Green Chemistry



PAPER

View Article Online



Cite this: *Green Chem.*, 2025, **27**, 5359

Deoxygenative dual CO₂ conversions: methylenation and switchable *N*-formylation/ *N*-methylation of tryptamines†

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The unprecedented one-pot synthesis of N-formyl/N-methyltryptolines from tryptamines was achieved via phenylsilane-assisted deoxygenative dual CO_2 conversions. Two CO_2 molecules acted as different synthons and were converted into methylene and N-formyl/N-methyl groups. The CO_2 reduction step was catalyzed by a pentanuclear zinc complex at atmospheric pressure under solvent-free conditions. The N-formyl/N-methyl products could be switched by changing the amount of phenylsilane, and the amounts of in situ generated bis(silyl)acetals and silyl formates were key to the chemoselectivity. Methylenation, N-formylation, and N-methylation proceeded via the Pictet-Spengler reaction, amine-acid condensation, and the Eschweiler-Clarke reaction, respectively. The CO_2 reduction with phenylsilane could also be applied to the one-pot three-step synthesis of spiro[oxindole-pyrrolidine]s.

Received 21st February 2025, Accepted 6th April 2025 DOI: 10.1039/d5qc00942a

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- 1. We have developed new types of deoxygenative dual CO₂ conversions in which two CO₂ molecules act as different synthons and are converted into methylene and N-formyl/N-methyl groups of tryptolines, known as important compounds in biology. These CO₂ fixation methods will expand the usefulness of CO₂.
- 2. The CO_2 conversions have been achieved under solvent-free conditions at atmospheric pressure. The CO_2 reduction step was catalyzed by a small amount (0.07 mol%) of zinc complex, which could be prepared easily, and therefore noble and toxic metals are not required. Moreover, H_2O could be used as an additive
- 3. Our methods could be made greener by catalyst reuse strategies in flow chemistry. In addition, methods that allow for the application of a variety of sustainable reductants are recommended.

Introduction

 ${\rm CO}_2$ is a renewable C1 building block and is expected to serve as an alternative to petroleum-based chemicals. Therefore, the development of fine organic synthetic methods with ${\rm CO}_2$ for value-added chemicals has become increasingly important. Among ${\rm CO}_2$ fixations, deoxygenative conversions involving C-H/C-C bond formation, such as conversion to methyl $(-{\rm CH}_3)^2$ or methylene $(-{\rm CH}_2-)^3$ groups, are still rare despite their importance. Deoxygenative ${\rm CO}_2$ conversions require reductants, and ${\rm H}_2$, hydroboranes, 5,6 and hydrosilanes 6,7 are often used in the presence of catalysts. In the case of hydrosilanes, the reduction of ${\rm CO}_2$ generates reactive species: silyl formates $({\rm HCO}_2Si)$, bis(silyl)acetals $(Si{\rm OCH}_2{\rm O}Si)$, and methoxysilanes

dehyde, and methanol, respectively (Scheme 1a). Among the silyl species, bis(silyl)acetals are potentially useful for C-H/C-C bond-forming reactions, but there are few reports. Double CO₂ conversions, where two CO₂ molecules are captured by one substrate molecule, are attractive molecular con-

(CH₃OSi), which are easily hydrolyzed to formic acid, formal-

tured by one substrate molecule, are attractive molecular conversions. Although several double carboxylations have been reported,8 the number of double deoxygenative CO2 conversions reported is severely limited. For example, the Yan-You-Jiang group reported the construction of a tetrahydropyrimidine ring in which two CO2 molecules were converted into two methylene groups,9 and our group reported the construction of a fused benzene ring by conversion into two aromatic CH groups. 10 In contrast, the Qi-Jiang group reported the synthesis of α-methyl-β-diketones from aryl iodides, alkynes, and CO2, where two CO2 molecules were transformed into two different moieties, carbonyl and methyl groups.11 The Nan group has recently developed the synthesis of methylindologuinoxalines from indolylanilines with CO₂ via double N-formylation in which two CO₂ molecules were converted into an aromatic carbon and a methyl group. 12 Such dual CO2 con-

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†Electronic supplementary information (ESI) available. CCDC 2413450 and 2413452. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d5gc00942a

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(a) CO₂ Si-H Catalyst H CO₃ H H CO₃ H H CO₃ H H CO₃ H H CO₂ H H CO₂ H H CO₃ H H CO₃ H H CO₃ H H CO₃ H H CO₄ H H CO₅ H H CO₄ H H CO₅ H CO

Scheme 1 CO₂ fixation with Zn^{II} complex 1.

(g) 2 CO₂ + PhSiH₃

(8 equiv for 5a.

12 equiv for 6a)

versions will expand the usefulness of CO₂, and the development of new types of conversions would be a highly valuable achievement.

NBS

5a: R = CHO, 6a: R = CH

We have previously reported a macrocyclic pentanuclear Zn^{II} complex 1, which can be easily prepared via the self-assembly of the binaphthyl-bipyridyl ligand H_2L and Zn (OAc)₂·2H₂O (Scheme 1b).¹³ Complex 1 exhibited catalytic activity toward deoxygenative CO_2 conversions via the hydrosilylation of CO_2 :¹⁴ temperature-switched N-formylation/N-methylation of amines (Scheme 1c),^{13,15} C-methylenation of arenes (Scheme 1d),^{14a} and the synthesis of 3,4-dihydropyrans from β-dicarbonyl compounds and styrenes (Scheme 1e).^{14b}

More recently, during the investigation of the scope of 1-catalyzed CO_2 fixation, we unexpectedly noticed that tryptamine (2a) was converted into 2-formyltryptoline (3a) (tryptoline is also known as 1,2,3,4-tetrahydro- β -carboline), a novel com-

pound (Scheme 1f). In this synthesis, two CO2 molecules were incorporated into two different moieties, methylene and N-formyl groups, and this type of CO₂ conversion is unprecedented. The Pictet-Spengler cyclization involving formaldehyde and amine-formic acid condensation seems to proceed. Tryptoline derivatives often exhibit pharmacological activities in the treatment of serious diseases such as mitochondrial disease, Alzheimer's disease, and malaria.¹⁶ Therefore, expanding the synthetic methods of tryptolines would be a significant contribution, and we decided to investigate this synthesis. As a result, we established the synthetic conditions leading to 3a and found that the product could be switched to 2-methyltryptoline (4a). In addition, one-pot threestep reactions, Br-assisted semi-pinacol rearrangement¹⁷ after the formation of 3a or 4a, proceeded to form spiro[oxindolepyrrolidine's 5a and 6a (Scheme 1g). Some derivatives with this spiro-skeleton also exhibit pharmaceutical activity, 18 and the method matches the pot-economy concept. 19 Therefore, this strategy is promising.

Results and discussion

Optimizing the reaction conditions

We first optimized the reaction conditions for the synthesis of formyltryptoline 3a from 2a (Table 1). After the reaction of CO_2 (1 atm) with $PhSiH_3$ (8 equiv.) in the presence of catalyst 1 (0.07 mol%) under solvent-free conditions, 2a was added along with additives AcOH and H_2O (entries 1–5). The yield was sen-

Table 1 Optimization of the reaction conditions^a

| Entry | X (equiv.) | <i>T</i> ₁ (°C) | T_2 (°C) | $Yield^b$ (%) | |
|--------|------------|----------------------------|------------|---------------|-------------|
| | | | | 3a | 4a |
| 1 | 8 | 45 | 100 | 38 | 5 |
| 2 | 8 | 55 | 100 | 62 | 8 |
| 3 | 8 | 65 | 100 | 49 | 12 |
| 4 | 8 | 55 | 120 | 83 $(80)^c$ | 6 |
| 5 | 8 | 55 | 140 | 29 | 4 |
| 6^d | 8 | 55 | 120 | 27 | 21 |
| 7^e | 8 | 55 | 120 | 60 | 19 |
| 8 | 6 | 55 | 120 | 43 | 3 |
| 9 | 10 | 55 | 120 | 64 | 34 |
| 10 | 12 | 55 | 120 | 14 | $82 (83)^c$ |
| 11^f | 14 | 55 | 120 | 4 | 82 |
| 12 | 14 | 55 | 120 | Trace | 76 |

^a Conditions: CO₂ (1 atm, balloon, 3.7 L), PhSiH₃ (6–14 equiv.), cat. 1 (0.07 mol% based on PhSiH₃), 2a (0.25 mmol), AcOH (200 μL), H₂O (100 μL). ^b Determined by ¹H NMR using styrene as an internal standard. ^c Isolated yield. ^d Absence of AcOH. ^e Absence of H₂O. ^f DMSO (100 μL) was added.

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sitive to temperature, and the optimal temperatures were 55 and 120 °C for the first and second steps, respectively (83%, entry 4).

In the first step, key C1 intermediates, bis(silyl)acetals and silyl formates, are considered to accumulate. When AcOH or H₂O was absent, the yields decreased (27-60%, entries 6 and 7). We also screened hydrosilanes and additives, which resulted in lower yields (Tables S1-S4†). We noticed that methyltryptoline 4a was generated as a byproduct (4-21%, entries 1-7) and changed the amount of PhSiH3 to increase

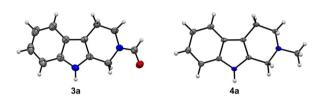
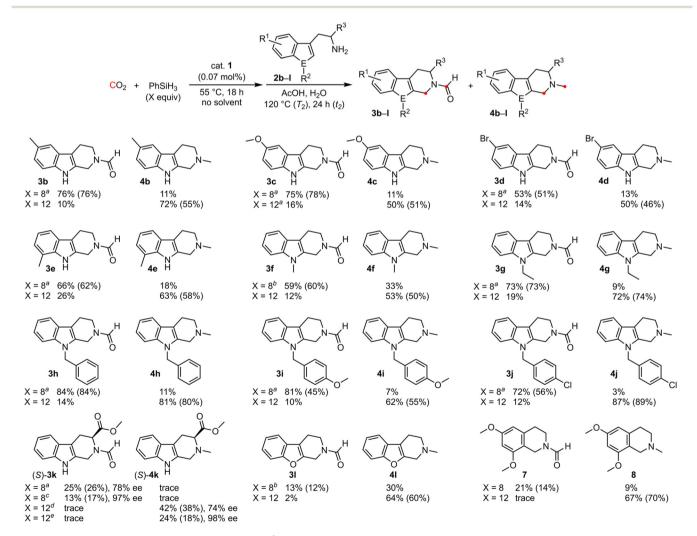


Fig. 1 ORTEP drawings of X-ray crystal structures of 3a and 4a. The thermal ellipsoids are scaled to the 50% probability level.

the yield of 4a (entries 8-12). Compound 4a was formed in the highest yield (82%, entry 10) when 12 equiv. of PhSiH3 were used. The addition of DMSO did not improve the yield (entry 11). On the basis of the above results, entries 4 and 10 were found to be the best conditions for the synthesis of 3a and 4a, respectively. The structures of 3a and 4a were unambiguously confirmed by X-ray crystallography (Fig. 1 and S2†).20

Substrate scope

We next investigated the substrate scope for the chemoselective dual CO2 conversions (Scheme 2). When 5-methyl-, 5-methoxy-, 5-bromo-, 7-methyl-, 1-methyl-, and 1-ethyl-substituted tryptamines were used as substrates, the corresponding formyltryptolines 3b-3g (51-78%) and methyltryptolines 4b-4g (46-74%) were obtained selectively in moderate to high yields, depending on the amount of phenylsilane. Moreover, 1-benzyl-, 1-(4-methoxybenzyl)-, and 1-(4-chlorobenzyl)-substituted tryptamines were also converted into formyltryptolines 3h-3j (45-84%) or methyltryptolines 4h-4j (55-89%) in gratifying



Scheme 2 Substrate scope. Yields were determined by ¹H NMR using styrene as an internal standard. Isolated yields are shown in parentheses. ^a T₂ = 130 °C. ${}^{b}T_{2}$ = 110 °C. ${}^{c}T_{2}$ = 90 °C. ${}^{d}T_{2}$ = 80 °C, t_{2} = 3 h. ${}^{e}T_{2}$ = 45 °C.

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yields despite the large steric hindrance. The fact that even 1-substituted tryptamines underwent the reactions demonstrates the usefulness of this synthetic method. In addition, (S)-tryptophan methyl ester could be transformed into (S)-3k (26%, 78% ee at T_2 of 130 °C) or (S)-4k (38%, 74% ee at T_2 of 80 °C) although partial racemization proceeded. The racemization could be suppressed to a minimum by lowering the reaction temperature ((S)-3k: 17%, 97% ee at T_2 of 90 °C; (S)-4k: 18%, 98% ee at T_2 of 45 °C). For the scope of substrates beyond tryptamines, benzofuran and dimethoxybenzene analogs were converted into methylated tetrahydrobenzofuropyridine 4l (60%) and tetrahydroisoquinoline 8 (70%), respectively, in gratifying yields, although the yields of formylated products were low. The aforementioned results indicate that the

Isotope-labeling and control experiments

substrate scope is relatively broad.

To elucidate the carbon and hydrogen sources for the construction of **3a** and **4a**, isotope-labeling experiments were conducted. When the reaction was performed with ¹³CO₂, **3a'** possessing one each of ¹³C-methylene and ¹³C-formyl groups and **4a'** possessing one each of ¹³C-methylene and ¹³C-methyl groups were obtained without the formation of **3a** and **4a** (Scheme **3a**). ²¹ When the reaction was performed with PhSiD₃, **3a"** possessing deuterated methylene and formyl groups and **4a"** possessing deuterated methylene and methyl groups were obtained without the formation of **3a** and **4a** (Scheme **3b**). These results clearly demonstrate that the incorporated carbon and hydrogen atoms originated from carbon dioxide and phenylsilane, respectively.

We performed control experiments to predict the reaction mechanisms. An experiment without catalyst 1 resulted in no formation of 3a or 4a, and Zn(OAc)2·2H2O showed no catalytic activity, both indicating that 1 is an essential catalyst (Scheme 3c). When formic acid and paraformaldehyde were used instead of CO2 and PhSiH3, 3a or 4a was obtained selectively according to the amounts of reagents (Scheme 3d and e).22 In contrast, the reactions did not proceed with paraformaldehyde or formic acid alone (not shown), which strongly suggests that the system requires both paraformaldehyde and formic acid (or their equivalents) as intermediates. When 3a was used as a substrate, 4a was hardly obtained, which indicates that 3a is not a major intermediate leading to 4a (Scheme 3f). When tryptoline (9) was used as a substrate, both 3a and 4a were obtained, indicating that 9 is a common intermediate (Scheme 3g). In contrast, formyltryptamine 10 did not give 3a, suggesting that 10 is not an intermediate and that the electron-withdrawing formyl group prevents the Pictet-Spengler cyclization (Scheme 3h). On the other hand, methyltryptamine 11 afforded 4a, which indicates that 11 as well as 9 is an intermediate for 4a (Scheme 3i).

Proposed pathways

The above isotope-labeling and control experiments enabled us to propose the following pathways (Scheme 4). First, (i-ii) silyl formates and bis(silyl)acetals are generated from CO₂ and

Scheme 3 Isotope-labeling and control experiments.

(a)
$$PhSiH_3$$
 $\xrightarrow{\text{cat. 1}}$ $Zn-H$ $\xrightarrow{\text{CO}_2}$ $\xrightarrow{\text{HCO}_2Si}$ $\xrightarrow{\text{H}_2O}$ $\xrightarrow{\text{HCO}_2H}$ $\xrightarrow{\text{HCHO}}$ (b) $\xrightarrow{\text{NH}_2}$ $\xrightarrow{\text{HCHO}}$ $\xrightarrow{\text{HCHO}}$ $\xrightarrow{\text{NH}_2}$ $\xrightarrow{\text{HCHO}}$ $\xrightarrow{\text{HCHO}}$ $\xrightarrow{\text{NH}_2}$ $\xrightarrow{\text{HCHO}}$ $\xrightarrow{\text{HCHO}_2H}$ $\xrightarrow{\text{HCO}_2H}$ $\xrightarrow{\text{$

Scheme 4 Proposed pathways for the synthesis of 3a and 4a.

PhSiH₃ *via* the formation of a Zn-hydride complex, and (iii) subsequent hydrolysis gives formic acid and formaldehyde (Scheme 4a).¹³ Next, (iv) the Pictet-Spengler reaction^{3d,e} of **2a** with formaldehyde affords **9**, and (v) the formylation with formic acid gives **3a** (Scheme 4b). Instead of this formylation, (vi) the Eschweiler-Clarke reaction with formaldehyde and formic acid gives **4a**. As for the synthesis of **4a**, another route is possible: (vii) the Eschweiler-Clarke reaction of **2a** to form

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11 and (viii) the subsequent Pictet–Spengler reaction. Because 3a could be generated enough experimentally, it is supposed that reaction (iv) is faster than reaction (vii) and that the route *via* 9 is the main pathway for the synthesis of 4a. Here, 9 was not detected experimentally even when the reaction time was shortened, which indicates that reaction (iv) includes the rate-determining step.

Chemoselectivity in the formation of 3a or 4a

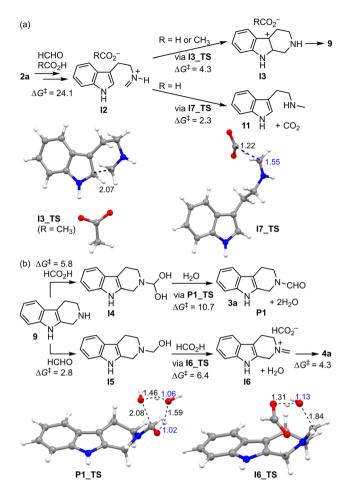
We next turned our attention to the origin of the chemoselectivity in the formation of 3a or 4a. The amounts and/or molar ratio of C1 intermediates generated in the first step (CO₂ reduction step) were strongly expected to depend on the amount of PhSiH₃, which could be considered a determinant of the selectivity. Therefore, we measured their amounts in the reaction mixtures from the first step under the standard conditions (Table 2 and Fig. S6†).23 When 2.00 mmol of PhSiH3 (for the synthesis of 3a) was used, 0.46 mmol of silyl formates and 0.35 mmol of bis(silyl)acetals were detected together with methoxysilanes. When 3.00 mmol of PhSiH₃ (for the synthesis of 4a) was used, 0.73 mmol of silyl formates and 0.60 mmol of bis(silyl)acetals were detected. Although the quantities changed, the proportions were remarkably similar: 30% for silvl formates, 25% for bis(silvl)acetals, and 45% for methoxysilanes. In other words, the amounts, not the ratio, of C1 intermediates determine the main product. In the case that an amount of bis(silyl)acetals is small, generated formaldehyde is depleted in the Pictet-Spengler reaction of 2a and cannot participate in the subsequent Eschweiler-Clarke reaction; thus, N-formylation proceeds selectively to give 3a. In the case that a sufficient amount of bis(silyl)acetals is accumulated, 4a forms selectively because the Eschweiler-Clarke reaction of 9 is faster than the N-formylation.

To more reliably elucidate the pathways and chemoselectivity, we carried out DFT calculations. Selected elementary reactions and overall pathways with energy profiles are shown in Scheme 5 and S2–S4,† respectively. As a result, the pathways shown in Scheme 4b are acceptable, and some highlights are as follows. Iminium salt I2 is formed from 2a as a common intermediate via a rate-determining dehydration step with a ΔG^{\ddagger} value of 24.1 kcal mol⁻¹ (Scheme 5a). Then, I2 branches into the reactions to I3 (for 9) and 11, and the ΔG^{\ddagger} value of the transition state (TS) to I3 (4.3 kcal mol⁻¹) is slightly greater than that to 11 (2.3 kcal mol⁻¹). Here, it should

Table 2 CO₂ reduction with PhSiH₃^a

| | Production amount ^b (mmol) | | | |
|------------------------------|---------------------------------------|--------------------------|--------------------------|--|
| $PhSiH_{3}\left(mmol\right)$ | HCO ₂ Si | Si OCH $_2$ O Si | CH ₃ OSi | |
| 2.00 3.00 | 0.46 (31%) 0.73 (31%) | 0.35 (24%) 0.60 (25%) | 0.65 (45%) 1.05 (44%) | |

 a Conditions: CO $_2$ (1 atm), PhSiH $_3$ (2.00 or 3.00 mmol), cat. 1 (0.07 mol%), 55 °C, 18 h. b Determined by proton-coupled $^{13}\mathrm{C}$ NMR using mesitylene as an internal standard. Product selectivity is shown in parentheses.



Scheme 5 Selected theoretical elementary reactions and TS structures for the formation of 3a and 4a at the B3LYP/6-31+G(d,p) level with the self-consistent reaction field method (H₂O) at 393.15 K. ΔG^{\ddagger} values and distances are shown in kcal mol⁻¹ and Å, respectively. ΔG^{\ddagger} values are based on each elementary reaction.

be noted that the counterion in **I2** for **I3** can be either a formate or an acetate ion, whereas that for **11** must be a formate ion. In the actual experiments, the amount of added AcOH (3.5 mmol, 200 μ L) is much larger than that of the generated formic acid (up to 0.73 mmol), which likely leads to the preferential production of **9** rather than **11**. The ΔG^{\ddagger} value of the TS from **9** to **3a** (10.7 kcal mol⁻¹) is larger than that from **9** to **4a** (6.4 kcal mol⁻¹), which suggests that **4a** is certainly formed preferentially when the reactive C1 intermediates are present in sufficient concentration (Scheme 5b). Several TSs are stabilized by water-involved hydrogen bonds, and the proton transfer is mediated by water; an example is **P1_TS**, which involves dehydration.

One-pot three-step reactions

Finally, we explored one-pot three-step reactions of 2 via 3 or 4 to demonstrate the potential of the aforementioned CO_2 conversions (Scheme 6). After the two-step reaction, hydrolysis of 3a with aqueous HCl gave tryptoline (9) in good yield (72%). When N-bromosuccinimide (NBS) was added in the third step,

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CO2

PhSiH₃

(12 equiv)

55 °C, 18 h

no solvent

HCl aq 100 °C, 24 h 72% 2a [3a] 55 °C. 18 h AcOH, H₂O PhSiH₃ H₂O, NBS no solvent 120 °C, 24 h (8 equiv) 30 °C, 1 h CO2 H₂O. NBS AcOH, THE 30 °C 1 h PhSiH₃ 55 °C, 18 h AcOH, H₂O (12 equiv) no solvent 78% 120 °C, 24 h coerulescine (6a) H₂O, NBS CO_2 AcOH, THE 30 °C. 1 h 55 °C. 18 h AcOH, H₂O PhSiH_o 61% no solvent 120 °C, 24 h (8 equiv) 5h Ŕп

Scheme 6 One-pot three-step reactions for the synthesis of **5**, **6**, and **9**.

AcOH, H₂O

120 °C, 24 h

H₂O, NBS

AcOH, THF

50 °C, 1 h

51%

6h Bn

formylated spiro[oxindole-pyrrolidine] 5a was obtained in a high yield (76%). This method could also be applied to 4a, and methylated spiro-compound 6a, which is known as coerulescine, was obtained. In addition, the spiro-ring formation from the 1-benzyl analog 2h to 5h and 6h was also achieved. These results further demonstrated the substantial potential of the one-pot synthesis strategy using mixtures of 1-catalyzed CO_2 reduction products.

Conclusions

We have developed new deoxygenative dual CO_2 conversions in which CO_2 molecules were converted into different groups, methylene and N-formyl/N-methyl groups. Phenylsilane and a pentanuclear Zn complex acted as a highly efficient reductant and catalyst, respectively, and the reactions proceeded at atmospheric pressure without rare and harmful metals and solvents. The chemoselectivity of N-functionalization was switched by modifying only the amount of phenylsilane. These new CO_2 conversions will contribute greatly to the further development of CO_2 fixation.

Author contributions

K. T. and T. E. conceived the project. H. M. and K. I. synthesized and characterized the compounds. K. T. conducted the DFT calculations. K. T. and T. E. wrote the initial draft of the manuscript, and all authors discussed the results and commented on the manuscript.

Data availability

The data supporting the findings of this study are available in the ESI. \dagger

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by the Takahashi Industrial and Economic Research Foundation, the Yakumo Foundation for Environmental Science, and a Grant for the Promotion of Science and Technology in Okayama Prefecture by MEXT. We thank Dr Shigeki Mori (Ehime University) for the X-ray analyses. The computations were performed using RCCS, Okazaki, Japan (project: 24-IMS-C097).

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