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Introduction of Azetidinimine Skeleton on C_{60}

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ABSTRACT: *The azacyclobutane structure is introduced into C_{60} fullerene using a photochemical reaction with formamidines. Three azetidinofullerenes (***2c–2e***) were synthesized; their molecular structures were characterized using ^{1}H, ^{13}C, and 2D NMR, matrix-assisted laser desorption ionization (MALDI) mass spectrometry, visible spectroscopy, and electrochemistry. Single crystal X-ray crystallographic analysis of* **2e** *reveals a unique strained four-membered ring including nitrogen atom attached on the fullerene cage.* © 2011 Wiley Periodicals, Inc. Heteroatom Chem 22:426–431, 2011; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20703

INTRODUCTION

C_{60} is a promising material because it has a unique molecular structure comprising a ball-like shape, a largely delocalized π-conjugation system, and a high molecular symmetry [1,2]. Recently, biochemical and medicinal applications were proposed for the use of fullerenes [3]. A key for the biological use is introducing nitrogen atoms on the fullerene cage to mimic bioactive molecules. For this purpose, numerous nitrogen-introduced fullerene derivatives have been reported to date [1,4,5].

Among many fullerene derivatization methods, the introduction of an azacyclobutane structure is interesting because it is possible to form a β-lactam structure and its bioactive derivatives [6,7]. A few reports have described introduction of a four-membered ring on fullerene cages. To the best of our knowledge, only benzyne adducts have been reported as C_{60} derivatives possessing a four-membered ring [8,9].

Here we report the synthesis of novel fullerene derivatives having an azetidinimine framework with their full characterizations, including structural elucidation using single-crystal X-ray crystallographic analysis of a compound (**2e**).

RESULTS AND DISCUSSION

Formamidines (**1a–1e**) were synthesized by referring to reported procedures (Scheme 1) [10,11]. We performed photoreaction of C_{60} using *N*,*N*′-bis(2,6-dialkylphenyl)formamidines (**1c–1e**) to afford corresponding C_{60} adducts (Scheme 2). The C_{60} adducts were isolated by two-step HPLC separation. However, the reactions did not proceed when **1a** or **1b** was used because of their poor solubility in the solvent system that was used: toluene.

Structural Determination

Structures of **2c–2e** were identified using spectroscopic methods. Matrix-assisted laser desorption-ionization–time-of-flight (MALDI-TOF) mass spectroscopic measurements confirmed the formation of **2c–2e**. The spectra of **2c–2e** respectively display parent peaks at *m*/*z* 970.3, 1026.9, and 1082.5.

Dedicated to Professor Kin-ya Akiba on the occasion of his 75th birthday.

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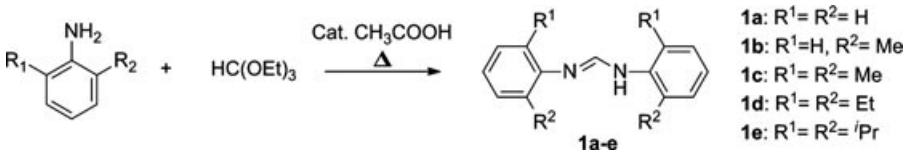
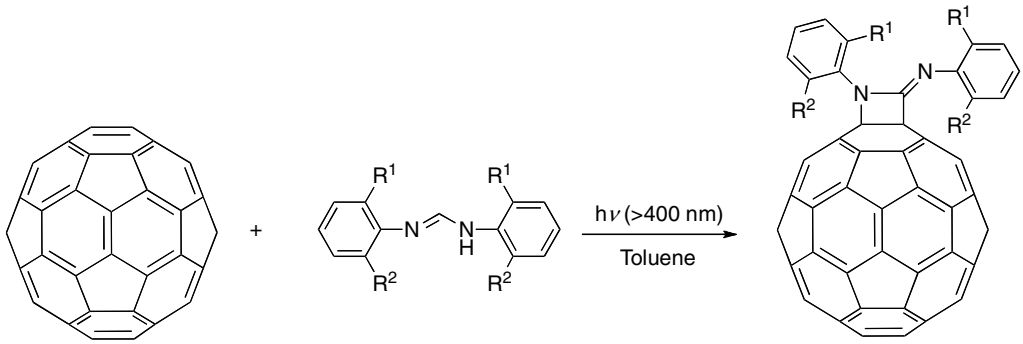


SCHEME 1



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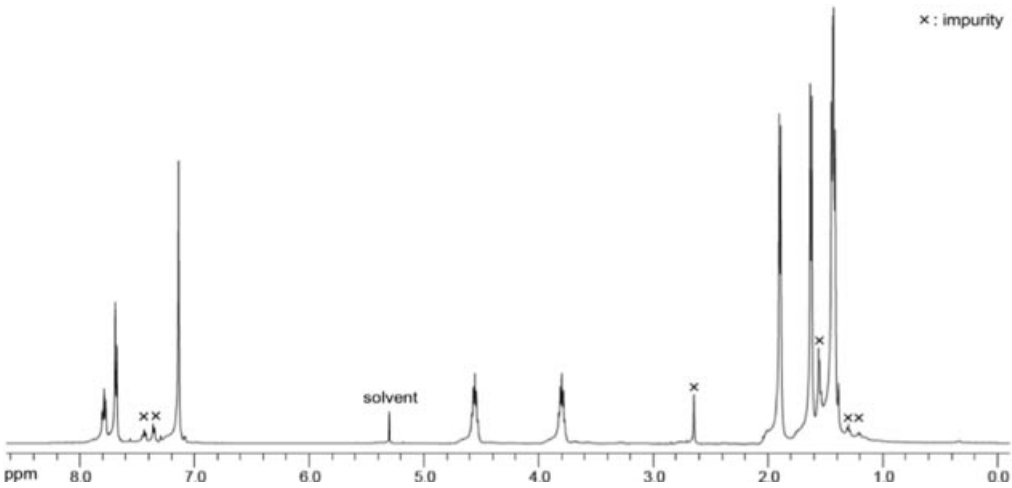
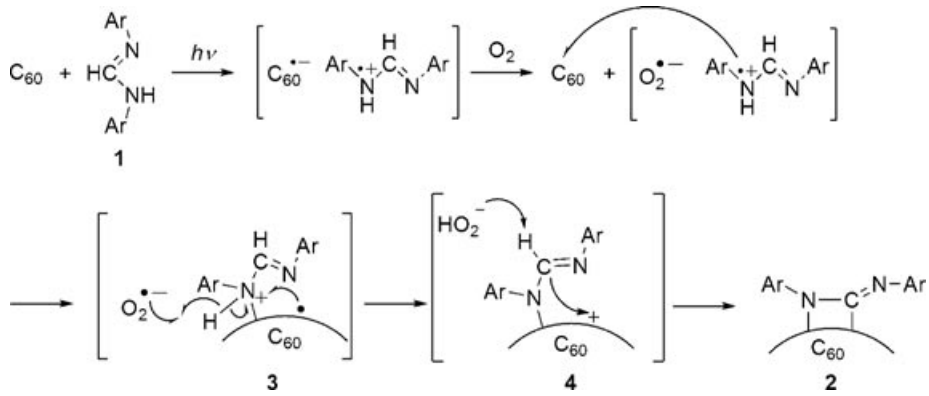


FIGURE 1 ^{1}H NMR spectrum of **2e** in 1:4 (v/v) = CD_2Cl_2/CS_2.

The ^{1}H NMR spectra of **2c–2e** show characteristic peaks attributed to the corresponding addends (Fig. 1 and the Supporting Information). For instance, the ^{1}H NMR spectrum of **2e** displays proton signals of the two isopropyl group attaching benzene rings at 1.40–1.89 ppm along with a multiplet signal from the protons in the aromatic rings at about 7.13–7.79 ppm, and two septet signals at 3.79 and 4.56 ppm from methine protons.

The ^{13}C NMR spectrum of **2e** shows two signals with relative intensities of 1 and 28 signals with the intensities of 2 from the sp^2 carbons of the fullerene cage (Fig. 2). The observed characteristic signals at δ = 79.6 and 89.3 ppm indicate a [6,6]-closed structure, which has two sp^3 carbons in the fullerene cage, and C_s symmetry of **2e**. The remaining signals are assigned to the aromatic and aliphatic carbon atoms. The 2D NMR (HMQC, HMBC) measurements of **2e** confirm correlations between the proton and the carbon signals of the addend.

It is noteworthy that the azacyclobutane framework was introduced to C_{60} through the reaction with formamidines. It was also found that the photoreactions did not proceed in the absence of oxygen. These results suggest that oxygen molecule plays an important role in the reactions to determine addition patterns to C_{60}. Isobe et al. [12] reported



SCHEME 3 Proposed reaction mechanism.

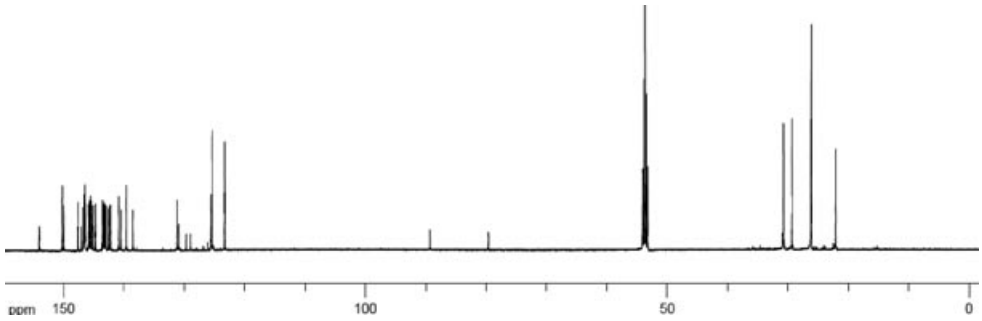


FIGURE 2 ^{13}C NMR spectrum of **2e** in 1:4 (v/v) = CD_2Cl_2/CS_2.

multiple additions of a secondary amine with C_{60} under photochemical aerobic conditions to produce tetra(amine)-fullerene epoxide.

In this regard, the reaction mechanism can be proposed as shown in Scheme 3. Initially, a single electron transfer occurred from the formation of a stable C_{60} anion radical and an amidinium cation radical through an electron transfer from a formamidine. Once generated, the C_{60} anion radical reduces molecular oxygen to generate superoxide anion radical. C_{60} and an amidinium cation react together to form a protonated **3**. The superoxide anion then deprotonates radical **3**; the resulting HO_2^- must be a sufficiently powerful oxidant to convert **4** into azetidinimine **2**.

The **2e** molecular structure was determined clearly by single-crystal X-ray structure analysis (Fig. 3). Unambiguously, 6,6-closed structure of the azetidino[60]fullerene was demonstrated. The characteristic strained azacyclobutane structure is shown clearly from the crystal structure with bond lengths of C1–C2 [1.551(2) Å], C2–C3 [1.606(2) Å], N2–C3 [1.480(2) Å], C1–N1 [1.261(2) Å], and C1–N2 [1.372(2) Å] (Fig. 4).

Electronic Properties

The visible absorption spectra of **2c–2e** and pristine C_{60} in toluene are shown in Fig. 5. **2c–2e** show characteristic absorption bands around 410 nm as

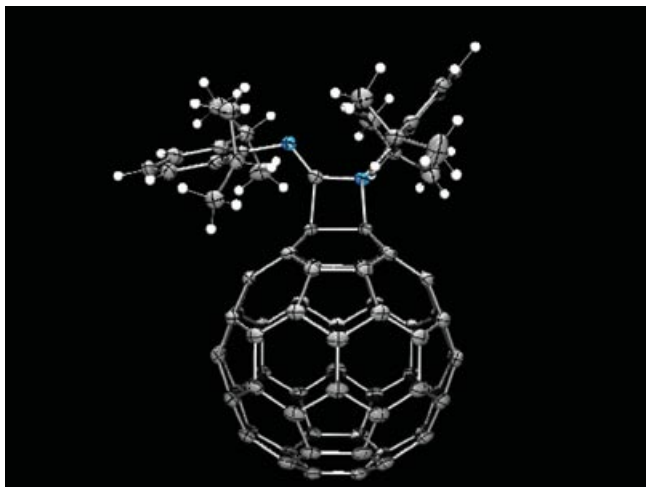


FIGURE 3 ORTEP drawing of **2e** with 50% probability ellipsoids.

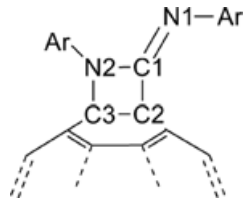


FIGURE 4 Schematic drawing of the azetidinimine framework in **2c–2e**.

broadening shoulder peaks, which are identical for [6,6]-closed fullerene derivatives [13,14].

The redox property of **2e** was investigated using cyclic voltammetry and differential pulse voltammetry measurements. Table 1 shows the redox potentials of the cycloadduct (**2e**) and C_{60} as a comparison. In addition, **2e** exhibits three one-electron reversible reduction steps and one-electron irreversible oxidation step, as well as pristine C_{60}. The reduction potentials of **2e** were almost unchanged from those of C_{60}, indicating that the introduction of the azacyclobutane ring has no important influence on the electron-accepting property. On the other hand, the first oxidation potential is shifted cathodically by 0.24 V, which may be rationalized by the attachment of nitrogen atom on the fullerene cage as described in the previous report for aziridino[60]fullerenes [15].

In conclusion, novel C_{60} derivatives were synthesized with a new methodology using formamidines. They were characterized using spectroscopic methods, revealing a unique four-membered ring containing a nitrogen atom. The introduction of the azacyclobutane structure did not change the electronic properties of the fullerene cage drastically, which indicates that this is a promising approach to functionalize C_{60} because it can be converted to a β-lactam framework, which is expected to be useful for biological applications [8].

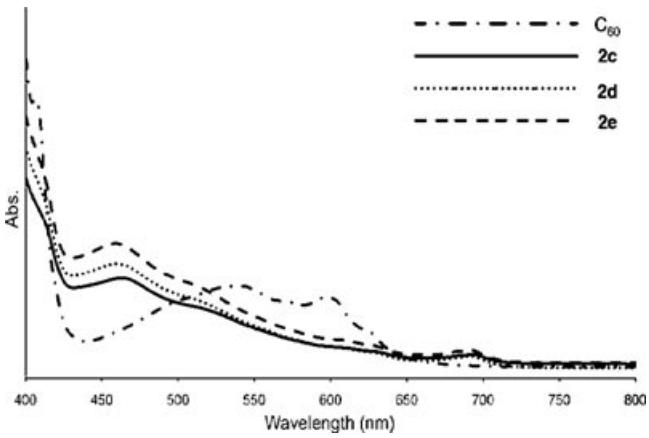


FIGURE 5 Vis-absorption spectra of **2c–2e** and C_{60} in toluene.

TABLE 1 Redox Potentials (V)[a]

Compound	$_{ox}E_1$	$_{red}E_1$	$_{red}E_2$	$_{red}E_3$
C_{60}	+1.21[b]	−1.12	−1.50	−1.95
2e	+0.97[b]	−1.11	−1.50	−2.02

[a]Values were obtained by differential pulse voltammetry/pulse amplitude = 50 mV; scan rate 20 mV s^{-1}. Versus F_c/F_c^+ in 1,2-dichlorobenzene with 0.1 M $(n\text{Bu})_4\text{NPF}_6$ at Pt working and counterelectrodes; scan rate = 20 mV s^{-1}.
[b]Irreversible.

EXPERIMENTAL

General

All chemicals and solvents were obtained from Wako (Wako Pure Chemical Industries, Ltd., Osaka, Japan) and Aldrich (Sigma-Aldrich, St. Louis, MO), and were used without further purification unless otherwise stated. Toluene was distilled over benzophenone sodium ketyl under an argon atmosphere prior to use in a reaction.

Matrix-assisted laser desorption ionization–time-of-flight mass spectra were measured (BIFLEX III; Bruker Analytik, GmbH, Germany) with 1,1,4,4-tetraphenyl-1,3-butadiene as a matrix. The visible absorption spectra were measured using a spectrometer (UV3150; Shimadzu Corp., Kyoto, Japan) in toluene. The ^{1}H, ^{13}C NMR, and 2D NMR (HMQC and HMBC) spectra were recorded on a spectrometer (AVANCE 300; Bruker BioSpin K.K., Karlsruhe, Germany), in CS_2 and CD_2Cl_2 (4/1 = v/v). Cyclic voltammograms and differential pulse voltammograms were measured on a potentiostat/galvanostat (BAS CW-50; BAS Inc., Tokyo, Japan), in *o*-dichlorobenzene with 0.1M $(n\text{Bu})_4\text{NPF}_6$ at a Pt working electrode. All potentials are referenced to the ferrocene/ferrocenium ion couple (Fc/Fc^+) as a standard.

*General Procedure for Synthesis of N,N′-Bis(2-Alkylphenyl)Formamidines (**1a–1b**) and N,N′-Bis(2,6-Alkylphenyl)Formamidines (**1c–1e**)*

N,N′-bis(2-alykylphenyl)formamidines **(1a–1b)** and *N,N′*-bis(2,6-alkylphenyl)formamidines **(1c–1e)** were prepared using the method described by Grubbs and coworkers [10].

Acetic acid (86 mL, 1.5 mmol, 0.050 equiv) was added to a round-bottomed flask charged with the corresponding aniline (60 mmol, 2.0 equiv) and

triethyl orthoformate (5.0 mL, 30 mmol, 1.0 equiv). The flask was fitted with a distillation head and was heated with stirring overnight. Upon cooling to room temperature, the solution solidified. The crude product was triturated with cold hexanes, collected by vacuum filtration, and dried *in vacuo*, providing the pure product as a white crystalline solid. The following formamidines were prepared using this procedure.

*N,N′-Bisphenylformamidine (**1a**)*

Yield 51%. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ = 7.01–7.31 (m, 5H), 8.21 (s, 1H), 10.1 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 119.0, 123.3, 129.4, 145.2, 149.7.

*N,N′-Bis(2-methylphenyl)formamidine (**1b**)*

Yield 76%. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δg = 2.29 (s, 6H), 6.97–7.18 (m, 8H), 8.03 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 17.9, 117.6, 123.4, 126.9, 130.7.

*N,N′-Bis(2,6-dimethylphenyl)formamidine (**1c**)*

Yield 28%. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ = 2.24 (s, H), 2.27 (s, H), 6.91–7.36 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 17.9, 18.7, 123.1, 126.3, 128.2, 128.3, 128.6, 128.8, 133.7 136.2, 145.1, 146.6.

*N,N′-Bis(2,6-diethylphenyl)formamidine (**1d**)*

Yield 29%. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ =1.15 (t, J = 7.5 Hz, 3H), 1.21 (t, J = 7.5 Hz, 6H), 1.26 (t, J = 7.5 Hz, 3H), 2.60 (q, J = 7.5 Hz, 4H), 2.66 (q, J = 7.5 Hz, 4H), 7.035–7.313 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 14.2, 14.8, 15.0, 24.1, 24.9, 24.9, 123.4, 126.2, 126.4, 126.9, 127.1, 134.4, 134.9, 140.6, 144.0, 147.2.

*N,N′-Bis(2,6-diisopropylphenyl)formamidine (**1e**)*

Yield 51%. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K): δ = 1.11 (d,J = 6.6 Hz, 15H), 1.18 (d,J = 6.6 Hz, 3H), 3.178–3.440 (sep, J = 6.6 Hz, 4H), 7.09–7.27 (m, 6H), 8.99 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 293 K): δ = 23.5, 28.0, 123.1, 125.4 (br), 134 (br), 143.5 (br), 154.0 (br).

Photoreaction of [60]Fullerene with N,N′-Bis(alkylphenyl)formamidine

Irradiation of toluene solution (20 mL) of [60]fullerene (20.0 mg, 28.0 nmol) and an excess molar amount of *N,N′*-bis(alkylphenyl)formamidine (0.84 mmol, 30 equiv) in a glass tube at room temperature for 48 h using a high-pressure mercury-arc lamp (cutoff < 400 nm) caused the formation of the adduct, which was purified using preparative HPLC with a Buckyprep column and a Buckyprep M column (nacalai tesque, Kyoto, Japan).

Spectrum data of **2c**:Yield 62%, ^{1}H NMR (300 MHz, CS_2/CD_2Cl_2, 293 K): δ = 2.42 (s, 6H), 3.01 (s, 6H), 6.23–6.87 (m, 2H), 7.06–7.22 (m, 2H), 7.35 (m, 1H); ^{13}C NMR (75 MHz, CS_2/CD_2Cl_2, 293 K): δ = 20.0, 21.0, 79.5, 89.2, 124.4, 128.3, 129.2, 129.3, 130.1, 134.2, 138.5, 139.3, 140.2, 140.6, 140.6, 141.9, 142.0, 142.3, 142.5, 142.7, 142.9, 143.0, 143.0, 143.1, 144.3, 144.7, 145.0, 145.2, 145.3, 145.3, 145.7, 146.1, 146.1, 146.2, 146.2, 146.3, 146.7, 147.0, 147.2, 149.1. MALDI-TOF mass: calcd: [M] 970.15, found: [M$^-$] 970.27. Vis (toluene) λ_{max}: 321, 459, 691 nm.

Spectrum data of **2d**: Yield 24%, ^{1}H NMR (300 MHz, CS_2/CD_2Cl_2, 293 K): δ = 1.08–1.20 (m, H), 2.20–2.70 (m, H), 6.50–7.50 (m, 6H). ^{13}C NMR (75 MHz, CS_2/CD_2Cl_2, 293 K): δ = 14.4, 15.1, 15.8, 25.3, 26.0, 26.1, 79.3, 89.0, 124.6, 126.3, 126.7, 127.2, 130.3, 135.1, 140.1, 140.4, 140.7, 141.9, 142.0, 142.3, 142.6, 142.7, 142.9, 143.0, 143.1, 143.2, 144.3, 144.7, 145.1, 145.1, 145.2, 145.3, 145.4, 145.5, 145.9, 146.1, 146.2, 146.2, 146.3, 146.4, 146.8, 146.9, 147.2, 147.3, 149.3, 154.0; MALDI-TOF mass: calcd: 1026.21, found: [M$^-$] 1026.87. Vis (toluene) λ_{max}: 325, 457, 693 nm.

Spectrum data of **2e**: Yield 51%, ^{1}H NMR (300 MHz, CS_2/CD_2Cl_2, 293 K): δ = 1.43 (m, 12H), 1.61 (d, J = 4.2 Hz, 6H), 1.88 (d, J = 4.2 Hz, 6H), 3.79 (sep, J = 4.2 Hz, 1H), 4.56 (sep, J = 4.2 Hz, 1H), .13 (s, 3H), 7.67–7.79 (m, 3H). ^{13}C NMR (75 MHz, CS_2/CD_2Cl_2, 293 K): δ = 22.3, 26.4, 26.4, 29.6, 31.0, 79.6, 89.3, 123.5, 125.6, 125.8, 131.4, 138.7, 139.8, 140.7, 141.0, 141.1, 142.4, 142.6, 142.8, 143.2, 143.3, 143.5, 143.5, 143.7, 143.7, 144.9, 145.4, 145.6, 145.7, 145.7, 145.9, 145.9, 146.1, 146.6, 146.7, 146.7, 146.8, 146.8, 147.0, 147.3, 147.8, 147.8, 150.2, 150.4. MALDI-TOF mass: calcd: 1082.27, found: [M$^-$] 1082.49. Vis (toluene) λ_{max}: 319, 461, 692 nm.

Crystal data of a black block of **2e** : MW: 1083.14, 0.14 mm × 0.11 mm × 0.09 mm, monoclinic, P21/n (No. 14), a = 10.3025(6) Å, b = 24.6572(12) Å, c = 19.2788(11) Å, β = 101.654(4)°, V = 4796.5(5) Å^3, Z = 4, D_{calcd} = 1.500, μ (Mo Kα) = 0.087 mm^{-1}, Rigaku R-AXIS RAPID θ = 6.13–47.99, T = 100 K, Number of observations (all reflections): 13502,

number of variables: 792, reflection/parameter ratio: 17.04, R_1 [7972$F_o > 2\sigma(F_o)$] = 0.0519, R (for all 13,502 data) = 0.0833, ωR_2 (all reflections) = 0.1255. Goodness of fit indicator 0.909, restrained goodness of fit indicator 0.909 for all data. CCDC 794153 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk.

SUPPORTING INFORMATION

The supporting information related to this article is available from the corresponding author (e-mail: akasaka@tara.tsukuba.ac.jp) on request.

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