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Catalytic Asymmetric Carbene Transfer Reactions of Diazo Oxime Ethers with Olefins and Their Synthetic Applications

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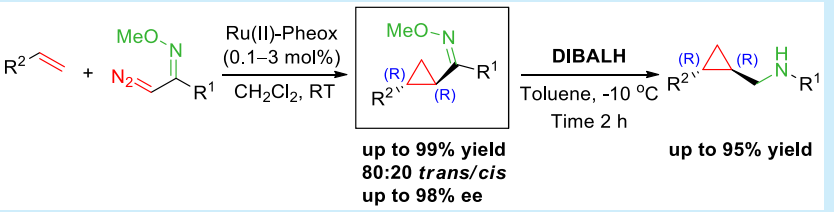
Supporting Information

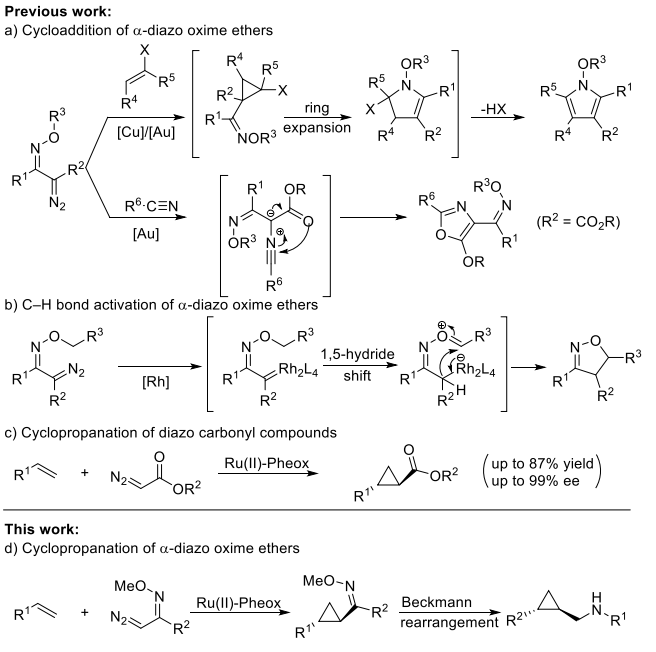


ABSTRACT: The first catalytic asymmetric cyclopropanation of diazo oxime ethers with olefins was developed. In the presence of a Ru(II)-Pheox catalyst, various optically active cyclopropyl oxime derivatives were obtained in high yields (up to 99%) with high enantioselectivities (up to 98% ee). Furthermore, optically active cyclopropyl oxime ethers could be successfully converted into the corresponding cyclopropyl methylamine derivatives via metal hydride and Grignard reagent mediated Beckmann rearrangement, which are potential candidates for the assessment of biological and pharmaceutical activities.

Organic compounds containing an oxime ether group are widespread in antifungal,[1] antibacterial,[2] and anticancer[3] agents as well as other medicinal compounds.[4] Oxime ethers also play an important and versatile role in organic synthesis. In particular, synthetic transformations of oxime ethers into various nitrogen- and oxygen-containing compounds, including amines, 1,2-amino alcohols, nitriles, α- and β-amino acids, and lactams via Beckmann rearrangement have been reported,[5] leading to the rapid and continuous development of oxime group chemistry in the past decades.

On the other hand, the first carbene transfer reaction for the synthesis of cyclopropanes was reported by Buchner in 1903.[6] Since then, organic synthesis involving diazo compounds has attracted the attention of organic chemists. Decomposition of diazo compounds by a transition-metal catalyst has been widely used as an effective tool to develop a novel synthetic pathway via a carbene intermediate.[7] α-Diazo carbonyl compounds have known extensive development because of their stability and ease of preparation.[8] However, there are limited reports on the application of α-diazo oxime ethers because of the harsh reaction conditions required for their preparation and the rapid isomerization of α-diazo imines to triazoles.[9] By overcoming the aforementioned drawbacks, various α-diazo oxime ethers have recently been prepared in good to excellent yields.[10] α-Diazo oxime ethers have been widely applied in heterocycle synthesis. For instance, the cycloaddition of α-diazo oxime ethers with enamines, enol ethers, and nitriles in the presence of [Au][10a] or [Cu][10e,g] catalysts gave the corresponding pyrroles and oxazoles in high yields (Scheme 1a). On the other hand, N−O moieties in heterocycles such as isoxazoles could be obtained by the C−H activation of the α-hydrogen adjacent to the oxygen in α-diazo oxime ethers[10f,h] (Scheme 1b). Furthermore, another heterocyclic synthesis based on 2*H*-azirine derivatives from α-diazo oxime ethers has been reported.[10b,d]

Scheme 1. Synthetic Applications of α-Diazo Oxime Ethers



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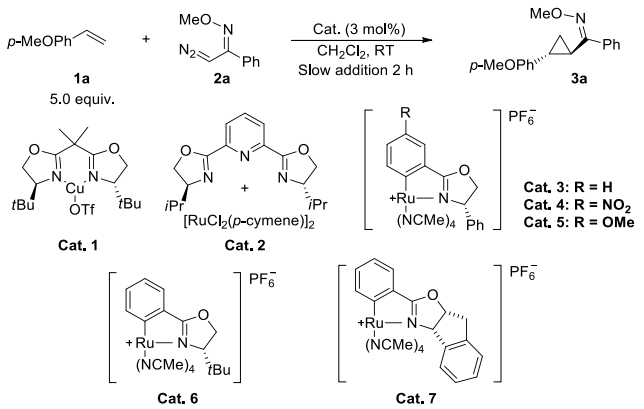
Despite the widespread research into the synthesis of heterocycles from diazo oxime ethers, cyclopropanation via a carbene transfer reaction has not been reported until now.[11] Since the oxime group can be transformed into various useful organic molecules via Beckmann rearrangement and other reactions, we examined diazo oxime ethers as carbene precursors having an oxime functional group for catalytic asymmetric cyclopropanation. Based on the results of our previous studies on the cyclopropanation of various diazo resources[12] (Scheme 1c), the Ru(II)-Pheox catalyst was examined for the metal-catalyzed decomposition of diazo compounds while controlling the enantioselectivity of the cyclopropyl oxime ether derivatives.

We first evaluated well-known carbene transfer catalysts and a series of Ru(II)-Pheox complexes in the asymmetric catalytic cyclopropanation of α-diazo oxime ether **2a** with *p*-methoxystyrene **1a**. The results are summarized in Table 1.

Table 1. Initial Catalyst Screening



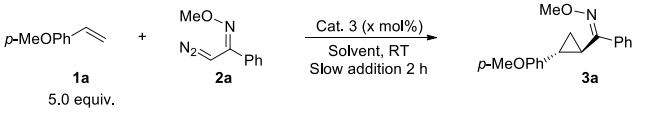
entry	cat.	3a [%][b]	*trans*/*cis*[c]	ee [%][d]
1	Cat. 1	65	43:57	41/7
2[e]	Cat. 2	24	76:24	4/-20
3	Cat. 3	99	80:20	94/86
4	Cat. 4	92	76:24	93/72
5	Cat. 5	90	79:21	82/69
6	Cat. 6	92	78:22	93/95
7	Cat. 7	89	80:20	93/88

[a]Reaction conditions: A solution of diazo oxime ether **2a** (0.2 mmol, 1 equiv) in CH_2Cl_2 (2.0 mL) was added slowly over 2 h to a solution of the corresponding catalyst (3 mol %) and **1a** (1.0 mmol, 5 equiv) in CH_2Cl_2 (2.0 mL) at room temperature, under argon atmosphere. [b]Isolated yield. [c]Determined by crude ^{1}H NMR. [d]Determined by chiral HPLC. [e]Reaction did not proceed to completion even in 48 h.

The reaction of **1a** with diazo oxime **2a** in the presence of the Box-Cu or Pybox-Ru complex gave cyclopropyl oxime product **3a** in low yield and with low enantioselectivity (Table 1, entries 1 and 2). In contrast, **2a** reacted smoothly with **1a** in the presence of Ru(II)-Pheox catalyst Cat. 3, without dimerization, to give **3a** in quantitive yield (99%) with high ee (up to 94% ee) (Table 1, entry 3). A series of Ru(II)-Pheox complexes (Cat. 4−7) were also evaluated for their catalytic efficiency. Catalysts (Cat. 4 and 5) with electron-donating or electron-withdrawing substituents as well as those with steric effects caused by the substituent on the oxazoline ring (Cat. 6 and 7) gave almost the same results in terms of the yield and stereoselectivity for the carbene transfer reactions (Table 1, entries 4−7). Among of Ru(II)-Pheox catalyst (Cat. 3) was found to be the best choice for the reaction. In our study, the desired cyclopropyl oxime products were only (*E*)-isomers.

Next, the reaction conditions were optimized in various solvents and temperatures using Ru(II)-Pheox (Cat. 3) as the catalyst. The results are summarized in Table S1 (see Supporting Information Table S1). No improvement was observed using Et_2O, THF, toluene, acetone, and acetonitrile as the solvent (Table S1, entries 2−6). When the reaction temperature was decreased, the enantioselectivity increased slightly to 95% ee, whereas the stereoselectivity and yield remained unchanged (Table S1, entries 1, 7, and 8). The effect of the catalyst amount was also investigated, as shown in Table 2. When decreasing catalyst loading to 0.1 mol %, the catalytic

Table 2. Catalyst Loading



entry	*x* [mol %]	yield [%][a]	*trans*/*cis*[b]	ee [%][c]	TON[d]	TOF [h^{-1}][e]
1	3	99	80/20	94/86	33	17
2	1	96	80/20	94/86	96	48
3	0.1	91	80/20	94/86	910	455
4[f]	0.01	55	73/27	57/16	5500	115

[a]Isolated yield. [b]Determined by crude ^{1}H NMR. [c]Determined by chiral HPLC. [d]TON (turnover number) = Product [mol]/cat. [mol]. [e]TOF (turnover frequency) = TON/time [h]. [f]Reaction did not proceed to completion even after 48 h of stirring.

asymmetric cyclopropanation proceeded smoothly to give the optically active cyclopropyl oxime **3a** in good yield (91%) with the same level of enantioselectivity and diastereoselectivity (Table 2, entry 3). However, the catalyst activity was drastically reduced when the catalyst amount was less than 0.1 mol %, and lower enantioselectivity and stereoselectivity were observed (Table 2, entry 4). The high TON (up to 5500) and TOF (up to 455) values were also remarked.

With the optimized reaction conditions in hand, we next examined the substrate scope of the cyclopropanation of diazo oxime ether **2a** with various olefins **1a**−**l**. The results are summarized in Scheme 2. Various *para*-substituted styrene derivatives were compared for the electronic effect in the cyclopropanation reactions (Scheme 2, **3a**−**f**). Electron-donating groups and electron-withdrawing groups affected the reactivity of the styrene derivatives with **2a**. When a more electron-rich substituent was installed at the *para*-position, better yield of the product was obtained (Scheme 2, **3a**−**f**). This phenomenon could be explained by the general mechanism of the cyclopropanation catalyzed by a transition-metal system. Electron-rich olefins reacted more smoothly with the metal−carbene complex intermediate having an oxime ether functional group as an electron-withdrawing group. In contrast, higher enantioselectivity was achieved for both styrenes containing electron-withdrawing groups, such as *para*-Cl and *para*-NO_2 substituents (96% ee and 95% ee, respectively). The highest enantioselectivity was observed in compound **3e**: 96% ee for the *trans* product and 99% for the *cis* product. On the other hand, both electron-withdrawing and electron-donating substituents at the ortho-position of styrene resulted in slightly lower dr and ee (Scheme 2, **3g**−**h**). The

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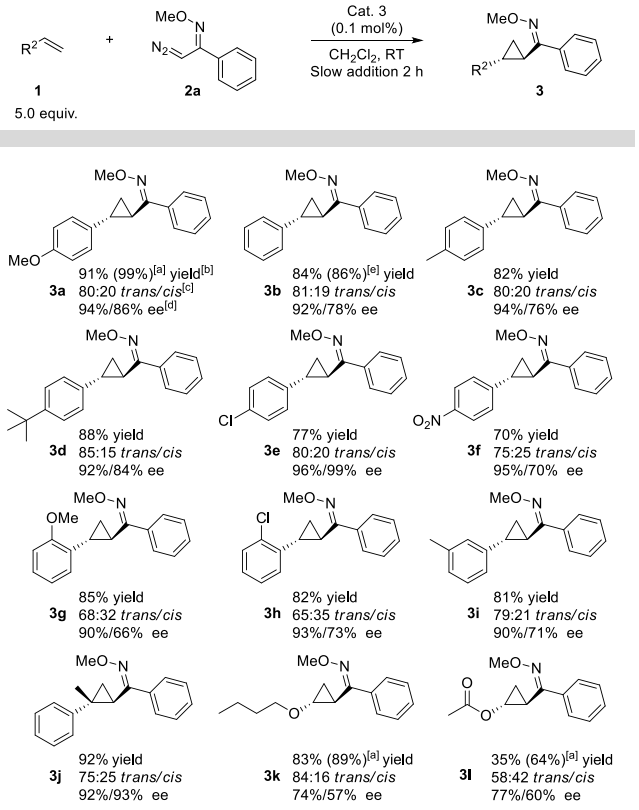
Scheme 2. Asymmetric Cyclopropanation of Various Olefins

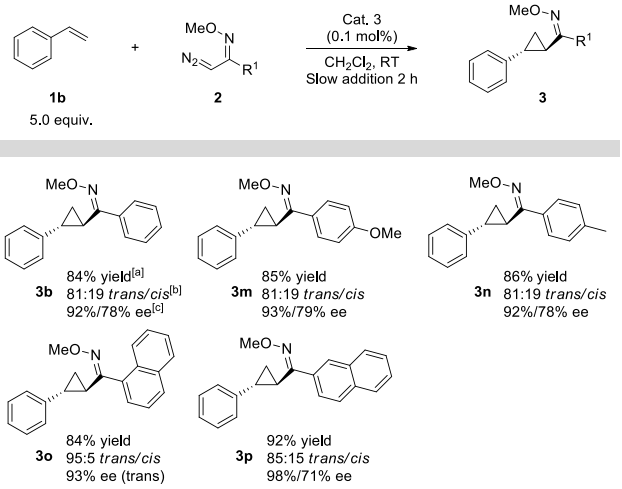


[a]Three mol % Ru(II)-Pheox was used. [b]Isolated yield. [c]Determined by crude ^{1}H NMR. [d]Determined by chiral HPLC. [e]0.22 g of **3b** was synthesized in 1 mmol scale in 86% yield, 81:19 *trans*/*cis*, and 92%/76% ee.

same result was observed in the case of styrene with a substituent at the meta-position, and the dr value could be well maintained; however, the enantioselectivity was 90% ee for product **3i** and 94% ee for **3c**. When 3 mol % of Cat. 3 was used, excellent yields of **3a** and **3b** were observed, with high stereoselectivity and enantioselectivity. α-Methylstyrene gave **3j** in high yield with high ee for both *trans* and *cis* isomers (92% ee for *trans* and 93% for *cis*). Unfortunately, tetra-substituted and inner olefins gave only the dimer of the diazo oxime ether. We then turned our attention to other olefins such as *n*-butyl vinyl ether and vinyl acetate. The reaction between **2a** and *n*-butyl vinyl ether furnished compound **3k** in 83% yield, with moderate enantioselectivity for the *trans* isomer (74% ee) but low ee for the *cis* isomer (57% ee). The electron-deficient olefin **1l** resulted in a slow reaction and gave a low yield of **3l** with moderate dr and ee. The 1 mmol scale reaction gave **3b** (0.22 g) in 86% yield and 92% ee (Scheme 2).

To expand the generality of cyclopropanation using α-diazo oxime ethers, a series of α-diazo oxime ethers were employed with styrene **1b** in the presence of Ru(II)-Pheox catalyst (Cat. 3). The results are listed in Scheme 3. The electronic effect on the benzene ring of the α-diazo oxime ether gave the same result of products **3b** and **3m**−**n** in yield, dr, and ee. However, steric hindrance strongly affected the stereoselectivity and enantioselectivity. When 2-naphthyl diazo oxime **2o** was used as the carbene source in the cyclopropanation with styrene, compound **3o** was obtained in high yield (84%), with high enantioselectivity (93% ee) and very high dr ratio (95:5 d.r.).

Scheme 3. Ru(II)-Pheox-Catalyzed Asymmetric Cyclopropanation of Various α-Diazo Oxime Ethers

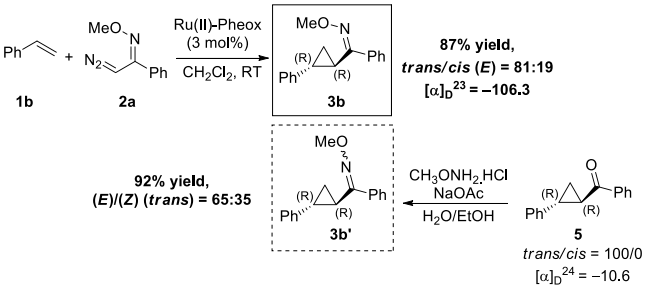


[a]Isolated yield. [b]Determined by crude ^{1}H NMR. [c]Determined by chiral HPLC.

Moreover, the reaction between 1-naphthyl diazo oxime **2p** and **1b** gave cyclopropyl oxime **3p** in high yield with excellent enantioselectivity (98% ee) and dr (Scheme 3, **3p**).

The structure and absolute configuration of cyclopropyl oximes (major *trans* product) were determined in an efficient manner by comparison of cyclopropyl oximes with the synthetic transformation of a cyclopropyl ketone into a cyclopropyl oxime product. As shown in Scheme 4, diphenyl

Scheme 4. Determination of the Structure and Absolute Configuration of the Cyclopropyl Oxime Product



cyclopropane ketone **5**[13] having only the *trans* isomer was successfully transformed into a mixture of *anti* and *syn* isomers **3b′** bearing an oxime functional group. Besides, *trans* and *cis* cyclopropyl oxime products **3b** were produced by the reaction of α-diazo oxime ether **2a** with styrene **1b**, as mentioned before. The absence of the NMR peak attributed to the *syn* isomer in the **3b** mixture as well as the absence of the peak due to the *cis* product in the **3b′** mixture helped identify the structure of the *trans* and *cis* cyclopropyl oximes in **3b** (see Supporting Information). Furthermore, the consistency between the measured $[\alpha]_D$ (Scheme 4) and the reported value[14] was used for determining the absolute configuration of the (*R*,*R*)-**3b** product. Moreover, the minor product *cis*-**3f** was successfully isolated by crystallization, and its absolute configuration was confirmed by single-crystal X-ray diffraction analysis.[15]

Further synthetic applications of cyclopropyl oxime ethers via metal hydride and Grignard reagent mediated Beckmann

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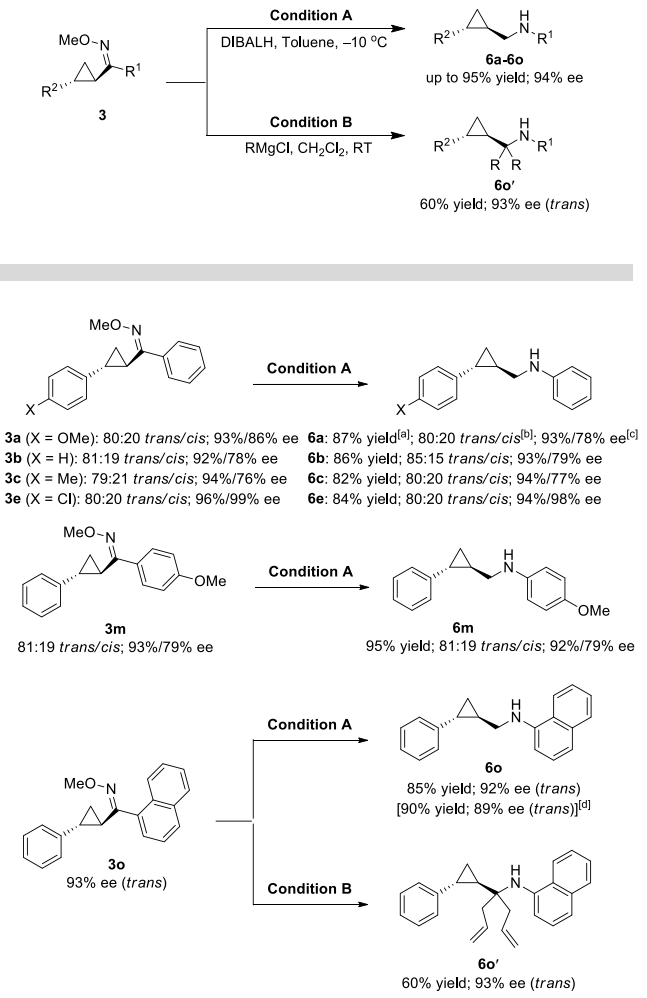
rearrangement were explored, as described in Scheme 5. To demonstrate the utility of our direct enantioselective cyclopropyl oxime ethers in synthetic transformations, we herein report the first DIBALH-mediated and Grignard reagent mediated Beckmann rearrangement[16,17] of **3** to obtain cyclopropyl methylamine derivatives **6a−6o** and **6o′**, which are candidates for Serotonin 2C receptor agonists.[18]

Scheme 5. Synthetic Transformation of Cyclopropyl Oxime Ethers



[a]Isolated yield. [b]Determined by crude ^{1}H NMR. [c]Determined by chiral HPLC. [d]Reaction was carried out at RT.

All of these cases proceeded in high yield with retained enantioselectivity. The reaction of DIBALH and **3o** was initially carried out at room temperature. A high yield was observed, whereas the enantioselectivity was slightly decreased (Scheme 5). To maintain the chiral environment in **6**, a low temperature is essential. At lower temperatures (−10 °C), the cyclopropyl oxime ethers were completely transformed into cyclopropyl methylamines in high yields (>80% yield) with the same ee and dr ratio. An excellent result was obtained in the reductive Beckmann rearrangement of **3m**, with 95% yield (Scheme 5).

In conclusion, we have developed the first catalytic asymmetric cyclopropanation of α-diazo oxime ethers with olefins in the presence of a Ru(II)-Pheox catalyst to obtain a variety of optically active cyclopropyl oxime derivatives in excellent yields (up to 99%) with high diastereoselectivities (up to 95:5) and enantioselectivities (up to 98% ee). In addition, the catalytic efficiency of Ru(II)-Pheox resulted in a high TON (5500) and TOF (455). We also successfully developed a synthetic pathway for optically active cyclopropyl methyl amine derivatives as useful bioactive intermediates starting from the cyclopropyl oxime ethers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02771.

Experimental procedures and characterization data (PDF)

Accession Codes

CCDC 1944711 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(13) (a) Diphenyl cyclopropane ketone **5** was synthesized according to Nicolas's procedure[13b] using *p*-nitro-Ru(II)-diphenyl-Pheox catalyst.[13c] (b) Nicolas, I.; Maux, P. L.; Simonneaux, G. *Tetrahedron Lett.* **2008**, *49*, 2111−2113. (c) Chi, L. T. L.; Suharto, A.; Da, H. L.; Chanthamath, S.; Shibatomi, K.; Iwasa, S. *Adv. Synth. Catal.* **2019**, *361*, 951−955.
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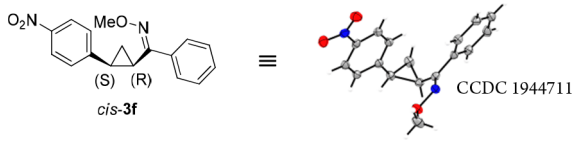
(15) The X-ray measurement was performed with the X-ray equipment at the institution of instrumental analysis in Tokyo University of Agriculture and Technology.



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