The synthesis of chiral Ni^{II} complex of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and 5-amino-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazol-5-carboxylic acid

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Dedicated to Professor Edmunds Lukevics on the occasion of his 70th birthday

Abstract
The chiral Ni^{II} complex of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and 5-amino-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazol-5-carboxylic acid (**6**) was prepared *via* the cycloaddition of chiral complex of Ni **5** with mesitonitrile oxide **1.** The cycloaddition proceeded with complete regioselectivity to provide 5-substituted isoxazolines **6** and **7**. The approach of the dipole takes place predominantly from the less sterically hindered side of dipolarophile **5**, the diastereoisomers were formed in 96:4 ratio. The detailed structure of **6** was established by X-ray analysis.

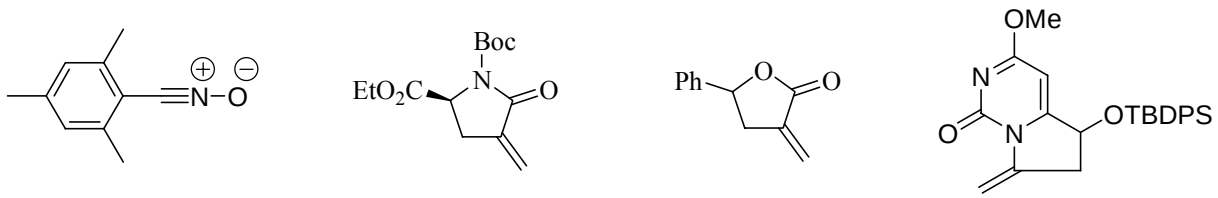
Keywords: Dipolar cycloaddition, diastereoselection, nitrile oxides, chiral complex, spiroisoxazolines, X-ray analysis

Introduction

Spiroisoxazolines are heterocyclic nuclei which have stimulated much interest in medicinal and biological chemistry.[1] Following the first reports of their herbicidal and plant hormonal activity[2-4] some naturally occurring spiroisoxazolines have been found useful in other biomedical areas. Examples include the naturally occurring araplysillins, which have been found to inhibit ATP-ase enzymes,[5] and naturally occurring agelorin, a spiroisoxazoline derived from bromotyrosine which has proved active against pathogens.[6-9] More recently it was found that spiroisoxazoline containing SJ755 shows a remarkable integrin antagonist behavior, showing a new application

for this class of compounds.[10] Some stereoselective synthesis of unnatural spiroisoxazolinoheterocycle-based derivatives in which exomethylene heterocyclic compounds react as a dipolarophile with nitrile oxides is also reported.[11-15]

We have found a strong evidence for a predictive *anti*-diastereoselective 1,3-dipolar cycloadditions of nitrile oxides and nitrones to the substituted heterocyclic compounds possessing an exocyclic double bond. [13-15] The attack of the 1,3-dipole occurred preferentially from the less hindered face of the dipolarophile.[13-15] For example, the reaction of chiral methylene pyrrolidinone **2** and stable mesityl nitrile oxide (**1**) proceeded under the formation of *anti* and *syn* diastereoisomers in the ratio of 67:33, in favor of *anti* diastereomer. The reaction of nitrile oxide **1** with methylenelacton **3** afforded a 90:10 mixture of cycloadducts in favor of *anti* diastereomer (Scheme 1).[13] On the other hand, cycloaddition of the dipolarophile **4** bearing a bulky silyl group proceeded with high stereoselectivity providing 5,7-*trans* isoxazoline exclusively.[14,15]



1 **2** **3** **4**

Scheme 1

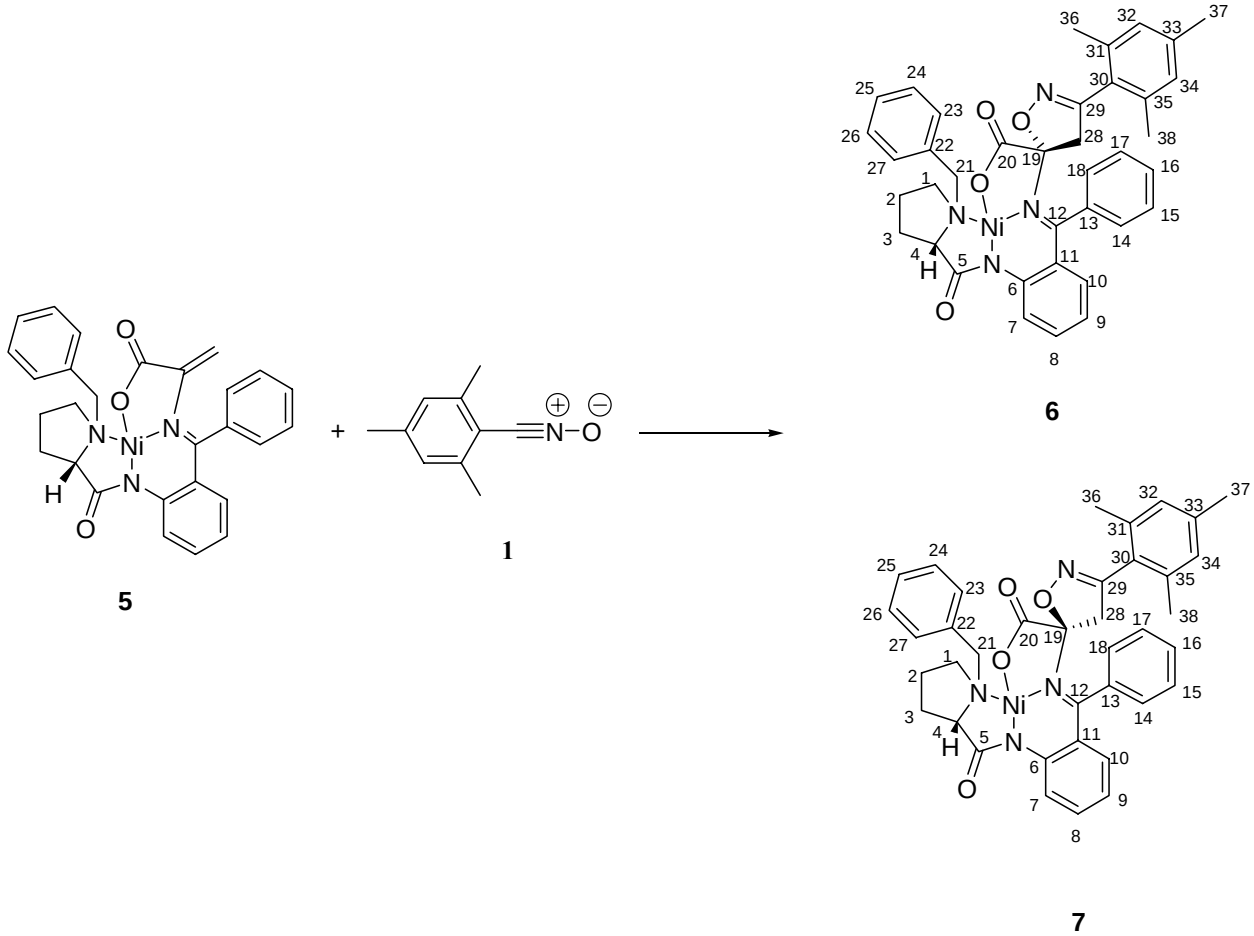
With the goal of developing a simple route to the synthesis of chiral isoxazolinylsubstituted amino acids we focused our attention on the cycloaddition of mesityl nitrile oxide with chiral Ni^{II} complex **5** derived from a Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and dehydroalanine. Some years ago Y. N. Belokon *et al.* described asymmetric synthesis of β-substituted α-amino acids via a chiral Ni^{II} complex **5**.[16,17]

Results and Discussion

The chiral Ni^{II} complex **5** of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and dehydroalanine was prepared according to ref.[18]. Cycloadditions of chiral Ni^{II} complex **5** with mesitonitrile oxide **1** proceeded with complete regioselectivity to provide 5-substituted isoxazolines **6** and **7** in 72% yield. The structures described were characterized *via* analysis of their respective ^{1}H- and ^{13}C- NMR spectra. The ratio of diastereoisomers was determined from quantitative ^{13}C NMR spectra, by integration of the peaks from spiro-carbon C-19 of the isoxazolines. The cycloaddition proceeded extremely slowly, but the diastereoselectivity was excellent, the diastereoisomers were formed in 96:4 ratio. (Scheme 2).

The major isomer Ni^{II} complex of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and 5-amino-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazol-5-carboxylic acid (**6**) was purified by column chromatography and was identified as 5-substituted isoxazoline by NMR spectroscopic analysis. The stereochemical arrangement and absolute configuration was subsequently confirmed by X-ray-crystallographic analysis (Figure 1 and experimental section). The analysis of the product configuration in **6** indicates that the major cycloadduct **6** arises from the cycloaddition that has occurred on the more sterically accessible face of the dipolarophile **5**. A chemical shift of spiro-carbon at C-19 of the isoxazoline ring in ^{13}C-NMR of both isolated products (101.9 ppm for **6** and 100.8 ppm for **7**) excludes the possibility that the second isolated product 7 is a regioisomer.

The high diastereoselectivity of the cycloaddition could be due to the fact that the *N*-benzylic group of the chiral Ni^{II} complex **5** is probably attached to the Ni atom and can effectively hinder the approach from *re* face of the alkene. Therefore, the cycloaddition of nitrile oxide **1** arises from the more sterically accessible *si* face of the exocylic double bond of the dipolarophile **5**.



Scheme 2

Conclusions

In conclusion, the chiral Ni^{II} complex of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and 5-amino-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazol-5-carboxylic acid (**6**) was prepared *via* the cycloaddition of chiral complex of Ni **5** with mesitonitrile oxide **1.** The cycloaddition proceeded with complete regioselectivity to provide 5-substituted isoxazolines **6** and **7** in 72% yield. The analysis of the product configuration in **6** indicates that the major cycloadduct **6** arises from the cycloaddition that has occurred on the more sterically accessible face of the dipolarophile **5**. Thus it is steric factors that are responsible for the observed diastereoselectivity (diastereoisomers were formed in 96:4 ratio).

Experimental Section

General Procedures. All starting materials and reagents are commercially available (Fluka, Merck, Avocado or Aldrich) and were used without further purification. Solvents were dried before use. Thin-layer chromatography (TLC glass plates coated with silica 60 F_{254} Merck) was used for monitoring of reaction courses; eluent is given in the text. For column chromatography the flash chromatography technique was employed using silica 60 (0.040-0.063 mm, Merck). Melting points (mp) were determined on a Kofler hot plate apparatus and are uncorrected.

The ^{1}H and ^{13}C NMR spectra of deuterochloroform solutions were obtained using Varian VXR-300 (300 MHz) instrument, tetramethylsilane (TMS) being the internal reference.

The chiral Ni^{II} complex **5** of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and dehydroalanine was prepared from the chiral Ni^{II} complex of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and glycine which, in turn was treated with formaldehyde and acetic anhydride in the presence of Na_2CO_3 according to ref.[18].

Cycloaddition of mesitonitrile oxide (1) with chiral Ni^{II} complex 5 of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and dehydroalanine. Mesitonitrile oxide (**1**) (161 mg, 1.000 mmol) and the chiral complex **5** (511 mg, 1.001 mmol) were dissolved under argon in anhydrous CH_2Cl_2 (10 ml) and kept at 0°C 40 d. When no starting material remained (TLC), the solvent was removed *in vacuo* and the mixture of two diastereoisomers (94:6) was purified and separated by flash column chromatography on silica gel, eluting with EtOAc/hexanes 25:75 to give major diastereoisomer **6 (**471 mg, 70%) and minor diastereoisomer **7** (12 mg, 2%).

***anti*-Ni^{II} complex of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and 5-amino-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazol-5-carboxylic acid** (**6**). Red solid, 70% yield. ^{1}H NMR δ 6.4-8.3 (m, 9H, H_{Ar}), 6.79 (s, 2H, H-32, H-34), 4.35 (d, J = 6.2 Hz, 1H, H-21a), 4.23 (ddd, J = 4.1, 6.8, 11.4 Hz, 1H, H-1) 3.66 (dd, J = 4.1, 9.7 Hz, 1H, H-4), 3.53 (d, J = 17.7 Hz, 1H, H-28a), 3.40 (d, 1H, H-21b), 3.40 (d, J = 17.7 Hz, 1H, H-28b), 2.74-2.83 (m, 1H, H-2), 2.63 (ddd, J = 6.3, 9.4, 11.4 Hz, 1H, H-1), 2.25-2.40 (m, 2H, H-3), 2.24 (s, 3H, CH_3-37), 2.07 (s, 6H, CH_3-36, CH_3-38), 1.96-2.10 (m, 1H, H-2). ^{13}C-NMR δ 181.9 (C-5), 174.7,

173.5 (C-20, C-12), 156.85 (C-29), 143.1, 139.1, 137.4, 135.8, 134.4, 128.5, 124.5 (C-6, C-11, C-13, C-22, C-30, C-31, C-33, C-35), 134.3, 132.9, 131.0, 130.7, 129.3, 129.1, 128.7, 127.8, 126.8, 123.6, 120.9 (C-7, C-8, C-9, C-10, C-14, C-15, C-16, C-17, C-18, C-23, C-24, C-25, C-26, C-27, C-32, C-34), 101.9 (C-19), 69.9 (C-4), 62.0 (C-21), 59.6 (C-1), 51.4 (C-28), 30.8 (C-3), 23.4 (C-2), 21.1 (C-37), 20.6 (C-36, C-38). Anal. Calcd for $C_{38}H_{36}N_4NiO_4$: C, 67.98; H, 5.40; N, 8.34. Found: C, 67.63; H, 5.61; N, 8.52.

***syn*-Ni^{II} complex of Schiff base of (*S*)-2-*N*-(*N*-benzylprolyl)aminobenzophenone and 5-amino-4,5-dihydro-3-(2,4,6-trimethylphenyl)isoxazol-5-carboxylic acid** (**7**). Red solid, 2% yield. ^{13}C-NMR δ 180.4 (C-5), 174.1, 172.5 (C-20, C-12), 156.3 (C-29), 142.1, 139.3, 137.3, 135.6, 133.5, 129.3, 124.2 (C-6, C-11, C-13, C-22, C-30, C-31, C-33, C-35), 133.5, 132.5, 131.4, 130.9, 129.1, 128.5, 127.6, 127.3, 126.3, 123.8, 121.1 (C-7, C-8, C-9, C-10, C-14, C-15, C-16, C-17, C-18, C-23, C-24, C-25, C-26, C-27, C-32, C-34), 100.8 (C-19), 70.6 (C-4), 63.6 (C-21), 57.6 (C-1), 54.2 (C-28), 30.6 (C-3), 24.2 (C-2), 21.0 (C-37), 20.4 (C-36, C-38).

X-ray Structure Determination of 6.[19-21] The suitable crystals were obtained by slow crystallization from a mixture of ethyl acetate and hexane at room temperature. The crystallographic data were obtained by CAD4 diffractometer. The relevant crystallographic data and structure refinement are given in Table 1. The structure was solved by direct methods and refined by anisotropic full-matrix least-squares technique. Perspective view and the numbering of the atoms are depicted in Figure 1. The hydrogen atoms were refined isotropically in idealized positions riding on the atom to which they are attached. Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. The corresponding deposition number is CCDC 603354. Copies of the data can be obtained free of charge on request to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Tel.: +44-1223-336408, Fax: +44-1223 336-033).

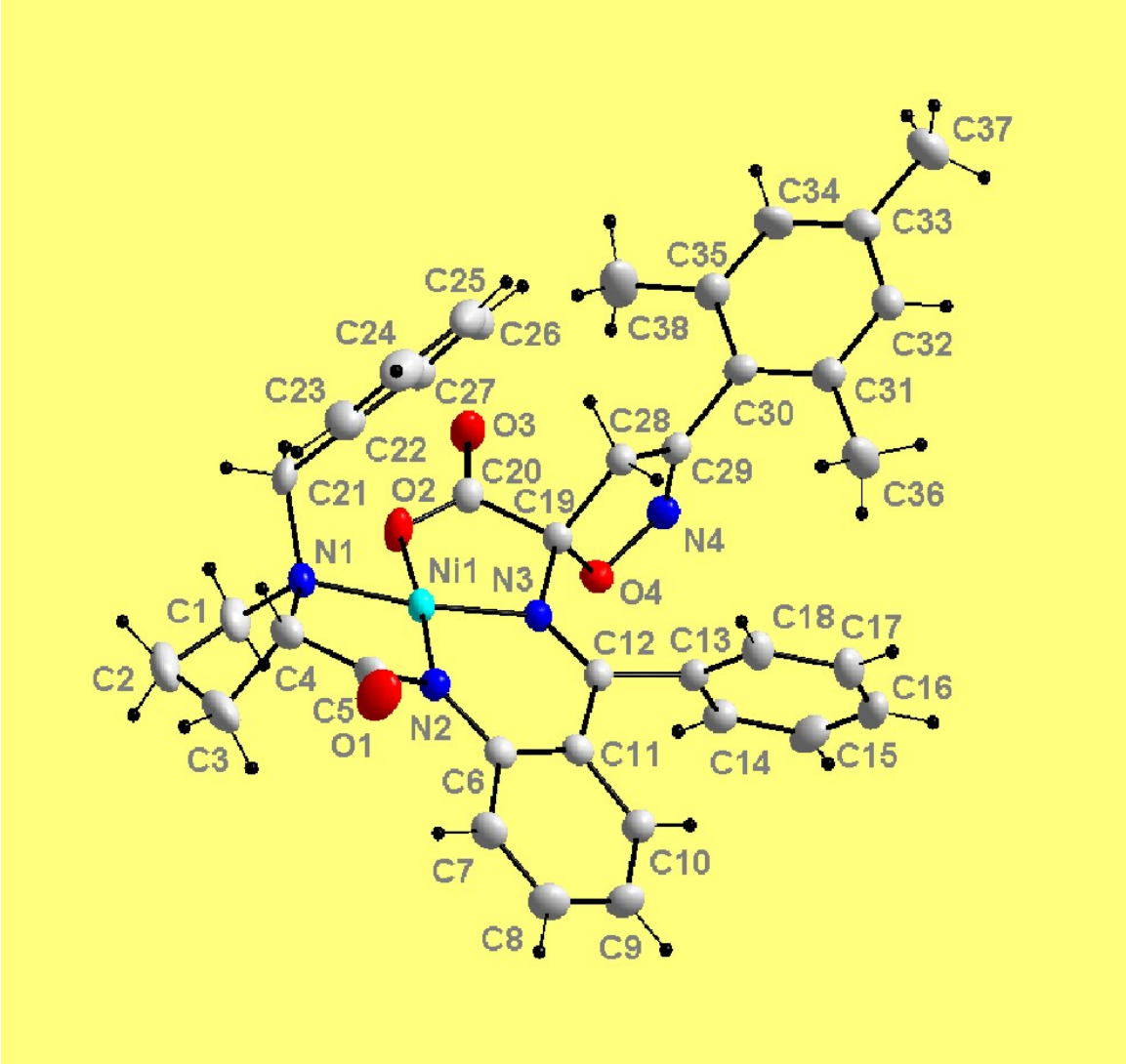


Figure 1. Crystalline structure of compound **6** with crystallographic numbering and 30% ellipsoids.

Table 1. Crystal and experimental data for compound **6**

Empirical formula	$C_{38}H_{36}N_4O_4Ni$
Formula weight	671.41
Temperature, T (K)	299(2) K
Wavelength, λ (Å)	0.71093
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions(Å)	a = 9.843(1) α = β = γ = 90°
	b = 11.165(2)
	c = 29.173(2
Unit-cell volume, V (Å^3)	3206(1)
Formula units per unit cell, Z	4
Calculated density, D_x (g cm^{-3})	1.391
Absorption coefficient, μ (mm^{-1})	0.080
F(000)	1408
μ (mm^{-1})	0.65
Crystal size (mm)	0.37 x 0.28 x 0.13
Diffractometer	Enraf-Nonius CAD4
Theta range for data collection, (°)	1.99 - 23.98
Index ranges	$-12 \le h \le 3$, $-13 \le k \le 1$, $-35 \le l \le 1$
Reflections collected	5169
Independent reflections [I>2σ(I)]	4633 (Rint = 0.031)
Absorption correction	Empiric Psi-scan
Max. and min. transmission	0.9151 and 0.8284
Refinement method	Full-matrix least-squares on F^2
Data / parameters	3602 / 209
Goodness-of-fit (all)	0.977
Final R indices [I>2σ(I)]	R1 = 0.0295, wR2 = 0.0725
R indices (all data)	R1 = 0.0632, wR2 = 0.0814
Extinction coefficient	0.011(14)
Largest diff. peak and hole	0.283 and -0.416 (e Å^{-3})

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References

1. Adamo, M. F. A.; Donati, D.; Duffy, E. F.; Sarti-Fantoni, P. *J. Org. Chem.* **2005**, *70*, 8395.
2. Howe, R. K.; Shelton, B. R. *J. Org. Chem.* **1990**, *55*, 4603.
3. De Amici, M.; De Micheli, M.; Misani, V. *Tetrahedron* **1990**, *46*, 1975.
4. Smietana, M.; Gouverneur, V.; Mioskowski, C. *Tetrahedron Lett.* **1999**, *40*, 1291.
5. Faulkner, J. *Nat. Prod. Rep*. **2001**, *18*, 1.
6. Wright, A. D.; King, G. M.; Sticher, O. *J. Nat. Prod* **1990**, *53*, 1615.
7. Harburn, J. J.; Rath, N. P.; Spilling, C. D. *J. Org. Chem.* **2005**, *70*, 6398.
8. Bardhan, S.; Schmitt, D. C.; Porco, J. A. Jr. *Org. Lett.* **2006**, 8 .
9. Tilvi, S.; Rodrigues, C.; Naik, C. G.; Parameswaran, P. S.; Wahidhulla S. *Tetrahedron* **2004**, *60*, 10207.
10. Cue, D.; Southern, S. O.; Southern, P. J.; Prabhakar, J.; Lorelli, W.; Smallheer, J. M.; Mousa, S. A.; Cleary, P. P. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 2858.
11. Kelly-Basetti, B. M.; Mackay, M. F.; Pereira, S. M.; Savage, G. P.; Simpson G. W. *Heterocycles* **1994**, *37*, 529.
12. Cheng, W-C.; Liu, Y.; Wong, M.; Olmstead, M. M.; Lam, K. S.; Kurth, M. J. *J. Org. Chem.* **2002**, *67*, 5673.
13. Mičúch, P.; Fišera, L.; Ondruš, V.; Ertl, P. *Molecules* **1997**, *2*, 57.
14. Fischer, R.; Hýrošová, E.; Drucková, A.; Fišera, L.; Hametner, C.; Cyrański, M. K. *Synlett* **2003**, 2364.
15. Fischer, R.; Hýrošová, E.; Fišera, L.; Hametner, C.; Cyrański, M. K. *Chemical Papers* **2005**, *59*, 275.
16. Belokon, Y. N.; Sagyan, A. S.; Djamgaryan, S. M.; Bakhmutov, V. I.; Belikov, V. M. *Tetrahedron* **1988**, *44*, 5507.
17. Belokon, Y. N.; Sagyan, A. S.; Djamgaryan, S. A.; Bakhmutov, V. I.; Vitt, S. V.; Batsanov, A. S.; Struchkov, Y. T.; Belikov, V. M. *J. Chem. Soc. Perkin Trans.* 1, **1990**, 2301.
18. Jirman, J.; Popkov, A. *Coll. Czech. Chem. Commun.***1995**, *60*, 990.
19. REDU 4, Stoe Four-Circle Data Reduction Program, Version 7.08. Stoe & Cie, Darmstadt: Germany, 1993.
20. Sheldrick, G. M. *Acta Cryst*. **1990**, *A46*, 467.
21. Sheldrick, G. M. Program for the Refinement of the Crystal Structures. University of Göttingen: Germany, 1997.