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Chiral ligand 2-(2′-piperidinyl)pyridine: synthesis, resolution and application in asymmetric diethylzinc addition to aldehydes

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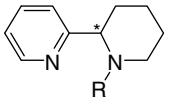
ABSTRACT

Chiral ligand 2-(2′-piperidinyl)pyridine **1** has been synthesized in good overall yield by sequential benzylation, hydrogenation and debenzylation of 2,2′-bipyridine. Its enantiomerically pure enantiomers have been obtained by resolution of 2-(1-benzyl-2-piperidinyl)pyridine **2** with D-tartaric acid (or L-tartaric acid) followed by debenzylation. The absolute configuration was determined by X-ray analysis of the (*S*)-**2** D-tartrate. It was demonstrated that **1** can be used as an effective enantioselective catalyst in the addition of diethylzinc to aldehydes. Optically active secondary alcohols with up to 100% enantiomeric excess were obtained in high yields.

1. Introduction

N,N-Bidentate ligands, such as diamine derivatives,[1] 1-substituted-1-(pyridyl)methylamines(py-amines)[2] and 2,2′-bipyridines[3] are under investigation in the field of coordination chemistry. Furthermore, chiral N,N-ligands have attracted attention due to their applications in metal complexes as asymmetric catalysts. For example, py-amines have displayed medium to excellent enantioselectivities in transfer hydrogenations, palladium-catalyzed allylic alkylations and additions of diethylzinc to aldehydes.[2] However, it is noteworthy that the chiral ligand 2-(2′-piperidinyl)pyridine **1**, an analogue of the tobacco alkaloid anabasine, has so far hardly drawn any attention. The racemate of **1** has only been prepared in very low yield according to the literature.[4] Recently, Gillespie et al. demonstrated that the (*S*)-enantiomer of **1** could be used as the fragment of inhibitors of 11B-hydroxysteroid dehydrogenase, but no details about the preparation of the enantiomer were reported.[5]

Herein, we have synthesized chiral ligand **1** in good yield by reduction of mono-benzyl salt of 2,2′-bipyridine according to a similar procedure described in our previous work.[6] The racemate of 2-(1-benzyl-2-piperidinyl)pyridine **2** was successfully resolved. The absolute configurations were determined. The effectiveness of the ligand in the asymmetric synthesis was primarily evaluated by the addition reaction of diethylzinc to aldehydes.



1 R = H
2 R = Bn

2. Results and discussion

2.1. Synthesis of racemic 1

Compound **1** can be obtained from **3** via two reported approaches. One involves the reduction of **3** by tin in hydrochloric acid or with nickel-aluminum alloy, but the mixtures produced were difficult to purify and the yields were no higher than 10%.[4] Another approach was the oxidation of **3** followed by hydrogenation with Pd/C.[7] However, the yield of the target product based on the second method is still too low in our laboratory. According to the strategy for the synthesis of isoanabasine in our previous work,[6] we proposed another effective approach to prepare **1** in three steps, as outlined in Scheme 1. Each step can be easily carried out with the overall yield being 68%, much higher than the yield reported previously. Pure benzyl salt **4** was obtained in 90% yield by stirring **3** with benzyl bromide in boiling acetonitrile under a dry nitrogen atmosphere for 3 days and then recrystallization of the product from ethylacetate/acetonitrile. Benzylation of **3** was more difficult than that of 2,3′-bipyridine for steric reasons. Hence, benzyl bromide was used as the nucleophilic acceptor instead of benzyl chloride which was more time-consuming.[8] Compound **2** was obtained in 85% yield by hydrogenation of **4** with PtO_2 as a catalyst in the presence of triethylamine. Removal of the benzyl group of **2** with palladium catalyst[9] gave **1** in 89% yield.

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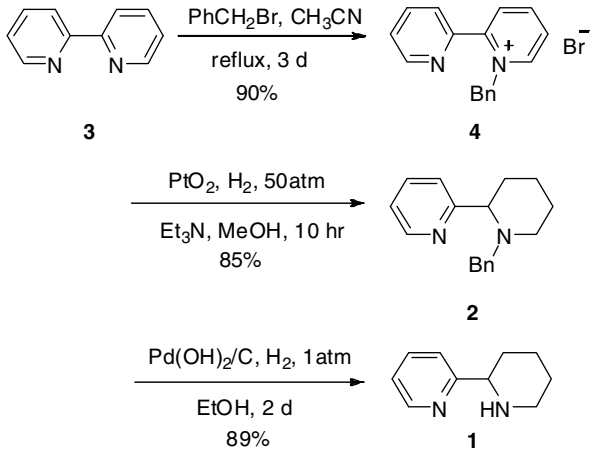


Scheme 1. Synthetic route to ligand **1**.

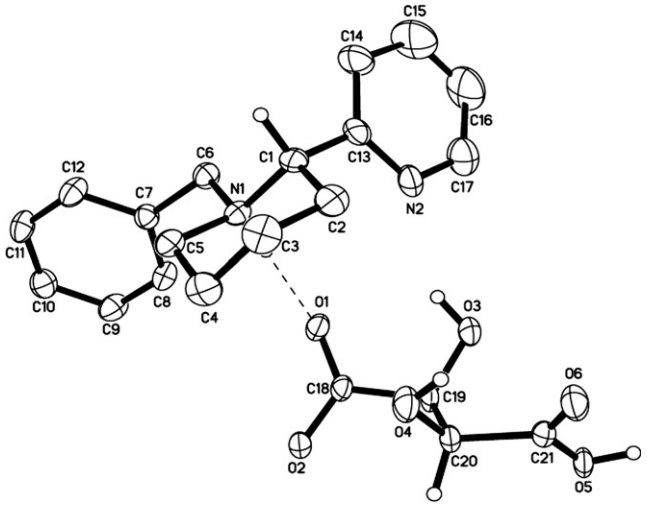


Figure 1. X-ray structure of D-tartaric acid and (*S*)-**2** complex (hydrogens, except on heteroatoms or stereogenic centers, omitted for clarity).

2.2. Resolution of the racemate and assignment of the absolute configuration

Resolution via diastereomeric salt formation is still an important technique for the preparation of enantiopure compounds.[10] Many optically active py-amines, such as nicotine,[11] nornicotine,[12] and 1-(pyridin-2-yl)ethylamine[13] have been obtained by the resolution of their racemates.

Five chiral organic acids, (+)-tartaric acid, dibenzoyl-(+)-tartaric acid, (*R*)-1,1′-bi-2-naphthol, (+)-camphoric acid and (+)-mandelic acid were examined by complexation with *rac*-**2** to find a suitable resolving agent. Among these agents, (*R*)-1,1′-bi-2-naphthol, (+)-camphoric acid and (+)-mandelic acid produced salts that failed to crystallize while dibenzoyl-(+)-tartaric acid gave crystalline salts from water/ethanol or water/methanol without enantiomeric enrichment. Fortunately, precipitation of *rac*-**2** with 0.5 equiv of D-tartaric acid from acetonitrile/tetrahydrofuran (5:1 in volume) gave a 1:1 (*S*)-**2** D-tartrate, as shown by ^{1}H NMR[14] and X-ray analysis. Treatment of the salt with alkaline afforded an enantiomer in 93% ee,[15] from which an enantiomerically pure (*S*)-**2** was obtained by recrystallization from ethanol/water in 65% yield based on half of the starting *rac*-**2**, with $[\alpha]_D^{20} = -60.5$ (*c* 0.55, ethanol). The mother liquor enriched in (*R*)-**2** was converted to the free base and treated with L-tartaric acid to generate (*R*)-**2** with 100% ee (Scheme 2).

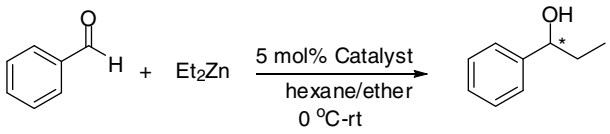
Debenzylation of both enantiomers of **2** produced the corresponding pure enantiomers of **1**, with $[\alpha]_D^{20} = +47.0$ (*c* 0.62, ethanol) in the same rotary direction to their benzyl precursors. It is reasonable to assume that no racemization occurred during debenzylation.[9]

To determine the absolute configuration, the complex of D-tartaric acid and (*S*)-**2** was crystallized and investigated by X-ray crystallography (Fig. 1).[16] The structure definitively indicates that the D-tartaric acid has crystallized with 1.0 equiv of (*S*)-**2**.

2.3. Enantioselective diethylzinc addition to aldehydes

It is well known that the enantioselective addition of diethylzinc to aldehydes is one of the most reliable methods to prepare chiral secondary alcohols, and it has been proven that many chiral amines can be used as effective catalysts for this reaction.[17] The addition of diethylzinc to benzaldehyde was first examined in the presence of catalytic amounts (5 mol %) of **1**–**2** in hexane/ethyl ether. As shown in Table 1, a high yield and high ee were achieved by using (*R*)-**1**, while (*R*)-**2** afforded 1-phenylpropanol with satisfactory yield but low enantioselectivity.

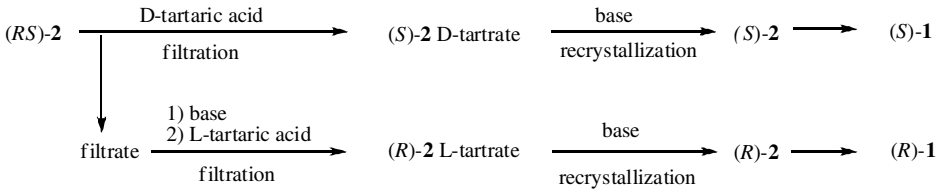
Table 1
Enantioselective addition of diethylzinc to benzaldehyde[a]



Entry	Ligand	Yield[b] (%)	ee[c] (%)	Configuration[d]
1	(*R*)-**1**	91	93	(*R*)
2	(*R*)-**2**	96	12	(*R*)

[a] Reaction was carried out in hexane/ether at 0 °C–rt with a molar ratio of Et_2Zn/benzaldehyde/ligand = 2/1/0.05.
[b] Isolated yield.
[c] The ee values were determined by HPLC with a Chiralcel-OD column.
[d] Configurations were assigned by comparison with the sign of the specific rotation of known compounds.

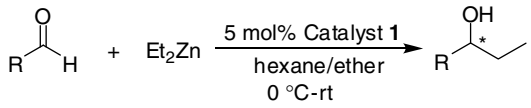
The high enantioselectivity of ligand (*R*)-**1** for the addition of diethylzinc to benzaldehyde prompted us to examine its use for the reaction of various aldehydes. These results are summarized



Scheme 2. Resolution of racemic **2**.

in Table 2. Aromatic aldehydes underwent the reaction smoothly to afford the desired ethyl carbinols with high yields (87–93%) and excellent enantioselectivities (91–100% ee). With heteroaromatic and aliphatic aldehydes (entries 8–10) good yields and good enantioselectivities were obtained as well. However, low enantioselectivity (40% ee) was observed when *trans*-cinnamaldehyde was used as the substrate. In all the cases examined, the absolute configurations of corresponding ethyl carbinols were (*R*).

Table 2
Enantioselective addition of diethylzinc to various aldehydes with (*R*)-**1**[a]



Entry	R	Yield[b] (%)	ee[c] (%)	Configuration[d]
1	*p*-ClC_6H_4	91	100	(*R*)
2	*p*-$CH_3OC_6H_4$	93	91	(*R*)
3	*o*-$CH_3OC_6H_4$	89	94	(*R*)
4	1-Naphthyl	92	96	(*R*)
5	2-Naphthyl	87	91	(*R*)
6	*p*-$CH_3C_6H_4$	93	100	(*R*)
7	*p*-BrC_6H_4	93	100	(*R*)
8	2-Furyl	87	85[e]	(*R*)
9	2-Thienyl	89	88[e]	(*R*)
10	Pentyl	90	85[e]	(*R*)
11	*trans*–PhCH=CH	89	40	(*R*)

[a] Reaction was carried out in hexane/ether at 0 °C–rt with a molar ratio of Et_2Zn/benzaldehyde/ligand = 2/1/0.05.
[b] Isolated yield.
[c] The ee values were determined by HPLC with a Chiralcel-OD or AD column.
[d] Configurations were assigned by comparison with the sign of the specific rotation of known compounds.
[e] Determined for the corresponding benzoate.

Inspired by the general catalytic model,[2e,f,18] the stereochemistry of the products can be interpreted by molecular models derived from the geometry optimization of transition states (TS) based on molecular mechanism. Three potential transition states are presented in Figure 2 when (*R*)-**1** is utilized as a catalyst and benzaldehyde as a substrate. As shown in TS **I**, the diethyl zinc coordinated on piperidyl nitrogen stands with aldehyde in the same side of the cyclopentyl plane composed of bidendate N–Zn complex. For this TS, one ethyl localizes in short contact with carbonyl nucleophile acceptor from the *Re* face of the aldehyde resulting in enantioselectivity of the (*R*)-form in high reaction rate. In TS **II** the aldehyde coordinates in another direction resulting in (*S*)-form enantioselectivity. In this case, a steric barrier between the hydrogen of the aldehyde and pyridyl ring and large distance between the ethyl and carbonyl may disfavor the reaction. Obviously the reaction is forbidden for diethylzinc and aldehyde in anti-conformation in TS **III**. Hence, (*R*)-form products are predominantly obtained over the (*S*)-form product in the addition of diethylzinc to aldehyde catalyzed by (*R*)-**1** through TS **I** catalysis model.

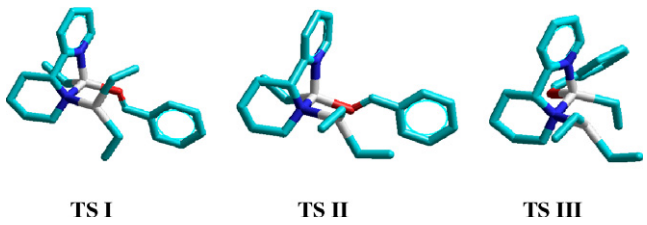


Figure 2. Transition states of addition of diethylzinc to aldehyde (H omitted for clarity).

3. Conclusions

In conclusion, the preparation of enantiomerically pure 2-(2′-piperidinyl)pyridine **1** has been described. Its evaluation as a chiral ligand in the asymmetric addition of diethylzinc to a variety of aldehydes was demonstrated, showing satisfactory results of up to 100% ee. Future efforts will be directed toward modifying the steric and electronic characteristics of the ligand and investigating applications in new asymmetric catalytic strategies.

4. Experimental

4.1. General

The ^1H and ^{13}C NMR spectra were recorded in deuterium chloroform or DMSO on a Bruker 600 MHz spectrometer with TMS as internal standard. Melting points were measured with a hot-stage microscope XT-4. ESI-MS measurements were conducted with an LCQ instrument. Optical rotations were measured on a Perkin Elmer 341LC polarimeter in an 1 dm tube. HPLC utilized a Shimadzu LC-6AD pump, a Shimadzu SPD-10A UV dectector, and Shimadzu Class-VP system controller software. Separations were carried out on Chiralcel-OD or AD analytical column with hexane/2-propyl alcohol as eluent. TLC was performed on aluminum TLC-layers Silica Gel GF-254 and Detected by UV light (254 and 365 nm). Silica gel (100–200 mesh) was used for column chromatography. All reactions were carried out under an argon atmosphere unless otherwise stated. All reagents and solvents employed were reagent grade materials purified by standard methods and redistilled before use. All the aldehydes employed were obtained by purification of commercial products.

4.2. Preparation of 1′-benzyl-2,2′-bipyridinium bromide 4

A stirred solution of 2,2′-bipyridine **3** (15.60 g, 0.10 mol) and benzyl bromide (35.9 mL, 0.30 mol) in dry acetonitrile (300 mL) under a nitrogen atmosphere was heated at reflux for 3 days. The solution was concentrated in vacuum and a precipitate was formed after ethyl acetate was added. The mixture was filtered and recrystallization of the precipitate from CH_3CN/AcOEt gave 29.4 g of 1′-benzyl-2,2′-bipyridinium bromide **4** as buff granules (90% yield). Mp 140–142 °C. ^1H NMR (600 MHz, DMSO-d_6): δ 6.09 (s, 1H), 6.93 (d, J = 6.49 Hz, 1H), 7.24 (m, 1H), 7.67 (dd, J = 7.64, 4.86 Hz, 1H), 7.72 (d, J = 7.84 Hz, 1H), 8.04 (dt, J = 7.80, 7.79, 1.62 Hz, 1H), 8.32 (dd, J = 15.40, 7.24 Hz, 1H), 8.82 (m, 1H), 9.42 (d, J = 5.80 Hz, 1H). ^{13}C NMR (150 MHz): δ 151.83, 149.76, 149.66, 147.42, 146.93, 138.19, 133.74, 130.67, 128.68, 128.63, 128.12, 127.67, 126.11, 125.83, 60.90. ESI-MS (m/z): $[M-Br]^+$ 247.0.

4.3. Preparation of racemic 2-(1-benzyl-2 piperidinyl)-pyridine 2

A suspension of **4** (12 g, 0.037 mol), triethylamine (5.1 mL, 0.037 mol), and PtO_2 (0.6 g) in methanol (100 mL) was stirred in an autoclave under a hydrogen atmosphere at 50 atm for 10 h at 40 °C. Upon deflation of the hydrogen, the insoluble species were removed by filtration through Celite. After evaporation of the methanol, the residues were dissolved in dichloromethane (100 mL) and dried over Na_2SO_4. The solvent was removed by evaporation to give the crude product which was recrystallized from EtOH/H_2O to give 7.9 g of pure 2-(1-benzyl-2-piperidinyl)pyridine **2** as white needles (85% yield). Mp 65–68 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 1.40 (m, 1H), 1.81 (d, J = 12.89 Hz, 1H), 1.89 (d, J = 13.06 Hz, 1H), 2.02 (s, 1H), 3.01 (m, 1H), 3.40 (d, J = 10.06 Hz, 1H), 3.68 (dd, J = 13.55, 5.73 Hz, 1H), 7.15 (m, 1H),

7.21 (dd, J = 8.45, 4.34 Hz, 1H), 7.28 (d, J = 4.41 Hz, 1H), 7.63 (d, J = 7.41 Hz, 1H), 7.68 (t, J = 7.56, 7.56 Hz, 1H), 8.54 (d, J = 4.61 Hz, 1H). ^{13}C NMR (150 MHz): δ 164.85, 148.80, 139.07, 136.51, 128.55, 127.90, 126.50, 121.76, 121.33, 77.32, 77.00, 76.68, 70.37, 59.91, 52.88, 35.21, 25.66, 24.62. ESI-MS (m/z): $[M+H]^+$ 253.1.

4.4. Preparation of racemic 2-(2′-piperidinyl)pyridine 1

A suspension of **2** (2.5 g, 0.01 mol) and 20% $Pd(OH)_2$ on carbon (0.2 g) in ethanol (30 mL) was stirred under a hydrogen atmosphere of 3–4 atm at room temperature for 2 days. The catalyst was filtered off, washed with ethanol. After evaporation of the ethanol, the residues were dissolved in dichloromethane (100 mL) and dried over Na_2SO_4. The solvent was removed by evaporation to give the crude product, which was purified by chromatography on silica using a solvent mixture (AcOEt/MeOH/Et_3N) into 1.42 g of **1** as a pale yellow oil (89% yield). Bp 115 °C/0.3 torr. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.52 (m, 1H), 1.66 (m, 1H), 1.94 (m, 1H), 2.13 (s br, 1H), 2.82 (td, J = 11.75, 2.85 Hz, 1H), 3.22 (m, 1H), 3.75 (m, 1H), 7.14 (m, 1H), 7.34 (d, J = 7.87 Hz, 1H), 7.64 (dt, J = 7.70, 7.69, 1.72 Hz, 1H), 8.53 (d, J = 4.20 Hz, 1H). ^{13}C NMR (150 MHz): δ 163.47, 148.99, 136.59, 121.96, 120.53, 62.47, 47.18, 33.13, 26.09, 25.04. ESI-MS (m/z): $[M+H]^+$ 163.1.

4.5. Resolution of *rac*-2 to enantiomers (*R*)-(+)-2 and (*S*)-(−)-2

To a stirred solution of D-tartaric acid (4.74 g, 31.6 mmol, 0.5 equiv) in a boiling mixture of tetrahydrofuran (30 mL) and acetonitrile (150 mL) was added *rac*-**2** (16 g, 63.2 mmol). Stirring was continued for 1 h at 70 °C. The mixture solution was allowed to stand at room temperature. Precipitates were formed, collected by filtration, suspended in 15% NaOH (50 mL) and extracted with dichloromethane (100 mL × 3). The extract was dried over Na_2SO_4 and evaporated to give the crude (*S*)-**2**, which was recrystallized from ethanol/water to furnish 5.2 g (*S*)-**2** of the 100% enantiomer as white needles in 65% yield. All filtrates were combined and evaporated in vacuum. The residues were dissolved in dichloromethane (100 mL) and washed with 15% NaOH (20 mL × 2) to remove the acid. The organic phase enriched with (*R*)-**2** was dried over Na_2SO_4 and evaporated to give a solid, which was resolved with L-tartaric acid (4.74 g, 31.6 mmol) in a similar procedure as described above to furnish 5.7 g (*R*)-**2** of the 100% enantiomer in 71% yield. Mp 82–84 °C. (*R*)-**2**: $[\alpha]_D^{20} = +60.5$ (c 0.55, ethanol), 100% ee [t_R (*R*) = 17.6 min]. (*S*)-**2**: $[\alpha]_D^{20} = -60.5$ (c 0.55, ethanol), 100% ee [t_R (*S*) = 19.5 min].[15]

4.6. (*R*)-(+)-1 and (*S*)-(−)-1

Compound (*R*)-**1** was prepared from (*R*)-**2** and (*S*)-**1** was prepared from (*S*)-**2** in a similar procedure to *rac*-**1** from *rac*-**2**. (*S*)-**1**: $[\alpha]_D^{20} = -47.0$ (c 0.62, ethanol).

4.7. General procedure for the asymmetric addition of diethylzinc to aromatic aldehydes

A solution of the ligand (0.05 mmol, 5 mol %) in ether (1 mL) was cooled at 0 °C. Diethylzinc (15% w/w, 2.3 mL, 2 mmol) in hexane was added over a period of 3 min. The mixture was stirred at 0 °C-rt for 30 min, added with aldehyde (1 mmol) then stirred for an additional 20 h. The reaction mixture was quenched with 10% H_2SO_4 (1.6 mL) then was extracted with ether (5 mL × 3) and the organic layer was washed with 10% H_2SO_4 (3 mL), saturated $NaHCO_3$ (3 mL) and dried over Na_2SO_4. The residue was distilled and purified by flash chromatography with dichloromethane as eluent. Enantiomeric excesses for the products were determined by HPLC analysis using a chiral column (OD or AD column).

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14. The integrals of all proton peaks in ^{1}H NMR spectra were matched with the formula of molecular complex (*S*)-**2** D-tartrate. ^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.35 (q, J = 12.81, 12.72, 12.72 Hz, 1H), 1.53 (m, 1H), 1.76 (dd, J = 25.80, 12.78 Hz, 1H), 2.07 (s, 1H), 2.50 (s, 1H), 2.89 (d, J = 11.30 Hz, 1H), 3.02 (d, J = 13.45 Hz, 1H), 3.44 (d, J = 10.29 Hz, 1H), 3.55 (d, J = 13.55 Hz, 1H), 4.26 (s, 1H), 7.26 (m, 1H), 7.61 (d, J = 7.83 Hz, 1H), 7.81 (t, J = 7.38, 7.38 Hz, 1H), 8.51 (d, J = 4.13 Hz, 1H).
15. Enantiomeric excess analysis was determined by HPLC with a Chiralcel-OD column at 254 nm (hexane/*i*PrOH in the ratio of 97/3, flow 0.5 mL/min; the retention time of (*R*)-**2** was 17.6 min, while that of (*S*)-**2** was 19.5 min).
16. Crystal data for (*S*)-**2** D-tartrate: $C_{23}H_{29}N_3O_6$, M = 443.49, colourless prism, size 0.28 × 0.14 × 0.05 mm^3, orthorhombic, space group $P2_12_12_1$, a = 8.3905(9), b = 14.2190(14), c = 19.911(2) Å, V = 2375.4(4) Å^3, T = 185 K, Z = 4, d_{calc} = 1.240 g cm^{-3}, μ = 0.090 mm^{-1}, $F(000)$ = 944, 12405 reflections in $h(-9/9)$,$k(-16/13)$, $l(-23/23)$, measured in the range $1.76° \leqslant \Theta \leqslant 25.05°$, completeness Θ_{max} = 99.9%, 4176 independent reflections, R_{int} = 0.0720, $R1_{obs}$ = 0.0606, wR^2_{obs} = 0.0884, $R1_{all}$ = 0.1149, wR^2_{all} = 0.1046, GOF = 1.006, with $I > 2\sigma(I)$, largest difference peak and hole: 0.140/−0.149 e Å^{-3}. X-ray data were collected with Bruker SMART APEX CCD diffractometer with graphite-monochromatized MoKα radiation (λ = 0.71073 Å) operated at 2.0 kW (50 kV, 40 mA). The structures were solved by direct methods with the program SHELXS-97. All non-hydrogen atoms were refined anisotropically. The details of the crystallographic data have been deposited with Cambridge Crystallographic Data Centre as supplementary publication NO. CCDC 682454.
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