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Synthesis and stability of new spiroaminoborate esters

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ABSTRACT

New spiroaminoborate esters derived from 1,1-diphenylprolinol, ephedrine, and dihydroquinine with different alkoxy substituents were prepared as stable crystalline compounds and characterized by spectroscopical analysis and specific rotation. The structure of the spiroborate **4** derived from 1,1-diphenylprolinol and dicyclohexyl-1,1′-diol was confirmed by X-ray analysis.

Chiral aminoborate esters derived from nonracemic amino alcohols are highly effective and efficient catalysts for the asymmetric borane-mediated reduction of prochiral ketones and oximes.[1–5] A series of spiroborate esters derived from nonracemic 1,2-amino alcohols were previously prepared in our laboratory and their enantioselectivity studied as a function of the amino alcohol structure. Spiroaminoborate ester **1** (Fig. 1), derived from (*S*)-1,1-diphenyl prolinol and ethylene glycol, achieved outstanding stereoselection in the reduction of a large variety of arylalkyl and aromatic heterocyclic ketones, comparable in their enantioselectivity to the CBS oxazaborolidine.[6,7] Additionally, spiroborate **6**, prepared from (*S*)-1,1-diphenyl prolinol and trimethoxy borate, was found to be an outstanding catalyst for the reduction of aryl ketones with only 1 mol % loading.[2a] Furthermore, the spiroborate ester derived from diphenyl valinol and ethylene glycol was the first effective catalyst for the asymmetric reduction of arylalkyl and heterocyclic benzyloxime ethers, therefore, it was successfully applied for the synthesis of a diverse group of aryl and heterocyclic enantiopure primary amines and amino ethers.[3] Recently, similar spiroborates derived from α-pinene as the amino alcohol source and different diols demonstrated to be excellent catalysts for the reduction of aromatic ketones.[5] Due to their Lewis acid-base nature, aminoborate esters can also be effective catalysts for other types of reactions, as it was recently reported in the selective reduction of ketones, esters, and amides using *N*,*N*-diethylaniline-borane.[8a] Additionally, spiroborate esters have been used as

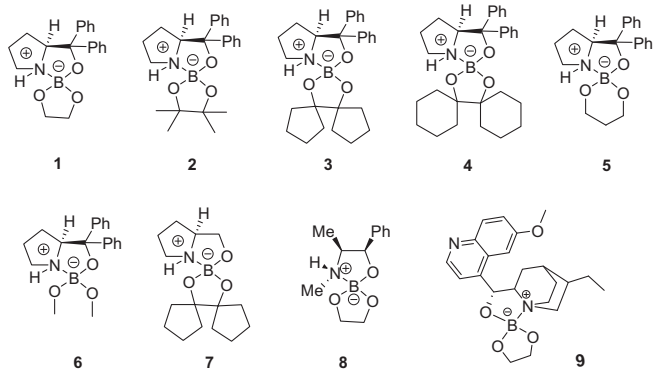

Figure 1. Spiroaminoborate esters.

synthetic templates for further asymmetric transformations.[8b] Aminoborate esters, in contrast to other chiral reducing catalysts, are stable to air and moisture and, consequently, they are easier to prepare, purify, store, and handle. Their outstanding enantioselectivity in the borane-mediated reductions may be attributed to their high purity.

Herein, we describe the synthesis and characterization of novel nonracemic spiroaminoborate complexes, in particular, with a variety of dialkoxy substituents. Furthermore, we are interested in studying the role that the dialkoxy fragment plays in the properties and stability of these catalysts.

The new spiroaminoborates **2**–**5,** and **7** (Fig. 1), derived from diphenyl prolinol and the corresponding diol, were successfully prepared and isolated as colorless crystalline materials. Similarly,

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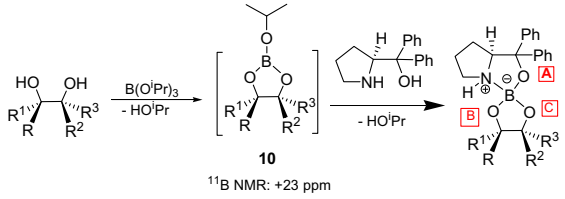
spiroborates **8** and **9** derived from (*R*,*S*)(−)-ephedrine and dihydroquinine, (9*R*)-10,11-dihydro-6′-methoxycinchonan-9-ol, respectively, were successfully prepared and characterized.[9]

The spiroborates **2**, **5**, **7**, **8,** and **9** were prepared as shown in Scheme 1 by gently heating isopropyl borate with the corresponding diol in toluene until a clear solution of the 2-isopropoxy[1,3,2]dioxaborolane **10** was observed, followed by the slow addition of the chiral β-amino alcohol in toluene.[1b,9]

The formation of intermediate **10** and the spiroborate was determined by ^{11}B NMR analysis. Initially, it was observed a strong signal around 23 ppm corresponding to **10**, together with a weak peak at 17.7 ppm, due to a slight excess of triisopropyl borate. A strong singlet between 5 and 10 ppm indicated the formation of the aminoborate ester. Surprisingly, the syntheses of the spiroborates **3** and **4** were not successfully achieved after several attempts using triisopropyl borate or trimethyl borate for the formation of intermediate **10**. However, a modified approach employing boronic acid under reflux in toluene with azeotropic removal of water, and subsequent reaction of the boric ester with the β-amino alcohol provided the desired compounds in quantitative yield.[10] In some cases, impurities of unreacted amino alcohols (ca. 10%) and/or borate species were removed by recrystallization, except for compound **5**, which was obtained after several attempts in a 90% purity by ^{11}B, ^{1}H, and ^{13}C NMR.[9] Borate **6** was prepared as reported



Scheme 1. General synthesis of spiroaminoborate esters.

Table 1
Spiroaminoborate esters characterization

Borate esters	Yield (%)	^{11}B NMR δ (ppm) (s)	Mp (°C)	$[\alpha]_D^{23}$
2	98	9.4	169–174	−101 (*c* 1.3, $CHCl_3$)
3	99	9.8	188–192	−95 (*c* 1.2, $CHCl_3$)
4	92	9.8	234–236	−74 (*c* 2.3, $CHCl_3$)
5	99[a]	6.1	120–123	−59 (*c* 4.3, $CHCl_3$)
6	68[b]	6.7	132–136	−130 (*c* 1.3, $CHCl_3$)
7	99	9.6	192–196	+13 (*c* 2.0, $CHCl_3$)
8	99	10.0	136–138	−37.5 (*c* 5.6, DMSO) −9 (*c* 2.9, $CHCl_3$)
9	97	10.2	177–182	−137 (*c* 2.17, $CHCl_3$)

[a] Purity, 90%.
[b] Recristalyzed in diisopropyl ether.

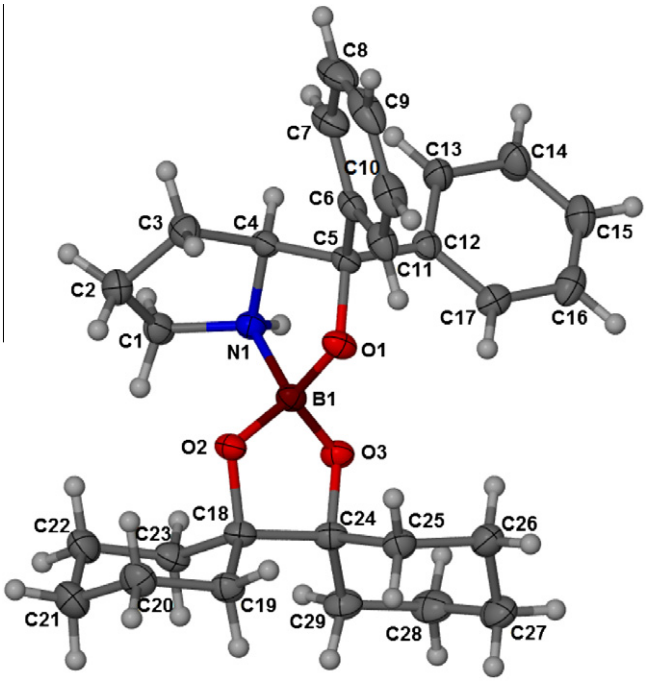


Figure 2. X-ray structure of spiroaminoborate ester **4**.

previously by transesterification with trimethyl borate and fully characterized.[2e,11]

In general, the pure spiroaminoborate esters were isolated as crystalline solids and fully characterized by mp, spectroscopic methods, and specific rotation (Table 1).

Additionally, as indicated in Figure 2, the structure of **4** was corroborated by X-ray analysis.[12]

Density functional theory calculations (DFT) were performed to obtain the relative energies of the aminoborate esters **1**–**8**, shown in Figure 1. The geometry pre-optimizations were performed in vacuum with the PM3 semi empirical method using the Polak–Ribiere conjugated gradient protocol. The final optimizations were performed with DFT [B3LYP/6-31G(d)OPT] using GAUSSIAN 03. All conformational and thermodynamical parameters were obtained with DFT single point calculations. The relative energy of compounds compared to the most stable spiroborate **4** was calculated by the Eq. (1).

$$\Delta E = (C_{\text{omp}} - E_1) * 627.503 \quad (1)$$

In Table 2 are indicated the relative energy of the selected aminoborates, the dipole moment, and the B–N bond order, and the conformational parameters: (a) the O_A–B–O_B–C torsion angle; (b)

Table 2
Relative energy and geometrical parameters of compounds **1**–**8**

Borate	$\Delta E \times 10^{-4}$ (Kcal/mol)	μ (D)	Torsion angle (degree)			B–N bond order
			a	b	c	
1	24.52	4.39	120.7	108.2	72.0	0.4631
2	14.65	3.91	110.3	113.4	69.9	0.4591
3	4.93	4.26	113.9	112.9	71.2	0.4695
4	—	3.92	108.6	113.0	66.6	0.4579
5	22.05	3.53	91.7	156.4	69.7	0.5046
6	24.44	3.61	59.1	103.1	66.7	0.4442
7	33.93	4.34	113.6	112.69	76.1	0.4318
8	43.87	4.44	142.2	131.8	79.4	0.4201

[a] Torsion angle for O_A–B–O_B–C.
[b] Torsion angle for N–O_C–C.
[c] Torsion angle for N–O_A–O_C–O_B.

the N–B–O_C–C torsion angle; and (c) the N–O_A–O_C–O_B torsion angle (Scheme 1). The thermal stability of compound **4** is, at least, 4.9×10^4 kcal/mol higher than the other derivatives. Systems with no phenyl groups on the oxazaborolidine ring, such as **7**, are less stable. The same behavior is observed for systems without a cyclic ring attached to the amino group, such as compound **8**.

It is well known that energy results by the DFT methods do not have a good correlation with the free energy, which is the best indicator for the thermal stability of a molecule.[13] Therefore, in this study, the stability trend in the series **1–8** was also rationalized in terms of the B–N bond order. For these compounds it is established that the smaller the bond order the weaker the B–N bond, therefore the lower the thermal stability of the compound. In this case, it is well known that calculated bond order is in good agreement with the experimental values for the method used in this work, B3LYP/6_31G(d).[13] Based on this principle, compounds **7** and **8** should be the less stable, while compound **5**, should have the highest thermal stability.

In summary, new stable spiroaminoborate esters were successfully prepared and fully characterized. Their structural parameters and thermal stability were studied by molecular calculations. Interestingly, structure **4** was the most thermally stable by the DFT calculations, however spiroborate **5** has higher stability using the B–N bond order method, although the difference in their bond order is small. The effect of the aminoborate structure and the role that the dialkoxy fragment plays on their reactivity toward borane and the mechanism in the enantioselective ketone reduction, will be addressed in future studies.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.054.

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9. General procedure for the synthesis spiroborate esters **1**, **2**, **5**, **7**, **8** and **9**: To a solution of the corresponding diol (5.05 mmol) in 15 mL of dry toluene under a nitrogen flow was added via syringe triisopropyl borate (1.17 mL, 5.1 mmol). The reaction mixture was gently heated to reflux until an homogeneous colorless solution was observed. A solution of (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol (1.267 g, 5.0 mmol) in dry toluene (10 mL) was added to the warm stirring solution. The reaction mixture was then gently heated to reflux until a homogeneous colorless solution was formed. After cooling, the resulting solution with a white solid was concentrated in the rotovaporator by heating at 80 °C/20 mm Hg for about 1 h. The white crystalline solid was then dried overnight using high vacuum (0.5 mm Hg). Generally, the desired compounds were obtained pure in quantitative yield. The impure spiroborates were further recrystallized in toluene. Compound (**2**): Yield 98%; mp 169–174 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (s, 6H), 1.20 (s, 6H), 1.54–2.67 (m, 3H), 1.89 (m, 1H), 2.96 (m, 1H), 3.60 (m, 1H), 4.17 (s, 1H), 4.39 (m, 1H), 7.04–7.27 (m, 6H), 7.55 (d, *J* = 7.2 Hz, 2H), 7.67 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 25.1, 25.4, 28.3, 46.6, 68.7, 79.3, 80.2, 125.7, 126.1, 126.5, 126.7, 127.6, 146.1, 146.8; ^{11}B NMR (128 MHz, $CDCl_3$): δ 9.40; IR (*v*, cm^{-1}): 3258 (NH), 2970, 2928, 1448, 1376, 1274, 1105, 1018, 973. $[\alpha]_D^{23}$ −101 (*c* 1.3, $CHCl_3$). HRMS *m*/*z*: 380.2396 found (calcd for $C_{23}H_{30}NO_3BH$, $(M+H)^+$ requires 380.2397). Compound (**5**): Yield 99% with 90% purity; mp 120–123 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51–1.85 (m, 6H), 2.96 (m, 1H), 3.33 (m, 1H), 3.82 (m, 4H), 4.27 (m, 1H), 4.63 (s, 1H), 7.06–7.28 (m, 6H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.59, 28.07, 28.50, 45.69, 61.32, 68.85, 81.16, 125.89, 126.05, 126.19, 126.54, 127.66, 127.78; ^{11}B NMR (128 MHz, $CDCl_3$): δ 6.09; IR (*v*, cm^{-1}): 3221, 2915, 2836, 1490, 1382, 1242, 1151, 1022, 935; $[\alpha]_D^{23}$ −59.4 (*c* 6.3, $CHCl_3$); HRMS *m*/*z*: 338.1871 found (calcd for $C_{20}H_{25}NO_3BH$, (M+H)+ requires 338.1927). Compound (**7**): Yield 99%; mp 192–196 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52–2.00 (m, 20H), 2.84 (s, 1H), 3.40 (m, 2H), 3.87 (t, *J* = 8.0 Hz, 1H), 4.01 (s, 1H), 6.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 26.1, 29.4, 36.6, 46.8, 60.6, 65.6, 90.3; ^{11}B NMR (128 MHz, $CDCl_3$): δ 9.59; IR (*v*, cm^{-1}): 3054, 2957, 2849, 1446, 1323, 1236, 1125, 1042, 1006, 950; $[\alpha]_D^{23}$+25.0 (*c* 2.3, $CHCl_3$); HRMS *m*/*z*: 280.2090 found (calcd for $C_{15}H_{26}NO_3BH$, (M+H)+ requires 280.2079). Compound (**8**): Yield 99%; mp 136–138 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (d, *J* = 7.2 Hz, 3H), 2.54 (s, 3H, NMe), 3.40–3.47 (m, 1H, NCH), 3.60–3.90 (m, 4H, OCH_2), 5.17 (d, *J* = 6 Hz, OCH), 6.10 (br s, 1H, NH), 7.22–7.25 (m, 1H), 7.26–7.33 (m, 2H), 7.36–7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.7, 30.6, 60.2, 64.5, 76.6, 126.4, 127.4, 128.0, 140.0; ^{11}B NMR (128 MHz, $CDCl_3$): δ 10.0; IR (*v*, cm^{-1}): 3099, 2870, 1452, 1131, 1114,1078, 965, 933; $[\alpha]_D^{23}$ −37.5 (*c* 5.6, DMSO), −9.0 (*c* 2.9, $CHCl_3$). HRMS *m*/*z*: 236.1455 found (calcd for $C_{12}H_{18}NO_3BH$, $(M+H)^+$ requires 236.1453). Compound (**9**): Yield 97%; mp 177–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (m, 1H), 0.95 (t, *J* = 7.4 Hz, 3H), 1.34–1.53 (m, 4H), 1.70 (m, 1H), 1.81 (m, 2H), 3.04 (m, 4H), 3.91 (s, 3H), 4.11 (m, 5H), 5.92 (d, *J* = 9.2 Hz, 1H), 6.82 (d, *J* = 2.8 Hz, 1H), 7.40 (dd, J_1 = 2.8 Hz, J_2 = 9.2 Hz, 1H), 7.92 (d, *J* = 4.4 Hz, 1H), 8.09 (d, *J* = 9.2 Hz, 1H), 8.82 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.1, 23.4, 25.2, 25.8, 27.5, 36.8, 44.2, 54.2, 55.6, 59.0, 64.9, 70.6, 101.5, 118.8, 121.1, 127.2, 132.0, 143.9, 145.2, 148.4, 157.5; ^{11}B NMR (128 MHz, $CDCl_3$): δ 10.2; IR (*v*, cm^{-1}): 2934, 2872, 1620, 1507, 1469, 1229, 1146, 1056, 856; $[\alpha]_D^{23}$ −137 (*c* 2.17, $CHCl_3$); HRMS *m*/*z*: 397.2411 found (calcd for $C_{22}H_{29}BN_2O_4H$, $(M+H)^+$ requires 397.2299). See Supplementary data.
10. Typical procedure for the synthesis of spiroborate ester **3**: A mixture of boric acid (618 mg, 10 mmol) and dicyclopentyl -1,1′-diol (1.70 g, 10 mmol) in dry toluene (40 mL) was gently heated with stirring up to 80 °C over 1 h using a Dean–Stark distillation trap. A homogeneous sample was analyzed by ^{11}B NMR, which exhibited the corresponding signal for the boronic acid intermediate, ^{11}B NMR (128 MHz, $CDCl_3$), δ: 22.7 ppm. A solution of (*S*)-diphenyl(pyrrolidin-2-yl)methanol (2.53 g, 10 mmol) in dry toluene (20 mL) was added to the reaction mixture and the resulting solution was refluxed in a Dean–Stark water removing system over 2 h. The reaction mixture was concentrated at 90 °C in a rotor evaporator under vacuum (10 mm Hg) and the white solid was further dried under high vacuum (0.5 mm Hg) over 12 h to give the final product in quantitative yield (99%); mp 188–192 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35–2.00 (m, 20H), 2.92–3.00 (m, 1H), 3.49–3.59 (m, 1H), 4.18–4.30 (m, 1H), 4.42–4.50 (m, 1H), 7.04–7.25 (m, 6H), 7.54 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.1, 23.6, 25.3, 28.3, 34.4, 35.4, 47.0, 68.2, 80.4, 90.1, 125.8, 126.1, 126.5, 126.6, 127.7, 127.7, 146.2, 146.7; ^{11}B NMR (128 MHz, $CDCl_3$): δ 9.8; IR (*v*, cm^{-1}): 3258, 2956, 2869, 1447, 1381, 1228, 1108, 1022, 1062, 945; $[\alpha]_D^{23}$ −95 (*c* 1.2, $CHCl_3$); HRMS *m*/*z*: 432.2709 found (calcd for $C_{27}H_{34}NO_3BH$, $(M+H)^+$ requires 432.2705). Compound (**4**): Yield 92%; mp 234–236 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11–1.27 (m, 6H), 1.56–1.81 (m, 17H), 2.07 (m, 1H), 3.04 (m, 1H), 3.62 (m, 1H), 4.36 (s, 1H), 4.52 (m, 1H), 7.11–7.37 (m, 6H), 7.62 (d, *J* = 7.6 Hz, 2H), 7.70 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 23.2, 24.9, 26.5, 28.0, 32.7, 33.1, 46.6, 67.96, 80.4, 126.0, 126.2, 126.5, 126.8, 127.7, 127.7, 146.4, 147.1; ^{11}B NMR (128 MHz, $CDCl_3$): δ 9.8; IR (*v*, cm^{-1}): 3055, 2932, 2853, 1488, 1444, 1308, 1226, 1153, 1034, 937; $[\alpha]_D^{23}$ −74 (*c* 2.3, $CHCl_3$); HRMS *m*/*z*: 460.3023 found (calcd for $C_{29}H_{38}NO_3BH$, $(M+H)^+$ requires 460.3018). See Supplementary data.
11. Preparation of (−)-(3a*S*)-1,1-dimethoxy-3,3-diphenyl-hexahydro-1*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborol-7-ium-1-uide (**6**): To a solution of (*S*)-diphenyl(pyrrolidin-2-yl)methanol (2.53 g, 10 mmol) in dry isopropyl ether (25 mL) was added drop-wise freshly redistilled trimethyl borate (3 mL, 28.9 mmol) at room temperature under nitrogen atmosphere. The resulting mixture was left without stirring over 24 h (after 2 h white crystals started to grow). The precipitate was filtered, washed with isopropyl ether (4 × 10 mL) under nitrogen atmosphere, and dried under vacuum at 60 °C over 12 h to give the final product as a white solid. Yield 68%; mp 132–136 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 1.42–1.66 (m, 4H, $2CH_2$), 2.0–3.2 (m, 8H, $B(OMe)_2$ and NCH_2), 4.26–4.31 (m, 1H, NCH), 6.37 (br d, *J* = 6.0 Hz,

1H, NH), 7.1–7.3 (m, 6H, CHAr), 7.46–7.50 (m, 4H, CHAr); ^{13}CNMR (100 MHz, $CDCl_3$): δ 24.8, 29.0, 46.7, 49.6 (br, 2MeO), 81.4, 126.1, 126.2, 126.3, 126.5, 127.7, 127.8, 146.2, 147.8; ^{11}B NMR (128 MHz, $CDCl_3$): δ 6.7 (*s*); IR (*v*, cm^{-1}): 3300 (NH), 3059, 2964, 1598, 1390, 1103, 1022; $[\alpha]_D^{23}$ −130 (*c* 1.3, $CHCl_3$); HRMS *m*/*z*: 326.1937 found (calcd for $C_{19}H_{24}BNO_3$, (M−H)+ requires 326.1927.

12. The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 844542. Formula: $C_{31}H_{44}B_1N_1O_4S_1$ Unit cell parameters: *a* = 8.6764(4) Å, *b* = 18.0726(8) Å, *c* = 9.2445(4) Å, alpha = 90°, beta = 95.5980(10)°, gamma = 90°. Crystal system, space group Monoclinic, P21. Crystal size 0.35 × 0.35 × 0.25 mm.
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