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Author(s)

Marina Oka, Daichi Katsube, Takeshi Tsuji, Hiroki Iida

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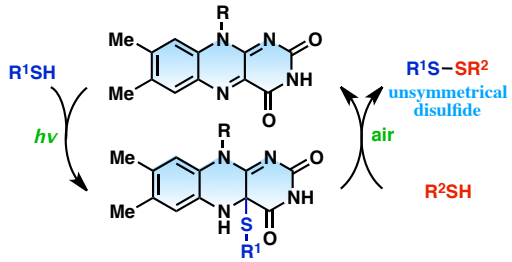
Phototropin-Inspired Chemoselective Synthesis of Unsymmetrical Disulfides: Aerobic Oxidative Heterocoupling of Thiols using Flavin Photocatalysis

Marina Oka, Daichi Katsube, Takeshi Tsuji, and Hiroki Iida*

Department of Chemistry, Graduate School of Natural Science and Technology, Shimane University, 1060 Nishikawatsu, Matsue, 690-8504 Japan

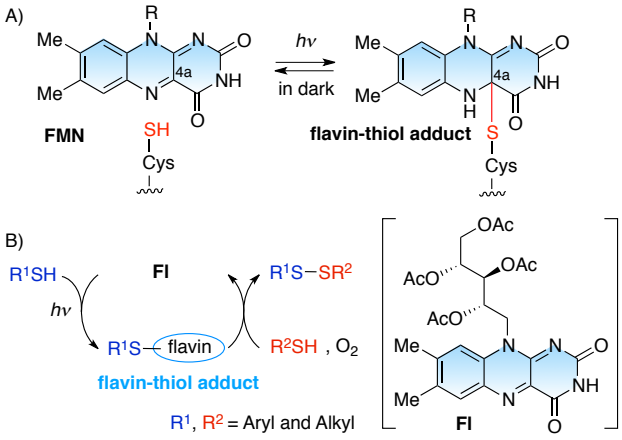


ABSTRACT: Inspired by the photochemical mechanism of a plant blue-light receptor, a unique flavin-based photocatalytic system was developed for the chemoselective heterocoupling of two different thiols, which enabled the facile synthesis of unsymmetrical disulfides. Owing to the redox- and photo-organocatalysis of flavin, the coupling reaction took place under mild metal-free conditions and visible light irradiation with the use of air, which is recognized as the ideal green oxidant.

Phototropin is a blue-light-sensitive photoreceptor that regulates the phototropic response of higher plants.[1] For example, the stem-bending of plants toward a light source is a phototropin-mediated process. Phototropin photoreceptors typically comprise two light-oxygen-voltage-sensing domains (LOV domains) which noncovalently bind a flavin mononucleotide (FMN) as the chromophore.[2] In response to blue light, the excited FMN reacts with the cysteine thiol group of a protein and thereby forms the flavin-thiol adduct between the C(4a) carbon of FMN cofactor and the protein (Scheme 1A).[3] The photoadduct thus formed, reverts to the initial form upon the change to the dark condition. While this photochemical process has attracted considerable interest in the field of biology and biochemistry until now, we anticipated that the visible-light-induced flavin-thiol adduct formation could be employed as an activated-intermediate in the organic synthesis of sulfur-containing compounds. Inspired by this biological photoreaction, we demonstrate herein, a novel green synthetic approach to unsymmetrical disulfides from two different thiols, in which, a riboflavin (vitamin B_2)-derived organocatalyst (**Fl**) promotes the chemoselective oxidative heterocoupling reaction of the thiols through flavin-thiol adduct formation using visible light irradiation in the presence of molecular oxygen (Scheme 1B). Recently, simple flavin molecules, including riboflavin and its derivatives, have received growing attention as unique redox organocatalysts that promote a variety of catalytic oxidations[4,5] and have also been applied to photocatalytic oxidations which cannot proceed thermally.[6,7] The use of flavin catalysis is recognized as an attractive approach for designing green and sustainable transformations. However, to the best of our knowledge, the flavin photocatalysis has not been applied to the synthesis of disulfides.[8]

Disulfides, containing two covalently linked sulfur atoms, are of importance in biological,[9] medicinal,[10] and materials chemistry.[11] While substantial efforts have been devoted to the synthesis of symmetrical disulfides (R^1S-SR^1), effective strategies for the synthesis of unsymmetrical disulfides (R^1S-SR^2) remain limited and very challenging despite their broad applications.[12] For example,

Scheme 1. (A) Photoreaction of LOV Domains and (B) Flavin-Catalyzed Heterocoupling of Thiols



unsymmetrical disulfides are extensively used in pharmaceuticals, as shown in Figure 1.[13] The direct oxidative heterocoupling of an almost equimolar amount of two different thiols is potentially the simplest and most atom-economical approach to access unsymmetrical disulfides and has hence been used as a promising strategy and a green and sustainable solution. However, this system suffers from inherent drawbacks, such as the competitive generation of two symmetrical disulfides, and the need for excess oxidants. Although there has been strong demand for the development of novel green chemoselective methods, successful examples that use metal catalysts or electrochemical equipment with Pt electrodes have scarcely been reported.[14] Moreover, these previous methods suffer from narrow substrate scope. For example, the chemoselective synthesis of an unsymmetrical alkyl-alkyl disulfide has never been reported apart from one recent example;[14c] hence, other approaches need to be developed.

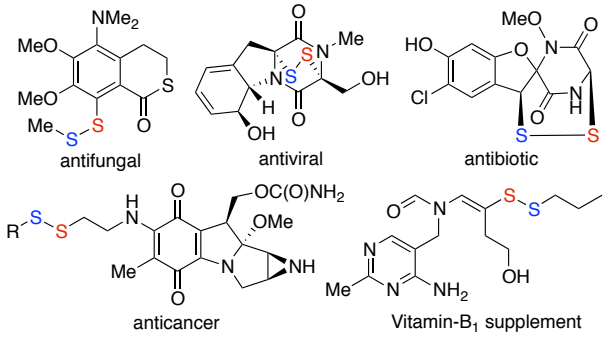
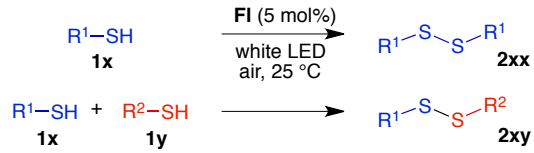
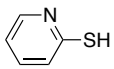
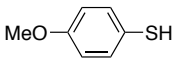


Figure 1. Pharmaceutically important unsymmetrical disulfides.

We first investigated the photocatalysis of the oxidative thiol homocoupling to the corresponding symmetrical disulfide with a readily available flavin compound. Using the tetraacetate of the commercially available riboflavin (**Fl**, 5 mol%) and white LEDs as the photocatalyst and light source, respectively, the reaction of a series of thiols (**1a-c**) was conducted under air (1 atm) at 25 °C for 2 h (entries 1-7, Scheme 2). We were pleased to find the successful conversion of 2-pyridinethiol (**1a**) to the corresponding symmetrical disulfide (**2aa**) in MeOH/H_2O (1:1, v/v) under the flavin-catalyzed aerobic photooxidation (entry 1). In contrast, aerobic oxidative coupling hardly takes place in the absence of **Fl**, without irradiation with LED light, or under N_2 (entries 2-4), which attests to the role of **Fl**-mediated photocatalysis and molecular oxygen. It is notable that this oxidative transformation occurs chemoselectively, and that overoxidizedbyproducts containing sulfide, sulfoxide, and pyridine-*N*-oxide moieties were not observed (entry 1). Although the coupling of the relatively electron-rich 4-methoxybenzenethiol (**1b**) gave a poor result (19% yield) in MeOH/H_2O (1:1, v/v), the corresponding disulfide (**2bb**) was obtained in 84% yield in a MeOH/H_2O/pyridine mixture (1:1:0.01, v/v), which suggested that a small amount of pyridine promotes the coupling reaction (entries 5 and 6). In contrast, probably due to the modest oxidative character of the flavin catalyst, tert-butanethiol (**1c**) hardly reacted in the present condition (entry 7).[15] With the expectation that this modest oxidizing ability of the flavin photocatalysis would have a positive influence on the chemoselective synthesis of unsymmetrical disulfides, we attempted the heterocoupling of the two thiols, **1a** and **1c**, in equimolar amounts. The corresponding unsymmetrical disulfide (**2ac**) was chemoselectively formed in 82% yield, while the symmetrical disulfides (**2aa** and **2cc**) were obtained insignificantly (2 and <1% yields, respectively) (entry 8).

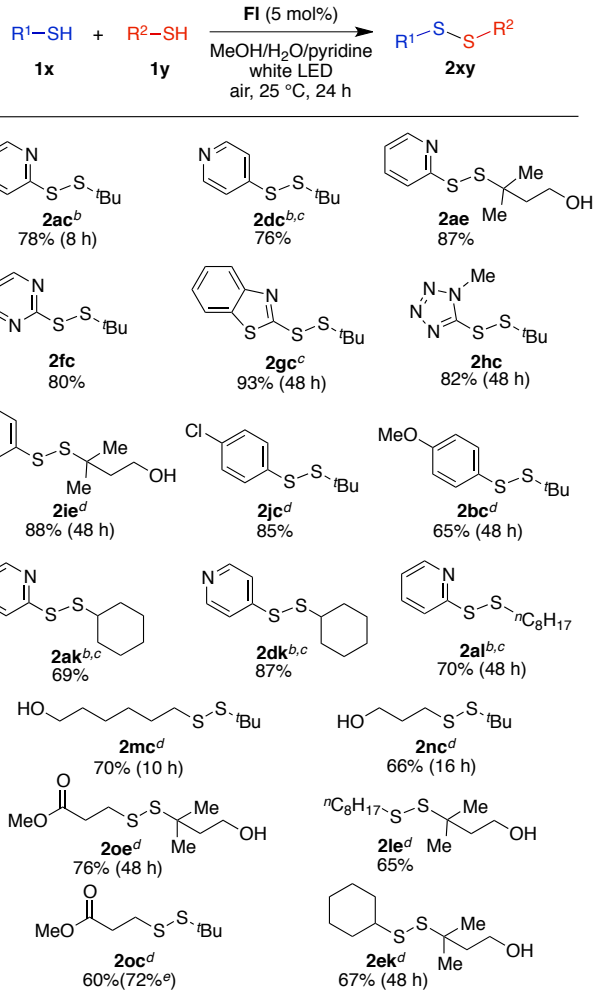
Scheme 2. Photocatalyzed Oxidative Homo- and Heterocoupling of Thiols[a]



Entry	R^1-SH	R^2-SH	Solvent	Time (h)	Product yield
1	 **1a**	–	MeOH:H_2O 1:1 (v/v)	2	**2aa** >99%
2[b]	**1a**	–	MeOH:H_2O 1:1 (v/v)	2	**2aa** 11%
3[c]	**1a**	–	MeOH:H_2O 1:1 (v/v)	2	**2aa** 2%
4[d]	**1a**	–	MeOH:H_2O 1:1 (v/v)	2	**2aa** 1%
5	 **1b**	–	MeOH:H_2O 1:1 (v/v)	2	**2bb** 19%
6	**1b**	–	MeOH:H_2O:pyridine 1:1:0.01 (v/v)	2	**2bb** 84%
7	^{t}Bu–SH **1c**	–	MeOH:H_2O:pyridine 1:1:0.01 (v/v)	2	**2cc** 15%
8[e]	**1a**	**1c**	MeOH:H_2O 1:1 (v/v)	6	**2ac** 82% (**2aa** 2% **2cc** <1%)

[a]Conditions: **1x** (0.05 M), **Fl** (5 mol%), and solvent, with white LED under air (1 atm) at 25 °C for 2 h. Yield was determined by GC. [b]Without **Fl**. [c]Without irradiation. [d]Under N_2. [e]Conditions: **1a** (0.05 M), **1c** (0.05 M), **Fl** (5 mol%), and solvent, with white LED under air (1 atm) at 25 °C for 6 h.

Scheme 3. Photocatalyzed Oxidative Heterocoupling of Thiols[a]



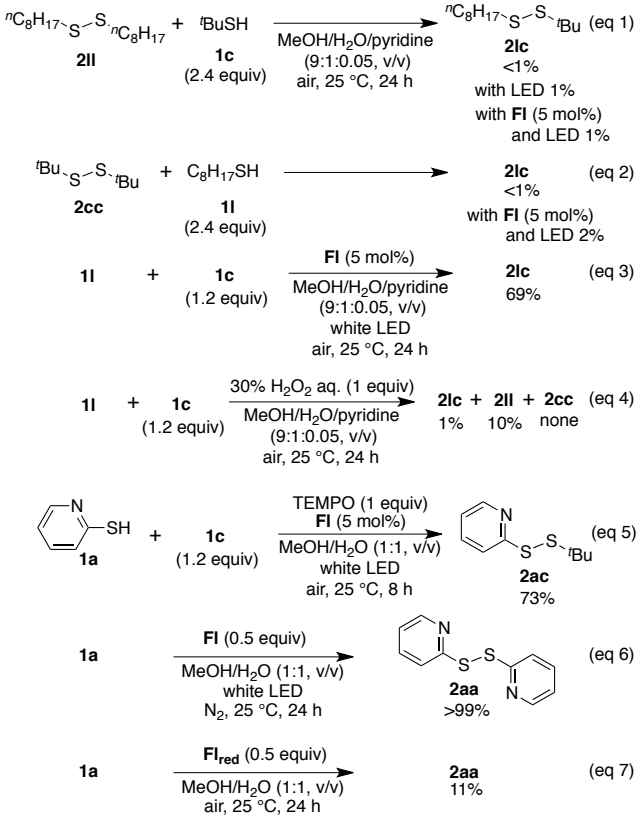
[a]Conditions: **1x** (0.05 M), **1y** (0.06 M), **Fl** (5 mol%), and MeOH/H_2O/pyridine (1:1:0.01, v/v) under air (1 atm) at 25 °C for 24 h. [b]Without pyridine. [c]MeOH/H_2O/pyridine (9:1:0.05, v/v). [d]Using **1x** (0.2 M), **1y** (0.24 M), and MeOH/H_2O/pyridine (9:1:0.05, v/v). [e]Yield was determined by GC.

Next, we investigated the scope and limitations of the heterocoupling reaction (Scheme 3). The reactions of diverse heteroarylthiols (**1a**,**d**,**f-h**) with tert-alkanethiols (**1c**,**e**) successfully furnished the corresponding unsymmetrical disulfides in 76–93% yields. The reactions of the arylthiols **1i**, **1j**, and **1b**, with **1c** and **1e** also gave the unsymmetrical disulfides in 65–88% yields, although the arylthiol bearing an electron-rich substituent (**1b**) exhibited a relatively low reactivity. Not only tert-alkanethiols but also secondary- and primary-alkanethiols (**1k**, **1l**) could be used as counterparts in this heterocoupling reaction, and delivered **2ak**, **2dk**, and **2al** in 69–87% yields. The substrate scope of the previously reported methods is mainly limited to the heterocoupling of aryl- and alkanethiols of different reactivities, which rendered the unsymmetrical alkyl-alkyl disulfide preparation challenging,[14] owing to the relatively similar reactivities of the two alkanethiols, which led to reduced chemoselectivity. In the light of such challenges, it is noteworthy that the present photocatalysis method allowed the heterocoupling of primary- and tertiary-alkanethiols to the corresponding unsymmetrical alkyl-alkyl disulfides (**2mc**,**nc**,**oe**,**le**, and **oc**), at ambient temperature and in 65-76% yields. The reaction of a secondary alkanethiol with a tertiary alkanethiol also successfully gave the heterocoupling product (**2ek**) in 67% yield. It is noteworthy that the green chemoselective heterocoupling of a secondary with a tertiary alkanethiol has never been achieved using previous methods.[14]

To gain insight into the reaction mechanism, control experiments were carried out (Scheme 4). The previously reported heterocoupling reactions of thiols proceed via the generation of the symmetrical disulfides R^1S-SR^1, that then participates in a thiol-disulfide exchange to generate the desired unsymmetrical disulfide R^1S-SR^2.[14] However, the reaction of symmetrical alkyl-alkyl disulfides **2ll** and **2cc** with alkanethiols **1c** and **1l**, respectively, did not yield the desired unsymmetrical alkyl-alkyl disulfide **2lc** (eqs 1 and 2) both in the absence or presence of **Fl**, which suggested that the alkyl-alkyl disulfides are not sufficiently reactive to promote the thiol-disulfide exchange reaction with the alkanethiol. However, our flavin-catalyzed system enabled the heterocoupling of **1l** and **1c**, to the desired unsymmetrical alkyl-alkyl disulfide **2lc** (eq 3). In sharp contrast, the homocoupling product **2ll** was preferentially obtained rather than the heterocoupling product **2lc** under the oxidative condition using H_2O_2 as an oxidant (eq 4). It is noteworthy that the yield of the heterocoupling product **2ac** did not decrease when the reaction of **1a** and **1c** was conducted in the presence of a radical inhibitor 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) as shown in eq 5 of Scheme 4. This result suggested that the present catalytic reaction does not proceed through the formation of thiyl radicals that are involved in the previous processes.[14] The use of **Fl** (0.5 equiv) under nitrogen promoted the quantitative coupling of **1a** to **2aa** (eq 6, Scheme 4).

Based on the experimental results and reported literature, we proposed a catalytic cycle for the present flavin-catalyzed system, as shown in Scheme 5A. The visible light excitation of **Fl** generates ^{3}**Fl*** via the intermediacy of ^{1}**Fl*** (step i), and the subsequent reaction of ^{3}**Fl*** with thiol forms **FlSR** (step ii), as observed for the LOV domain of phototropin.[3a, 16] Because the flavin unit of **FlSR** is a better leaving group in comparison with the sulfenyl group (**RS**-) of disulfide, a portion of **FlSR** undergoes nucleophilic substitution with the thiol, thus providing the disulfide and reduced flavin ($\mathbf{Fl_{red}}$, step iii). This is likely the reason for the successful formation of the unsymmetrical **2lc** in the present flavin-catalyzed system (eq 3), which was hardly promoted through the conventional thiol-disulfide exchange reaction (eqs 1 and 2). Given that **FlSR** can function similarly to the flavin-thiol adduct of LOV domain in vivo,[3a, 16] although **FlSR** rapidly eliminated thiol to give **Fl**, **FlSR** would be continuously generated from **Fl** through the reversibility of this process, and was always present in the reaction mixture in the

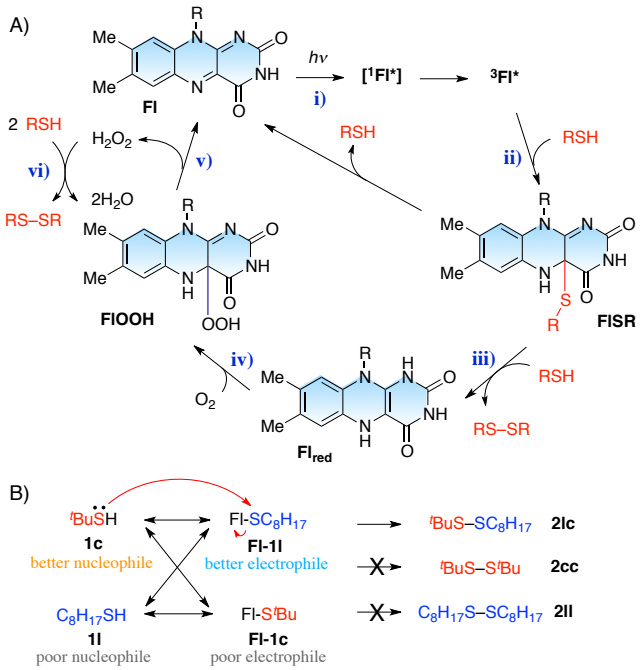
Scheme 4. Control Experiments



photostationary state; hence, it was possible to efficiently promote the following nucleophilic substitution with the thiol at **FlSR**. When the basic pyridine is used as a co-solvent, the nucleophilic substitution of thiol is probably enhanced (entries 5 and 6, Scheme 2). The obtained $\mathbf{Fl_{red}}$ is known to react with molecular oxygen and reverts to the initial **Fl** through the formation of the hydroperoxy intermediate (**FlOOH**) with the generation of H_2O_2 (steps iv and v).[18] Because **1a** was partially converted to **2aa** in the presence of $\mathbf{Fl_{red}}$ (0.5 equiv) under air without light irradiation (eq 7, Scheme 4), H_2O_2 generated by $\mathbf{Fl_{red}}$ and molecular oxygen may play a minor role in the formation of the disulfide (step vi). In the case of the heterocoupling, two different thiols such as **1c** and **1l** would afford the corresponding two flavin adducts (**Fl-1c** and **Fl-1l**), and could thus potentially yield three disulfides (**2lc**, **2cc**, and **2ll**) as shown in Scheme 5B. However, the gentle reactivity of the photo-induced **FlSR** enables chemoselective coupling in this system; the relatively electron-rich thiol **1c** with a better nucleophilicity preferentially reacts with the relatively electron-deficient flavin adduct **Fl-1l** with a better electrophilicity.

To confirm the catalytic intermediate in this system, we studied the reaction of **1l** in the presence of **Fl** under a nitrogen atmosphere with nanosecond laser flash spectroscopy, as shown in Figure 2. Interestingly, the changes in the spectral characteristics were almost identical to those observed for the LOV domain of phototropin.[3a,16] The laser pulse excitation resulted in a decrease of the characteristic absorption bands of **Fl** at around 360 and 450 nm (Supporting Information, Figure S1) and the appearance of new species with absorptions in the 600–700 nm region are attributed to the triplet state of the flavin chromophore (^{3}**Fl***) within 20 ns (Figure 2a). The triplet state decayed within 10 μs to leave the metastable intermediate state behind (Figure 2b). The metastable intermediate state is possibly attributable to the flavin-thiol adduct (**FlSR**), which

Scheme 5. (A) Proposed Catalytic Cycle and (B) Mechanism of Flavin-Thiol Adduct Mediated Heterocoupling Reaction



absorbs at 390 nm;[3a,16] however, we cannot rule out the possibility that the 4a-methoxy and 4a-hydroxy flavins (**FlOMe** and **FlOH**), whose absorptions are expected to be almost identical to that of **FlSR**, were generated in the MeOH/H_2O solution, due to poor nanosecond laser flash spectroscopy resolution. After 10 s, the metastable intermediate reverted to the original ground state (**Fl**) under these dilute conditions (Figure 2c), which may be due to the elimination of thiol, MeOH, or H_2O from its adduct (**FlSR**, **FlOMe**, or **FlOH**). These results show that this photo-triggered process, which involves the formation of ^{3}**Fl***, is reversible.

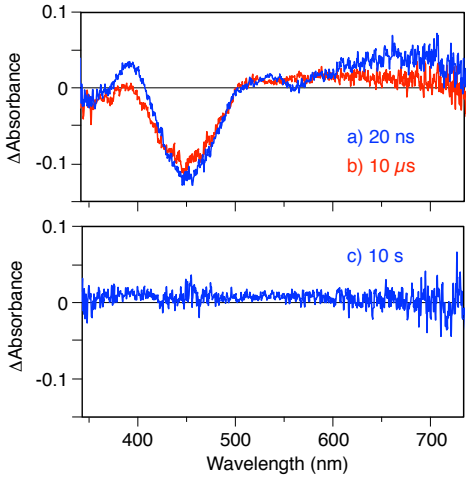


Figure 2. Difference absorption spectra of **Fl** (0.12 mM) in MeOH/H_2O/pyridine (9:1:0.05, v/v) in the presence of **1l** (13 mM) under nitrogen atmosphere collected after excitation with a 355 nm laser pulse. Spectra were collected at 20 ns (a), 10 μs (b), and 10 s (c).

In summary, we have developed a novel strategy for the chemoselective synthesis of unsymmetrical disulfides using the oxidative heterocoupling reaction of two different thiols. Upon visible light irradiation, the commercially available riboflavin-based catalyst successfully promoted the formation of the phototropin-like flavin-thiol adduct, the mild reactivity of which played a crucial role in the chemoselective cross-coupling. Due to the photo- and redox-organocatalysis of flavin, this green oxidative transformation is driven by visible light and molecular oxygen under mild metal-free conditions. Although there are some limitations of the efficiency and substrate scope at this stage, the present system comprising photo-induced thiol-flavin adducts will provide new paradigms for catalytic organic synthesis of sulfur-containing compounds. Further studies using this strategy are currently underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, compound characterization data, additional figure and table, NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

Hiroki Iida – E-mail: iida@riko.shimane-u.ac.jp

Notes

The authors declare no competing financial interest.

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