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Stereoselective Transesterification of *P*-Chirogenic Hydroxybinaphthyl Phosphinates

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The substitution reaction of phosphinates with a binaphthyloxy group at the phosphorus atom with lithium alkoxides proceeded with good to high efficiencies to give *P*-chirogenic phosphinates with a high enantiomeric ratio. As alcohols, primary, secondary, and tertiary alcohols could be used, and the use of *tert*-butyl alcohol yielded the products with a higher enantiomeric ratio. A substrate with two different alkyl groups on the phosphorus atom could also participate in the substitution reaction to give the corresponding products in good yields with excellent selectivity. The molecular structures of one of the substrates and the corresponding products, determined by X-ray analyses, proved that the substitution reaction at the phosphorus atom proceeded with inversion of the absolute configuration. The usefulness of the reaction was demonstrated by using it to prepare a drug candidate for Duchenne muscular dystrophy. Finally, thionation of the resulting phosphinates was carried out to form *P*-chirogenic phosphinothioates.

Introduction

Four-coordinate pentavalent organophosphorus compounds are an important class of compounds because of their wide applicability as optically active ligands and biologically relevant compounds.[1] A range of carbon-, nitrogen-, and oxygen-containing substituents can be introduced to the phosphorus atom, and their combinations provide a wide range of derivatives.[2]

Among them (Figure 1), *P*-chirogenic phosphinates **I**, wherein two carbon-containing substituents and one oxygen-containing substituent are attached to the phosphorus atom with a P=O bond, have also received much attention because of their usefulness as precursors to a range of *P*-chirogenic organophosphorus compounds. For that purpose, compounds **II** having a menthyloxy group[3] and other optically active alkoxy groups[4] have been used. Some *P*-chirogenic phosphinates are biologically active compounds.[5] For example, phosphinates **III** are drug candidates for Duchenne muscular dystrophy.[6] To provide *P*-chirogenic phosphinates with a range of alkoxy- and carbon-containing functional groups, the desymmetrization or the

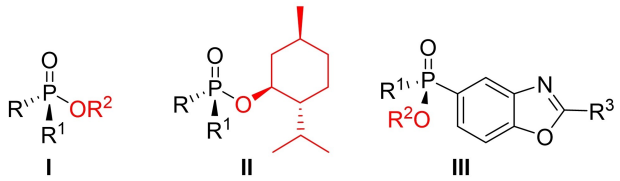

Figure 1. *P*-Chirogenic Phosphinates.

deracemization of prochiral organophosphorus compounds has been developed.[7] The addition of optically active secondary diaryl phosphine oxides to aromatic aldehydes gives optically active *O*-benzylic phosphinates with a high enantiomeric ratio.[8] Kinetic resolution of *P*-vinyl *P*-methoxy phenylphosphinates using a rhodium-catalyzed hydrogenation yields enantioenriched products.[9] The stereoselective substitution reaction at the phosphorus atom of one of the diastereomers of organophosphorus compounds featuring a chiral auxiliary with alcohols is a possible route to *P*-chirogenic phosphinates having a range of alkoxy groups, but the reported method can only use methanol.[10] Although these reactions accessed the desired *P*-chirogenic phosphinates with a relatively high enantiomeric ratio, they give products with a limited number of combinations of the carbon-containing substituents and alkoxy groups at the phosphorus atom. During our studies on organosulfur[11] and -phosphorus compounds,[12] we recently found that the reaction of phosphonates having a binaphthyloxy group **IV** with Grignard reagents gave *P*-chirogenic phosphinates **V** with high diastereoselectivity.[13] The reaction proceeded with transfer of the axis chirality of a binaphthyl group to the central chirality of products **V** (Scheme 1).

We then considered that the stereoselective substitution reaction at the phosphorus atom with a range of nucleophiles could lead to the formation of *P*-chirogenic four-coordinate pentavalent organophosphorus compounds. Herein we report the stereoselective transesterification of *P*-chirogenic phosphinates **V** with lithium alkoxides leading to the formation of *P*-chirogenic phosphinates **I** with a good to high enantiomeric ratio.

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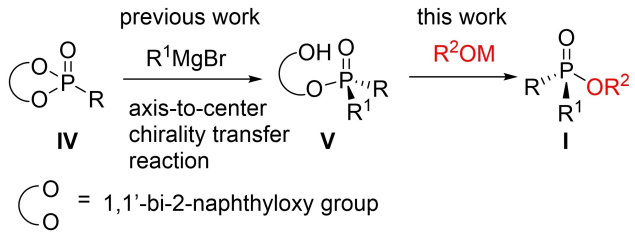


Scheme 1. Substitution reaction at the phosphorus atom.

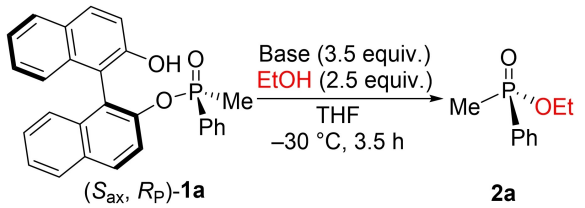
Results and Discussion

Initially, we reacted (S_{ax}, R_P)-**1a** with ethanol in the presence of a base (Table 1). While no reaction took place with DBU, Cs_2CO_3 or DABCO, the reaction proceeded smoothly in the presence of NaHMDS, *n*-BuLi, LiHMDS, or LDA, and binaphthyloxy group acted as a leaving group to give the expected product **2a** (entries 4–7). Notably, lithium salts (LiHMDS and LDA) showed high efficiency and enantioselectivity, whereas NaHMDS gave **2a** with a much smaller enantiomeric ratio.

The absolute configuration of the major products was estimated on the basis of the specific rotation of the products (Table 2).[14] The stereochemistry of the substrate **1a** has been previously determined to be S_{ax}, R_P (Figure 2).[13] As a result, the substitution reaction of **1a** at the phosphorus atom proceeded exclusively with inversion of the absolute configuration at phosphorus. This result implies that an S_N2-type reaction takes place at the phosphorus atom, but further studies are necessary to determine the stereochemical pathway of the present reaction since the stereochemical outcome of substitution reactions at the phosphorus atom is still a hot topic.[15]

To investigate the factors controlling stereoselectivity, several experiments were carried out (Scheme 2). Compound **2a**, previously isolated with a high enantiomeric ratio, was subjected to different reaction conditions. The use of Na salt completely racemized the product **2a**, while the treatment with lithium salt gave **2a** with a slightly better enantiomeric ratio. The reaction of (S_{ax}, R_P)-**1a** with LiOEt in the presence of 12-crown-6 reduced the enantiomeric ratio of **2a**. The reaction

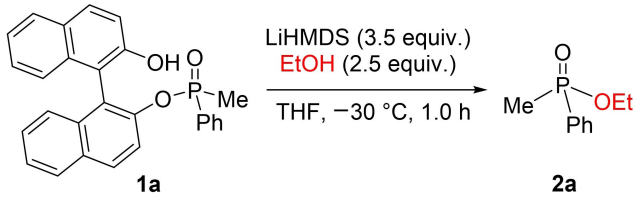
Table 1. Optimization of reactions between phosphinate **1a** and EtOH in the presence of a base.[a]



Entry	Base	Yield **2a** [%][b]	Enantiomeric Ratio (er)[b]
1	DBU	n.d.	–
2	Cs_2CO_3	n.d.	–
3	DABCO	n.d.	–
4	NaHMDS	>95	53:47
5	*n*-BuLi	79	91:9
6	LiHMDS	>95	98:2
7	LDA	>95	98:2

[a] Reaction conditions: (Sax, R_P)-**1a** (0.3 mmol), Base (1.05 mmol), EtOH (0.75 mmol), THF (1.5 mL), −30 °C, 3.5 h; [b] determined by ^{31}P NMR-spectroscopic analysis of the crude reaction mixture; [c] the enantiomeric ratio of the isolated compounds was determined by HPLC on a chiral stationary phase (CHIRALPAK IH).

Table 2. Reaction of of **1a** with LiOEt generated in situ.



Substrate **1a**	Enantiomeric Ratio (er)[a]	Optical Rotation ($[\alpha]_D$)[b]	Absolute Configuration
(S_{ax}, R_P)	96:4	−35.3	S_P
(R_{ax}, S_P)	4:96	+32.6	R_P

[a] The enantiomeric ratio was determined by HPLC analysis using a CHIRALCEL IH column; [b] 20 °C, chloroform, c = 1.0 g/cm^3.

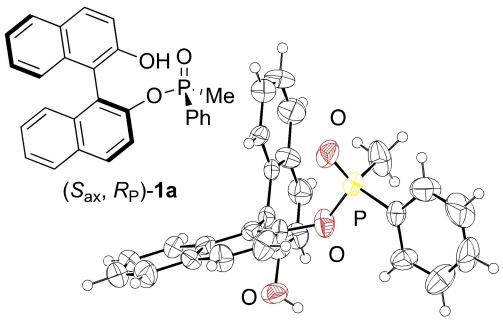
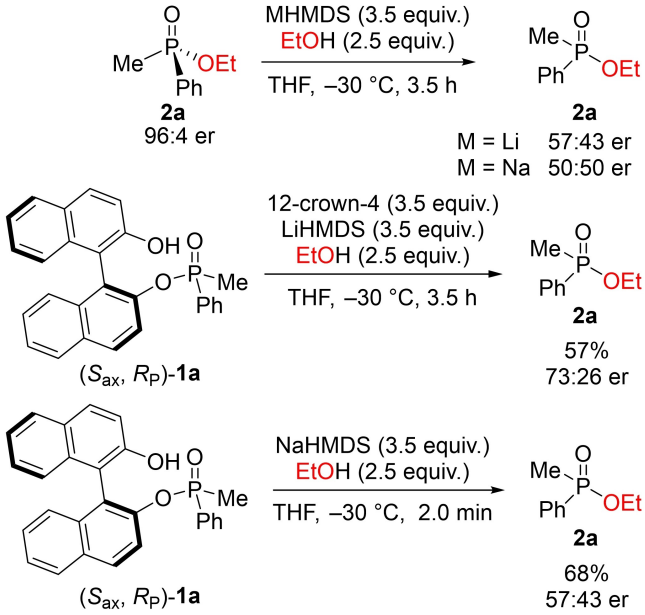


Figure 2. ORTEP drawing of (*Sax*, R_P)-**1a**.[13] Displacement ellipsoids are shown at the 50% probability level.



Scheme 2. Elucidation of factors controlling the enantiomeric ratio.

with Na salt proceeded very quickly, and quenching of the reaction mixture after 2 min gave the product **2a** with a different enantiomeric ratio. Based on these results, in both cases, stereoselective substitution reaction may take place at the phosphorus atom, but the presence of a sodium salt may also facilitate the racemization of **2a** to give a very low enantiomeric ratio of **2a**, although further studies are necessary before we can draw any definite conclusions.

To elucidate the reaction pathway, the conformation of the initial intermediates derived from the starting material and lithium salts was estimated with ADDF routine[16] of the GRRM17 program.[17] The ADDF calculation was carried out with the Hartree–Fock method, and LADD = 4, NLowest = 40, and EQOnly keywords were used to efficiently find out low-energy conformers. The 3–21G* and 3–21G basis sets were adopted for P atom and other atoms, respectively. The ADDF results were then refined by B3LYP-GD3/6-311G* calculation,[18] in which the THF solvent effect was included by the PCM method. As a model compound of the starting material, biphenyloxyphosphinate **VI** was used as an initial structure (Figure 3). To save calculation time, the chemical bonds in the compounds were set to not be cleaved except for the OLi···O bond. As a result, in all the stable structures calculated, the coordination of the oxygen atom of the O=P bond to lithium was present. Therefore, this intramolecular coordination of the oxygen atom of the O=P group to the lithium on the hydroxy group in the binaphthyloxy group may solidify the conformation of the leaving binaphthyloxy group, and the trajectory of the attack of the alkoxy group may be controlled.

We then used a variety of alkoxides generated from a range of alcohols by using LDA or LiHMDS (Table 3). The reaction of lithium alkoxides derived from primary alcohols such as benzyl alcohol, allyl alcohol, and protected α-D-galactopyranose proceeded smoothly to give the phosphinates **2b**–**2d** in good to high yields (entries 1–6). The enantiomers of the substrate **1a** gave the enantiomers of the products **2b** and **2c** (entries 1–4), although the enantiomeric ratio of **2c** slightly decreased. The reaction of secondary alcohols such as cyclohexanol and 2-adamantanol also

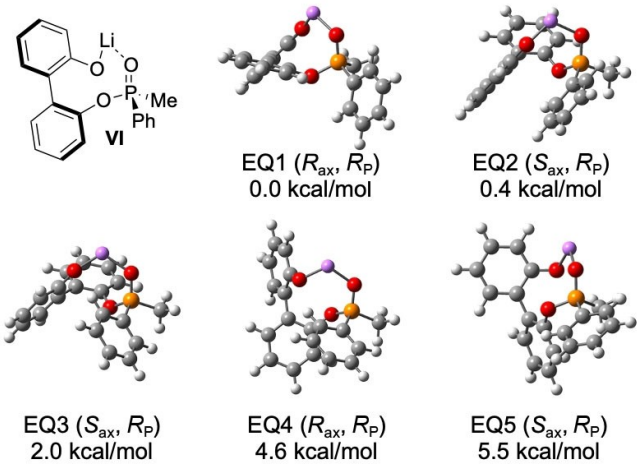
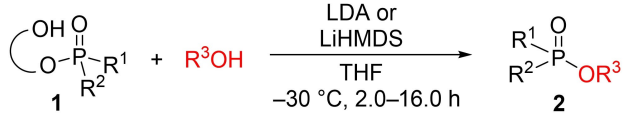


Figure 3. Some of the equilibrium structures obtained by ADDF calculations. Values are energies relative to that of EQ1.

Table 3. Investigation of the substrate scope.[a]



Entry	R^1/R^2	Substrate	Isolated Yields [%] (Enantiomeric Ratio er)[b]	Product
1	Me/Ph	(S_{ax}, R_P)-**1a**	82 (93:7)	
2		(R_{ax}, S_P)-**1a**	96 (7:93)	**2b**
3	Me/Ph	(S_{ax}, R_P)-**1a**	84 (85:15)	
4		(R_{ax}, S_P)-**1a**	98 (15:85)	**2c**
5	Me/Ph	(S_{ax}, R_P)-**1a**	73 (>95:5 dr)	
6		(R_{ax}, S_P)-**1a**	65 (>95:5 dr)	**2d**
7	Me/Ph	(S_{ax}, R_P)-**1a**	88 (94:6)	
8		(R_{ax}, S_P)-**1a**	95 (6:94)	**2e**
9[c]	Me/Ph	(S_{ax}, R_P)-**1a**	73 (99:1)	
10[c]		(R_{ax}, S_P)-**1a**	71 (1:99)	**2f**
11[d]	Me/Ph	(S_{ax}, R_P)-**1a**	79 (99:1)	
12[d]		(R_{ax}, S_P)-**1a**	77 (1:99)	**2g**
13	Et/Ph	(S_{ax}, R_P)-**1b**	73 (94:6)	
14		(R_{ax}, S_P)-**1b**	76 (4:96)	**2h**
15[e]	*i*-Pr/Ph	(S_{ax}, R_P)-**1c**	84 (98:2)	
16[e]		(R_{ax}, S_P)-**1c**	86 (2:98)	**2i**
17[c]	*i*-Pr/Ph	(S_{ax}, R_P)-**1d**	88 (>99:1)	
18[c]		(R_{ax}, S_P)-**1d**	83 (1:>99)	**2j**

[a] Reaction conditions: **1** (0.3 mmol), base (1.05 mmol), EtOH (0.75 mmol), THF, −30 °C, 2.0–16.0 h; [b] the enantiomeric ratio of the isolated compounds was determined by HPLC on a chiral stationary phase (CHIRALPAK IH); [c] the reaction was carried out at −15 °C; [d] The reaction was carried out at 0 °C; [e] The reaction was carried out at r.t.

gave the corresponding products **2e** and **2f** in good yields with high enantioselectivity (entries 7–10). Notably, the reaction of tertiary butanol gave the phosphinate **2g** with higher enantiose-

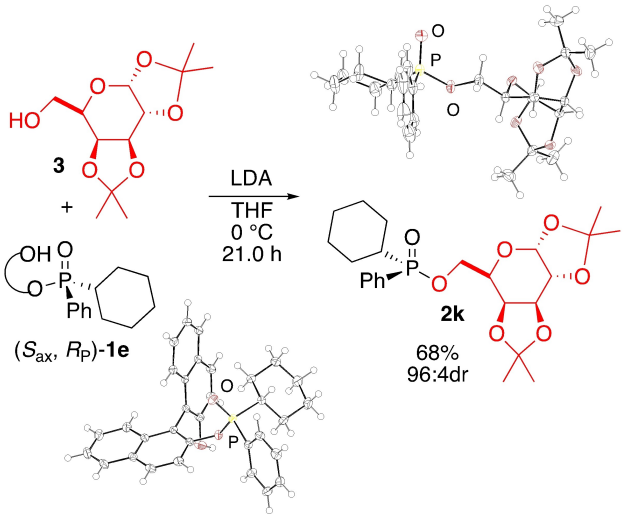
lectivity (entries 11 and 12). As the substituents on the phosphorus atom, ethyl and isopropyl groups gave products **2 h** and **2 i** (entries 13–16). Finally, substrate **1 d** with two different alkyl groups on the phosphorus atom was subjected to the reaction with lithium benzylalkoxide to give the desired products **2 j** in good yields with high enantioselectivity (entries 17 and 18). In all cases, bi-2-naphthol was recovered in yields nearly equal to the yields of the products.

To unequivocally determine the stereochemical course of the substitution reaction at the phosphorus atom, the molecular structures of the substrate (S_{ax}, R_P)-**1 e** and the products **2 k** were determined by X-ray structure analyses (Scheme 3).[19,20]

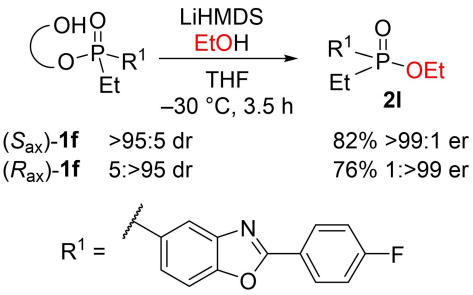
The reaction of (S_{ax}, R_P)-**1 e** with lithium alkoxide derived from alcohol **3** and LDA gave the product **2 k** in 68% yield with high diastereoselectivity. The *R* configuration at the phosphorus atom in (S_{ax}, R_P)-**1 e** was converted to an *S* configuration in **2 k**. This result clearly showed that the substitution reaction at the phosphorus atom proceeds with inversion of the absolute configuration at the phosphorus atom.

To demonstrate the applicability of the present reaction, the drug candidate **2 l** was prepared (Scheme 4). The product **2 l** was obtained in good yield with an enantiomeric ratio nearly identical to the diastereomeric ratio of **1 f**.

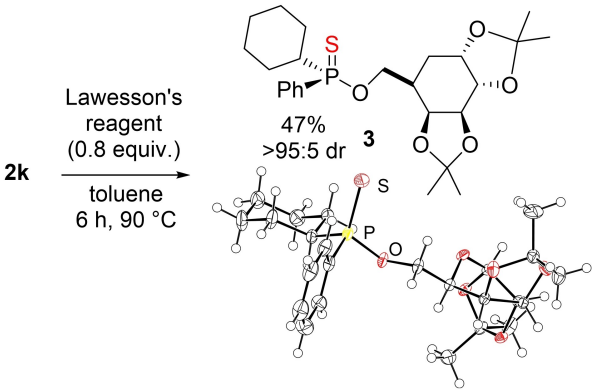
As further transformation of the resulting phosphinates, an exemplary thionation of the product **2 k** was carried out with Lawesson's reagent,[21] since metabolic stability is believed to be enhanced by replacing the P=O with a P=S group. As a result, the reaction gave the corresponding phosphinothioate **3** in moderate yield (Scheme 5). X-ray structure analysis[22] of **3** clearly showed the reaction proceeded with the retention of the configuration at the phosphorus atom.



Scheme 3. Substitution reaction of (S_{ax}, R_P)-**1 e** at the phosphorus atom and ORTEP drawings of (S_{ax}, R_P)-**1 e** and product S_P-**2 k** (displacement ellipsoids are shown at the 50% probability level).



Scheme 4. Synthesis of drug candidate **2 l**.



Scheme 5. Thionation of **2 k** with Lawesson's reagent and ORTEP drawing of product **3** (displacement ellipsoids are shown at the 50% probability level).

Conclusion

In summary, we have demonstrated that the transesterification of *P*-chirogenic phosphinates with a binaphthyl group with lithium alkoxides gave *P*-chirogenic phosphinates in good to high yields with good to excellent enantiomeric ratios. The binaphthyloxy group acted as a good leaving group. The reaction was generally complete within 5 h, although bulkier carbon-containing substituents retarded the reaction. As sources of lithium alkoxides, primary, secondary, and tertiary alcohols were all suitable. The molecular structures of one of the substrates and the corresponding products suggested that the substitution reaction took place with inversion of the absolute configuration at the phosphorus atom. Further studies on *P*-chirogenic organophosphorus compounds are in progress.

Experimental Section

A typical experimental procedure for the synthesis of *P*-chirogenic phosphinates: Alcohol (2.5 equiv.) and LDA (3.5 equiv.) were added to a THF solution of 2′-hydroxy-[1,1′-binaphthalen]-2-yl) phosphinate in a 20 mL two-necked flask at −30 °C, and the reaction mixture was stirred for the appropriate amount of time. After that, saturated NH_4Cl aqueous solution was added to the reaction mixture. The aqueous phase was extracted with ether three times. The combined organic layer was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel to give *P*-chirogenic phosphinate.

Deposition Numbers 2123947 (for **1e**), 2123948 (for **2k**) and 2153471 (for **3**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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Conflict of Interest

The authors declare that there are no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: binaphthyoxy group · chirality transfer · *P*-chirogenic phosphinates · substitution reaction

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[19] Crystallographic data for **1e**: $C_{32}H_{29}O_3P$, Fw: 492.52, $T=100$ K, orthorhombic, $P2_12_12_1$, $=13.1716(8)$ Å, $b=13.7479(8)$ Å, $c=13.8602(8)$ Å, $V=2509.8(3)$ Å^3, $Z=4$, $D_{calcd}=1.303$ g cm^{-3}, 5773 unique reflections out of 59340 with $I>2\sigma(I)$, Flack −0.12(7), $GOF=1.042$, $R_1=0.0265$; R_2 (all data) $=0.0701$. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre: Deposition number CCDC-2123947.

[20] Crystallographic data for **2k**: $C_{24}H_{35}O_7P$, Fw: 466.49, $T=100$ K, orthorhombic, $P2_12_12_1$, $=9.633(6)$ Å, $b=10.952(8)$ Å, $c=27.170(16)$ Å, $V=2444(3)$ Å^3, $Z=4$, $D_{calcd}=1.268$ g cm^{-3}, 5624 unique reflections out of 57679 with $I>2\sigma(I)$, Flack 0.08(10), $GOF=1.044$, $R_1=0.0302$; R_2 (all data) $=0.0789$. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre: Deposition number CCDC-2123948.

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[22] Crystallographic data for **3**: $C_{24}H_{35}O_6PS$, Fw: 482.55, $T=100$ K, orthorhombic, $P2_12_12_1$, $=9.5971(7)$ Å, $b=11.2054(8)$ Å, $c=23.5425(17)$ Å, $V=2531.7(3)$ Å^3, $Z=4$, $D_{calcd}=1.266$ g cm^{-3}, 5791 unique reflections out of 59266 with $I>2\sigma(I)$, Flack 0.05(4), $GOF=1.042$, $R_1=0.0246$; R_2 (all data) $=0.0663$. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre: Deposition number CCDC-2153471.

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