.2 (m, 3H; py-H, phenol-H), 7.66 (td, 1H; py-H), 8.58 (d, 1H; py-H). Compound **5**: Yield, 12%; elemental analysis (%) calcd for $C_{35}H_{50}N_2O_2CuCl_2$: C 63.19, H 7.58, N 4.21; found: C 63.07, H 7.532, N 4.27. HL′: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.11$ (s, 9H, $(CH_3)_3C$), 1.33 (s, 9H, $(CH_3)_3C$), 1.37 (s, 9H, $(CH_3)_3C$), 1.47 (s, 9H, $(CH_3)_3C$), 3.47 (q, 2H; CH_2), 3.73 (q, 2H; CH_2), 6.27 (d, 1H; phenol-H), 6.90 (d, 1H; phenol-H), 7.14 (dd, 1H; py-H), 7.16 (d, 1H; phenol-H), 7.19 (d, 1H; py-H), 7.37 (d, 1H; phenol-H), 7.60 (td, 1H; py-H), 8.52 (d, 1H; py-H).

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[9] X-ray crystal structure determination: The X-ray diffraction data were collected at 295 K with a Rigaku AFC-5R four-circle diffractometer using graphite-monochromated $Cu_{K\alpha}$ radiation ($\lambda = 1.54178$ Å). Crystal data for **1**: Formula $C_{76}H_{108}N_4O_9Cu_2$, $M_w = 1348.80$, crystal size: 0.3 × 0.1 × 0.1 mm, monoclinic, space group $P2_1/n$, $a = 26.782(4)$, $b = 10.672(2)$, $c = 26.819(3)$ Å, $\beta = 94.33(1)°$, $V = 7643(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.352\,g\,cm^{-3}$, $\mu = 12.39\,cm^{-1}$, $F(000) = 3112.00$, 13682 independent reflections, 8230 reflections used, 821 parameters, $R = 0.074$, $R_w = 0.085$ ($I > 2.00\sigma(I)$). In the asymmetric unit there were two crystallographically independent complex molecules, which have very similar structures and may be regarded as mirror images arising from the coordination of the tertiary amine nitrogen to Cu^{II}. Crystal data for **4**: Formula $C_{37}H_{56}N_2O_3Cl_2Cu$, $M_w = 711.31$, crystal size: 0.17 × 0.10 × 0.06 mm, triclinic, space group $P\bar{1}$, $a = 13.865(4)$, $b = 16.048(5)$, $c = 10.378(5)$ Å, $\alpha = 98.69(5)$, $\beta = 104.67(4)$, $\gamma = 112.64(2)°$, $V = 1980(1)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.193\,g\,cm^{-3}$, $\mu = 22.80\,cm^{-1}$, $F(000) = 758.00$, 5791 independent reflections, 5791 reflections used, 407 parameters, $R = 0.083$, $R_w = 0.128$ ($I > 2.00\sigma(I)$). Crystal data for **5**: Formula $C_{35}H_{50}N_2O_2Cl_2Cu$, $M_w = 665.24$, crystal size: 0.20 × 0.15 × 0.03 mm, monoclinic, space group $P2_1/a$, $a = 18.054(4)$, $b = 12.712(7)$, $c = 18.314(4)$ Å, $\beta = 116.00(1)°$, $V = 3783(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.168\,g\,cm^{-3}$, $\mu = 23.35\,cm^{-1}$, $F(000) = 2256.00$, 5357 independent reflections, 4926 reflections used, 380 parameters, $R = 0.069$, $R_w = 0.107$ ($I > 2.00\sigma(I)$). Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-136595, -136596, and -136821. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk)..

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Reaction of Organic Selenocyanates with Hydroxides: The One-Pot Synthesis of Dialkyl Diselenides from Alkyl Bromides

Alain Krief,* Willy Dumont, and Cathy Delmotte

Dedicated to Professor Bernd Giese
on the occasion of his 60th birthday

Since the beginning of organoselenium chemistry, organoselenocyanates have occupied a privileged position.[1] They are easily prepared, are stable to atmospheric conditions, and have widely contributed to the use of organoselenium compounds in synthesis due to their exceptional versatility.[1] They react with a large variety of compounds, producing chemoselectively, in a single step and in almost quantitative

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[*] Prof. Dr. A. Krief, Dr. W. Dumont, Dipl.-Chem. C. Delmotte
Laboratoire de Chimie Organique de Synthèse
Département de Chimie
Facultés Universitaires Notre-Dame de la Paix
61 rue de Bruxelles, 5000 Namur (Belgium)
Fax: (+32) 81-724536
E-mail: alain.krief@fundp.ac.be