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Very Important Publication

Selective Catalytic Cross-Cyclotrimerization En Route to 1,4-Diborylated Benzenes and Their Synthetic Transformations

Alexander A. Fadeev,[a] Gabriele Manca,[b,*] and Martin Kotora[a,*]

[a] Department of Organic Chemistry, Faculty of Science, Charles University, Albertov 6, 128 43 Praha 2 (Czech Republic)
+420 221 951 053, +420 221 951 326
E-mail: kotora@natur.cuni.cz
[b] CNR-ICCOM, 50019 Sesto Fiorentino, Firenze (Italy)
E-mail: gabriele.manca@iccom.cnr.it

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This work is dedicated to Professor Masahiro Murakami, Kyoto University, Japan, on the occasion of his retirement.

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Abstract: A synthesis of 1,4-diborylated benzenes was achieved by the Ru-catalyzed regioselective co-cyclotrimerization of alkynes with a commercially available ethynyl boronate. The reaction is applicable to a wide array of alkynes with metal-coordinating groups, providing synthetically useful diborylated benzenes in 23–68% isolated yields. DFT calculations shed light on the reaction course and the origin of its remarkable regioselectivity. Selected diborylated benzenes were converted into various products, such as quinones and hydroquinones, including three natural bioactive small molecules.

Keywords: Catalytic cyclotrimerization; Borylated arenes; DFT calculations; Regioselectivity; Natural products

Development of chemo- and regioselective reactions aiming at specifically substituted products is one of the pivotal points of current synthetic chemistry.[1] In this respect, synthesis of selectively functionalized benzene derivatives possessing reactive functional groups (such as halides[2] or boron-based[3] groups) is of a considerable interest, because they can be used as advanced intermediates for synthesis of more complex molecules.[4] Therefore, creating new methods and strategies to fulfill this goal is a highly sought activity.

Transition-metal-catalyzed [2+2+2] cycloaddition of unsaturated substrates is a useful and atom-economical method for the synthesis of substituted six-membered rings.[5] In particular, the [2+2+2] cyclotrimerization of alkynes enables synthesis of densely substituted benzenes and has been most actively investigated to date.[6]

Although the catalytic alkyne cyclotrimerization is a highly atom efficient process, it is difficult to control regioselectivity of reactions involving two different unsymmetrically substituted monoalkynes. Such processes are rare and represented only by a limited number of examples.[7] The course of the reaction strongly depends on the nature of substituents, and that makes it hard to generalize such protocols. Besides that, introduction of heteroatom substituents to the triple bond can be hampered by instability of such starting alkynes, which often only exist as protected surrogates. As typical examples of the above-mentioned processes can serve Rh-catalyzed co-cyclotrimerization of aryloxyalkynes[8] or silylalkynes[9] with propynoates leading to mixtures of regioisomeric products.

From a synthetic point of view, a powerful cyclotrimerization method should not only allow for a chemo- and regioselectivity control, but also provide a molecular platform with a high synthetic modification potential. In this regard, co-cyclotrimerizations of various alkynyl halides,[10] boronates,[11] and triazenes[12] have been shown to give valuable arene building blocks. However, selective fully intermolecular co-cyclotrimerizations, giving rise to a monocyclic benzene core that could serve as a versatile multipurpose building block, have not been reported yet.

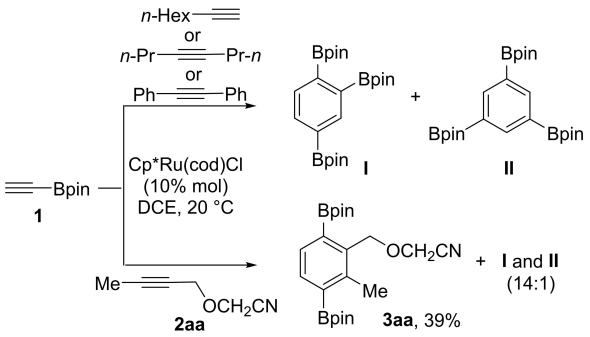
To address the above issues, we show how unsymmetrical 1,2,3,4-tetrasubstituted benzenes with boronate groups in positions 1 and 4 can be rapidly and

selectively assembled by catalytic co-cyclotrimerization of two molecules of ethynyl boronate **1** with an internal alkyne. Thanks to high synthetic versatility of boron, the constructed benzene ring can be further diversified and used to access various aromatic and quinoid compounds, including natural products and their congeners.

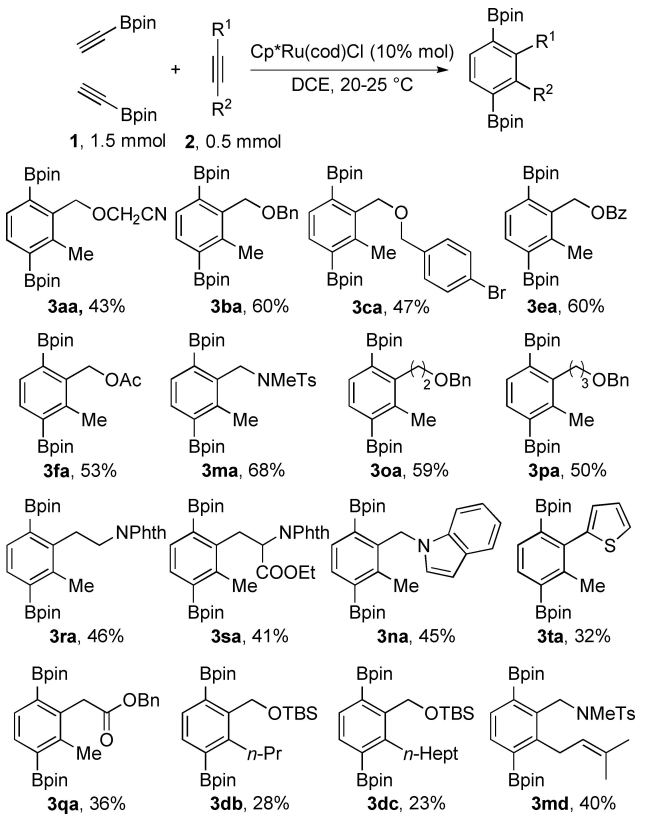
Initially, we hypothesized that selective synthesis of 1,4-diborylated benzenes could be achieved using Ru catalysis via a selectively formed ruthenacycle intermediate.[13,14] In particular, we presumed that *stereoelectronic* properties of ethynyl boronate **1**[15] would allow the reaction to proceed with a high preference for the 2,5-diborylated ruthenacycle formation. If so, a controlled insertion of a different alkyne into such ruthenacycle followed by reductive elimination would lead to the desired 1,4-diborylated benzene. To verify this hypothesis, we attempted to carry out a co-cyclotrimerization between **1** and simple alkynes (1-octyne, 4-octyne and diphenylacetylene) using Cp*Ru(cod)Cl[16] as the model catalyst. However, only trace amounts of homotrimerization products of **1** were detected in these reactions, strongly favoring 1,2,4-isomer **I** over 1,3,5-isomer **II** (Scheme 1). We envisioned that reactivity of the alkynes **2** may be increased by the presence of metal-coordinating groups in their structure. Gratifyingly, cyanoalkyne **2aa**[17] gave the desired 1,4-diborylated benzene **3aa** in 39% isolated yield.

This result prompted us to screen other commonly used transition metal-based catalytic systems in the same reaction, but the product was only formed with Cp*Ru-type catalysts, among which Cp*Ru(cod)Cl fared the best (for detailed optimization studies, please see the Supporting Information, Tables S2–S8). The yield was improved to 63% (60% isolated on preparative scale) by performing addition of the alkynes dropwise and keeping their ratio close to stoichiometric.

Preparative examples of co-cyclotrimerization of **1** with **2** under optimized reaction conditions are shown in Scheme 2. Propargyl ethers **2aa**–**2ca** reacted with **1**



Scheme 1. Initial attempts to perform cross-cyclotrimerization between **1** and different alkynes.



Scheme 2. Ru-catalyzed co-cyclotrimerization of **1** with various alkynes **2** into 1,4-diborylated benzenes **3**.

to give the respective products **3aa**–**3ca** in 43–60% yields showing good functional group tolerance: nitrile group of **2aa** as well as bromine atom in **2ca** stayed untouched. The reactions with esters **2ea** and **2fa** furnished **3ea** and **3fa** in 60% and 53% yields, respectively. Interestingly, reversed placement of the ester group in **2qa** provided **3qa** in only 36% yield. The use of propargyl amide **2ma**, however, exhibited better result yielding **3ma** in 68% yield, likely due to increased interaction of the sulfonamide group with the metal center. Increasing the spacer length between the triple bond and the metal-coordinating group had little effect on the reaction outcome. Thus, it was possible to prepare homologs of **3oa** and **3pa**, as well as diborylated arylethylamine **3ra** and phenylalanine derivative **3sa** in reasonable yields of 59, 50, 46, and 41%, respectively. Similarly, alkynes bearing heteroatoms as a part of a tethered heteroaromatic ring **2na** and **3ta** were reactive as well, affording diborylated arenes **3na** and **3ta**, albeit in lower yields (45% and 32%).

Next, we found that the reaction is sensitive to the increased size of substituent R^2 in the alkyne **2**, possibly due to steric hinderance caused by the bulky Cp* ligand in the intermediate ruthenacycle. Thus, substrates with *n*-propyl (**2db**), *n*-heptyl (**2dc**), and

prenyl (**2md**) groups showed lower conversion into the corresponding products **3db**, **3dc**, and **3md** that were obtained 28, 23, and 40% yields, respectively.

After demonstrating the scope of the reaction with respect to alkynes **2**, we attempted to involve various alkynyl boronates in the reaction with **2aa**. Thus, phenylethynylboronic acid pinacol ester, ethynylboronic acid MIDA ester (MIDA = *N*-methyliminodiacetic acid) and 2-MOM-ethynylboronic acid pinacol ester were found unreactive even at 80 °C. Absence of homotrimerization products of **1** suggests that formation of ruthenacycle intermediate from **1** under the employed reaction conditions is energetically unfavorable.

The fact that homotrimerization of **1** yields a mixture of regioisomeric products **I** and **II** raised a question whether the process of formation of **3** is accompanied by formation of other cyclotrimerization products. ^{1}H NMR analysis of the crude reaction mixtures (see Supporting Information for representative spectra) did not show presence of other products in substantial amounts (< 10%), except trimers **I** and **II**. The amount of **I** and **II** was typically lower than that of product **3**, despite 3:1 molar ratio of **1** to **2** was used in preparative experiments (addition order only slightly shifts the product ratio). This allows to avoid using large excess of a terminal alkyne that is typically required to compensate for its unwanted homotrimerization.[18]

In order to shed light on the course of the reaction and the observed regioselectivity, we carried out DFT calculations for the reaction between **1** and the acetate **2fa** (as a representative of the alkyne partners that gave one of the highest product yields) catalyzed by Cp*Ru(cod)Cl.[19] The free energy pathway is depicted in Figure 1. In the first step, the intermediate **A** is formed, featuring the coordinated alkynes **1** and **2fa**. After that, the system evolves toward the ruthenacycle **B′** with the free energy gain of −33.2 kcal·mol^{-1}. In contrast to the precedent related work,[19] computational analysis revealed that the chloride dissociation is an essential step. This is a fundamental point, since the chloride dissociation is estimated to be as large as +22.3 kcal mol^{-1} when two molecules of **1** is coordinated to the metal (this pathway is presented in details in SI). This value is lower in **B′** (+13.4 kcal mol^{-1}) due to the coordination of the peripheral oxygen of the carboxylate substituent in the alkyne moiety to the metal. The dissociation of the chloride ligand is required for the coordination of the second molecule of **1** to **C**$^+$ forming **D**$^+$ with a free energy gain of −8.2 kcal·mol^{-1}. Then, the reaction evolves trough Transition State $\mathbf{E_{TS}}^+$ with a free energy barrier of +11.2 kcal·mol^{-1} to give ruthenacycle **E**$^+$ with a final free energy gain of −12.1 kcal mol^{-1}. The next step of the catalytic cycle proceeds through another transition state $\mathbf{F_{TS}}^+$ with a free energy barrier of

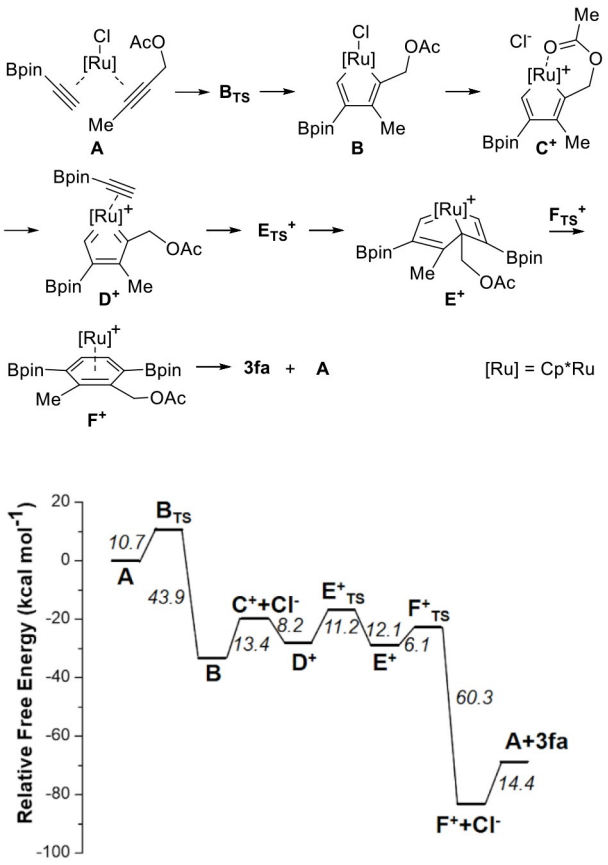
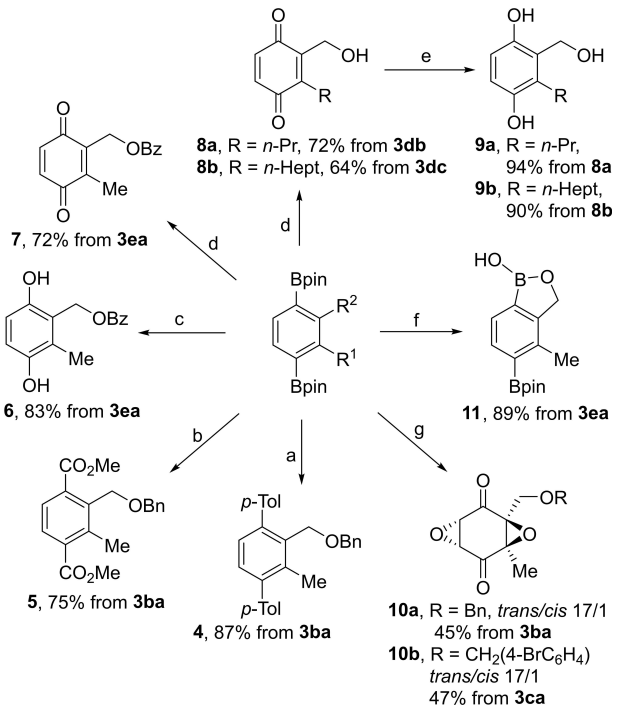


Figure 1. Free energy pathway (kcal mol^{-1}) for the catalytic formation of **3fa**.

+6.1 kcal mol^{-1} leading to the arene complex **F**$^+$. Its formation has been estimated to be exergonic by −60.3 kcal mol^{-1}. The following dismissal of **3fa** (with a free energy cost of +14.4 kcal mol^{-1}) frees coordination sites that are immediately filled by the chloride and the alkyne ligands, thus restoring the key intermediate **A**. The total free energy gain for the catalytic cycle in Figure 1 has been estimated to be as large as −68.7 kcal mol^{-1}.

With a number of diborylated cyclotrimerization products in hand we explored their transformations into other 1,2,3,4-tetrasubstituted arenes starting with most widely used cross-coupling reactions. Thus, twofold Suzuki-Miyaura coupling of **3ba** with 4-iodotoluene under typical conditions[20] yielded substituted terphenyl **4**. Similarly, twofold Pd-catalyzed carbonylation[21] of **3ba** in MeOH furnished terephthalic acid diester **5** in a 75% yield.

To access various gentisyl alcohols and quinones, we studied first oxidation of 1,4-diborylated benzenes **3** by hydrogen peroxide under acidic and basic conditions (Scheme 3). Oxidation under basic conditions selectively afforded hydroquinone **6** in 83% yield. Acidic peroxide treatment of benzoate **3ea** led



Scheme 3. Transformations of **3ea**, **3db**, **3dc**, **3ba**, and **3ca**. a) $Pd(PPh_3)_4$ (5 mol%), Tol-I; KOH, THF/H_2O, 50 °C; b) $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), *p*-benzoquinone, CO (1 atm), MeOH, RT; c) H_2O_2, Na_2CO_3, MeCN/H_2O, 0 °C; d) H_2O_2, AcOH, RT; e) $Na_2S_2O_4$, Et_2O/H_2O, 0 °C; f) NaOH, DMSO/H_2O, RT; g) H_2O_2, DMSO/H_2O, RT, then K_3PO_4, RT.

exclusively to quinone **7** in 72% yield. However, cleavage of the benzoate group in thus obtained compounds was found to be problematic, likely due to prominent behavior of benzoate as a leaving group, leading to degradation *via* formation of an *ortho*-quinone methide (*o*-QM). In contrast, oxidation of silyl ethers **3db** and **3dc** in the acidic conditions led directly to quinones **8a** and **8b** in 72 and 64% isolated yields. The former compound **8b** is a natural quinone identified in a high-throughput screening of Costa Rican microbial sources.[22]

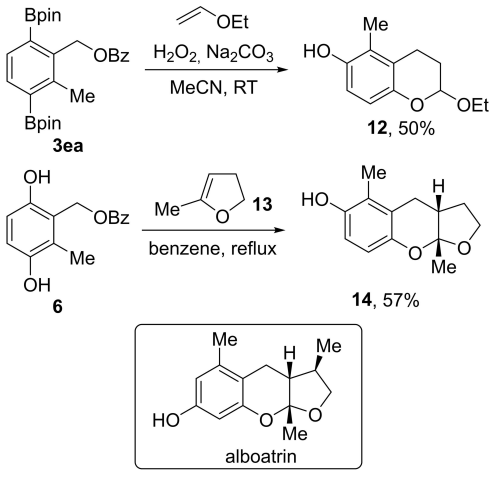
A subsequent reduction of these quinones **8b** and **8c** by sodium dithionite afforded natural bioactive hydroquinones mirandamycin (**9a**)[22] and violaceoid C (**9b**).[23] The latter was isolated from the culture broth of *Aspergillus violaceofuscus* Gasperini.

Quinones are not the end point of oxidation of **3**. Treatment of **3ba** and **3ca** with an excess of H_2O_2 in aqueous DMSO, followed by addition of K_3PO_4 led exclusively to *trans*-diepoxides **10a** and **10b** in 17:1 *dr* and 45 and 47% yield, respectively. Crystallization of **10b** from cold hexane-MTBE yielded crystals suitable for X-ray diffraction analysis that allowed to unequivocally confirm their structure and relative stereochemistry. Interestingly, when oxidation of **3ba** was carried out in MeCN **10a** was obtained as 4/1 mixture of diastereoisomers in 49% yield.

Lastly, we anticipated that condensation of the benzylic fragment with the adjacent Bpin group in **3ea** can be used to create the benzoxaborole ring junction, which has recently started to gain increased interest in medicinal and materials chemistry.[24] We were pleased to find out that basic hydrolysis of **3ea** can give benzoxaborole **11** in 89% yield, leaving the distant boryl group intact.

Intrigued by a possibility of *o*-QM generation from **3**,[25] we performed a base-mediated peroxide oxidation of **3ea** at 25 °C in the presence of ethyl vinyl ether, which is typically used to trap *o*-QMs in the oxa-Diels-Alder reaction. To our delight, the cycloadduct **12** was formed in 50% yield as a single product (Scheme 4). This result prompted us to access the tricyclic skeleton of natural product alboatrin,[26,27] isolated from the fungus *Verticillium alboatrum*, using **3ea** and commercially available dihydrofuran **13**. In the above conditions, however, mainly decomposition was taking place and only traces of product **14** were detected. Nonetheless, using Baldwin's method,[27] simple reflux of the intermediate hydroquinone **6** with **13** in benzene smoothly yielded alboatrin analog **14** in 57% yield.

In summary, we have developed a fully intermolecular chemo- and regioselective Ru-catalyzed co-cyclotrimerization reaction allowing synthesis of 1,4-diborylated benzenes from commercially available ethynylboronic acid ester **1** and alkynes bearing heteroatom-based functional groups. DFT calculations shed light on the course of the reaction and origin of its regioselectivity, indicating that formation of the key intermediate ruthenacycle from alkynyl boronate **1** and alkyne **2** is more energetically favorable than from two molecules of **1**. As in the well-established hydroboration-oxidation reaction, the borylated products can



Scheme 4. Conversion of **3ea** into **12** and **6** into the alboatrin analog **14**.

be oxidized by hydrogen peroxide. Depending on reaction conditions, hydroquinones, benzoquinones and benzoquinone diepoxides can be formed selectively. Three natural bioactive small molecules were prepared by this method in only 4 steps from the products of cyclotrimerization. Besides that, the obtained 1,4-diborylated benzenes can be used as substrates for cross-coupling reactions, *o*-QM generation and construction of benzoxaborole skeleton. These results bring a new paradigm in application of "Bpin-acetylene" in organic synthesis as a building block for preparation of different 1,2,3,4-tetrasubstituted benzenes and beyond.

Experimental Section

General procedure for the Ru-catalyzed [2+2+2] cyclotrimerization. To a solution of Cp*Ru(cod)Cl (0.05 mmol, 19 mg) in dry degassed DCE (4 mL) under Ar atmosphere was added 2/3 of a solution of ethynyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**1**) (1.5 mmol, 228 mg) in DCE (2 mL) in a single portion at 25 °C and the mixture was stirred for 5 min. Next, a solution of an alkyne (0.5 mmol) in DCE (2 mL) was added dropwise in a course of 1 min. Finally, the remaining 1/3 of the **1** solution was added dropwise in the course of 30 minutes and the reaction mixture was left to stir at 25 °C for 24 h. Volatiles were removed under reduced pressure. Column chromatography of the residue on silica gel (step-gradient elution from 100/1 hexanes/EtOAc to 1/1 hexanes/EtOAc) gave the corresponding product.

2-Methyl-3,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl benzoate (3 ea). The title compound was prepared according to the general procedure from **2 ea** (0.5 mmol, 87 mg). Column chromatography yielded 143 mg (60%) of the title compound as a colorless solid. M.p. 114 °C. TLC $R_f = 0.50$ (3/1 hexanes/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.02$–7.99 (m, 2H; Ar–H), 7.74 (d, $^3J_{H,H} = 7.4$ Hz, 1H; Ar–H), 7.65 (d, $^3J_{H,H} = 7.4$ Hz, 1H; Ar–H), 7.53–7.49 (m, 1H; Ar–H), 7.41–7.36 (m, 2H; Ar–H), 5.70 (s, 2H; CH_2), 2.63 (s, 3H; CH_3), 1.35 (s, 12H; $4\times CH_3$), 1.27 (s, 12H; $4\times CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 166.7$, 144.3, 139.0, 135.5, 132.7, 132.5, 130.8, 129.8 (2 C), 128.3 (2 C), 84.0 (2 C), 83.9 (2 C), 64.2, 25.0 (4 C), 24.9 (4 C), 18.3 (C–B carbon signals were not observed due to quadrupolar relaxation). IR (KBr): $\tilde{\nu} = 3062$, 2979, 2933, 1720, 1601, 1485, 1452, 1391, 1369, 1313, 1271, 1142, 1043, 1026, 860, 717 cm^{-1}. HRMS (APCI): m/z calcd for $C_{27}H_{40}O_6NB_2^+$: 496.30363 $[M+H]^+$; found: 496.30380.

Further complete experimental procedures, characterization of compounds, copies of NMR spectra are in the SI section.

CCDC 2217082 and 2217083 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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