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Communication

A Self-Catalyzed Visible Light Driven Thiol Ligation

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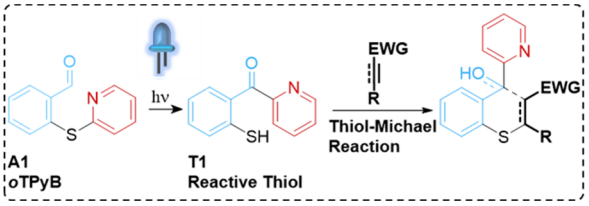
ABSTRACT: We introduce a highly efficient ligation system based on a visible light-induced rearrangement affording a thiophenol which rapidly undergoes thiol-Michael additions. Unlike conventional light-triggered thiol−ene/yne systems, which rely on the use of photocaged bases/nucleophiles, (organo)-photo catalysts, or radical photoinitiators, our system provides a light-induced reaction in the absence of any additives. The ligation is self-catalyzed *via* the pyridine mediated deprotonation of the photochemically generated thiophenol. Subsequently, the thiol-Michael reaction between the thiophenol anion and electron deficient alkynes/alkenes proceeds additive-free. Hereby, the underlying photoinduced rearrangement of *o*-thiopyrinidylbenzaldehyde (*o*TPyB) generating the free thiol is described for the first time. We studied the influence of various reactions conditions as well as solvents and substrates. We exemplify our findings in a polymer end group modification and obtained macromolecules with excellent end group fidelity.

Highly efficient, catalyst free chemical processes that proceed under mild conditions, tolerate various solvents and functional groups, and have a broad substrate scope are in high demand in modern chemistry.[1,2] Reactions featuring such properties were categorized as click reactions in 2001 by Sharpless[3] and have been widely applied in chemical biology[4,5] and material science.[6,7] Reactions that adhere to the click paradigm, besides the popular CuAAC reaction,[8] include metal-free dipolar cycloadditions, *e.g.*, the strain-promoted azide−alkyne cycloaddition,[9,10] Diels−Alder reactions,[11] and a series of thiol-based reactions such as thiol−ene/yne or thiol−isocyanate additions.[12] Within the toolbox of click chemistry, thiol−ene/yne reactions are highly selective, exhibit high reaction rates and are therefore often utilized in surface functionalization,[13] polymer network synthesis,[14,15] material synthesis,[16] and the modification of biomolecules.[17] Generally, they proceed *via* one of two mechanisms: (1) free-radical addition or (2) base- or nucleophile-catalyzed Michael addition.

In recent years, the use of light to gain spatial and temporal control of these reactions has been intensively studied.[18] Light enabled reactions are critical in applications such as 3D laser lithography, photopatterning, and adhesives.[19,20] In a light triggered thiol−ene/yne process, the required thiol,[21] alkyne,[22] or base[23,24] can be caged with a photolabile group and activated on demand. Caging the thiol moiety prevents its aerobic oxidation to the disulfide and therefore increases, for example, its versatility in biomaterial engineering.[25] Similar, the utilization of a photocaged base, such as diazabicycloundecene (DBU) to catalyze a ring-opening thiol−ene reaction, was introduced by Yeo *et al.* for micropatterning.[13,26] Unfortunately, photo protective groups (PPG) often release potentially toxic and reactive fragments, for instance in the case of the *o*-nitrobenzyl PPG.[27] In addition, light-triggered thiol−ene/yne reactions mainly rely on the use of organo-photo catalysts[28] or radical photo initiators,[29] potentially causing side reactions.[30]

A light-induced intramolecular rearrangement, which unmasks a reactive moiety upon rearrangement, is a potential strategy to circumvent the aforementioned disadvantages, however, such reactions have rarely been employed in photoligations.[31,32] Herein, we introduce the visible light-induced rearrangement of *o*-thiopyrinidylbenzaldehyde (*o*TPyB, **A1**), quantitatively yielding a reactive thiol which subsequently undergoes a self-catalyzed additive-free thiol-Michael addition (Scheme 1).

Scheme 1. Reaction Overview[a]



[a]Irreversible light-induced rearrangement of *o*TPyB to form a reactive aromatic thiol, undergoing a thiol-Michael reaction with electron deficient alkynes/alkenes. EWG: electron-withdrawing group.

Unlike common PPGs such as BODIPY, coumarine, and bimane, which require time-consuming synthetic procedures,[33] *o*TPyB can be prepared in a one-step procedure *via* nucleophilic substitution of *o*-fluorobenzaldehyde with 2-mercaptopyridine in very good yields (81%, **A1**, Supporting Information (SI), section 2.1).[34] *o*TPyB has a maximum

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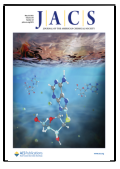

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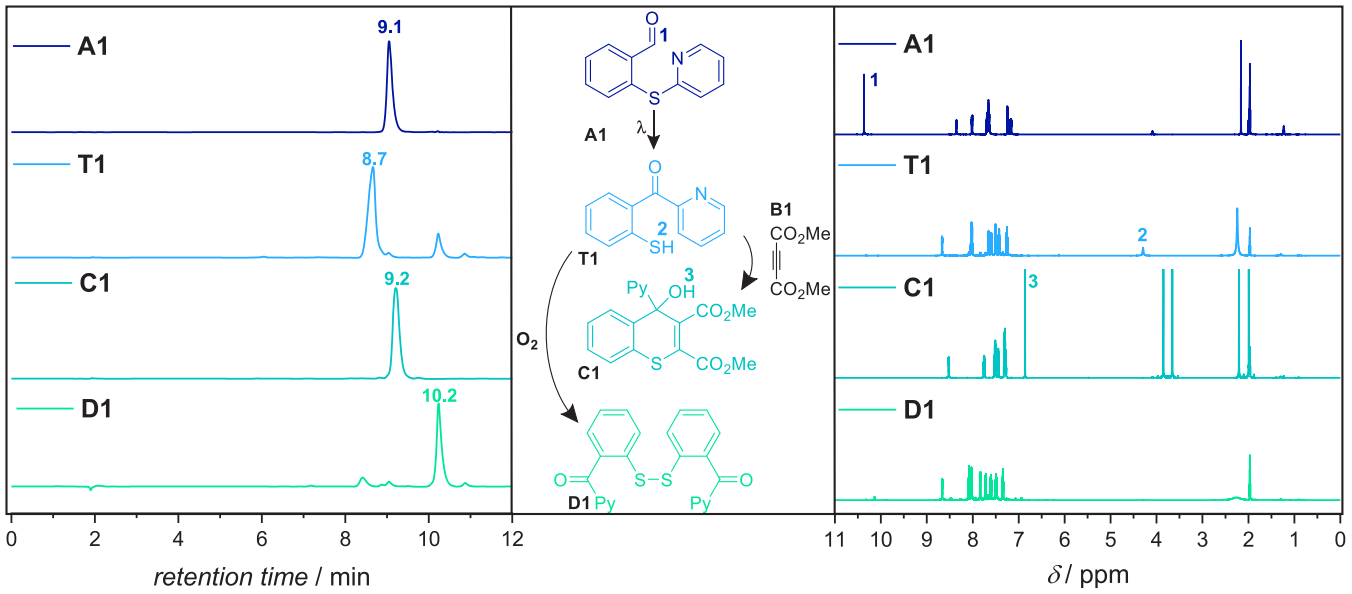

Figure 1. (left) LC-MS chromatograms and (right) ^{1}H NMR spectra of the light-induced rearrangement of *o*TPyB **A1** resulting in the stable, yet reactive intermediate **T1** and subsequent Michael addition with DMAD **B1** to form the ligation product **C1** are shown. Under nondeoxygenated conditions, intermediate **T1** forms disulfide **D1**. Depicted are the purified **A1** and the ring closed isomer $\mathbf{C}_{ring}\mathbf{1}$ (refer to Scheme 2), the spectra of **T1** and **D1** were recorded without further purification. Py = pyridine.

Table 1. Solvent Screening[a]

no.	solvent	B1	coreagent	*t* [min]	λ_{max} [nm]	Y^D_{LCMS} [%]	Y^D_{NMR} [%]
1	ACN	start		5	385	97.6	96.3
2	ACN	start		60	415	99.0	97.1
3	ACN	start	DTT	5	385	85.9	84.6
4	ACN	end		5	385	93.7	93.3
5	H_2O:ACN 1:1	start		10	385	90.6	89.5
6	toluene	start		5	385	93.0	93.1
7	MeOH	start		10	385	98.4	95.7
8	DMSO	start		10	385	81.5	81.0
9	DCM	start		5	385	98.6	97.4

[a]Photoligation reaction of *o*TPyB **A1** (25 mmol L^{-1}, 1.00 equiv) and alkyne **B1** (26.25 mmol L^{-1}, 1.05 equiv), addition of **B1**, irradiation time (*t*), irradiation wavelength λ_{max}, Y^D_{LCMS} yield determined *via* LC-MS, Y^D_{NMR} yield determined *via* ^{1}H-NMR. DTT= dithiothreitol, reductant.

absorbance at 360 nm tailing into the visible range, hence permitting activation with either UV (385 nm) and visible (415 nm) light. We first irradiated *o*TPyB (**A1**, 1.00 equiv, 25 mmol L^{-1}) with a 385 nm LED for 5 min in deoxygenated deuterated acetonitrile (ACN-d_3). The formation of the free thiol intermediate **T1** was monitored *via* LC-MS and ^{1}H NMR spectroscopy (Figure 1). When an electron-deficient alkyne, namely acetylenedicarboxylic acid dimethylester (DMAD, **B1**, 1.05 equiv, 26.25 mmol L^{-1}) was added to the reaction mixture, the rapid formation of thiol-Michael addition product **C1** was observed. The chemical structure of **C** and its isomers were intensively elucidated using ^{1}H-, ^{13}C-, 2D-NMR techniques, single-crystal X-ray diffraction and LC-MS (Schemes 2 and 3; SI, Figures S14–S34, S50, S54–S62, and S80). The ^{1}H/^{13}C HMBC spectrum of **C1** shows the key correlation of the hydroxyl proton with a pyridine carbon, the newly formed double-bond carbon and the phenyl carbon (SI, Figure S16), confirming the structure of **C1**. Inspection of the LC-MS chromatogram of **T1** (Figure 1) reveals partial formation of the disulfide product **D1** (retention time = 10.2 min), which is caused by oxygen exposure during the sample preparation.

The influence of the reaction conditions including solvent and irradiation wavelength was investigated next using *o*TPyB **A1** and the symmetric substrate **B1** (Table 1). For each table entry, the yield and purity of the Michael adduct was determined by LC-MS analysis of the crude reaction and by ^{1}H NMR spectroscopy using DMF as an internal standard (SI, Figures S41–S50 and S63–S72). Initially, ACN was used as the solvent to test various reaction protocols (entries 1–4). Irradiation with UV light (385 nm) or visible light (415 nm) appears to have no significant influence on the reaction outcome (both yields >95%). At 415 nm, a longer irradiation time was required to reach full conversion of **A1**, most likely due to the lower molar extinction coefficient at 415 nm (SI, Figure S78).

To minimize formation of disulfide **D1**, dithiothreitol (DTT) was added as a reducing agent (entry 3, Table 1), however, this led to a lowered yield, probably due to the competing heterodisulfide formation between the newly released thiol **T1** and DTT. Therefore, DTT appears not to benefit the reaction outcome. To investigate whether the rearrangement is affected by the presence of alkyne **B1** and to assess the stability of the thiol intermediate **T1**, *o*TPyB **A1** was irradiated for 5 min, followed by the addition of **B1** in the dark (entry 4, Table 1). LC-MS and ^{1}H NMR data (SI, Figures S14–S16 and S54) indicate **C1** is obtained, confirming the light-induced rearrangement is independent of the subsequent thiol-Michael reaction. Additionally, in entries 5–9 (Table 1), a range of polar and nonpolar solvents was investigated and good (81%, DMSO) to excellent yields (>90% for all other solvents) were obtained. Furthermore, the concentration dependence was investigated, revealing that the optimal substrate concentration of **A1** is 5–100 mmol L^{-1}, while at low concentrations (0.1–5 mmol L^{-1}), residual oxygen leads

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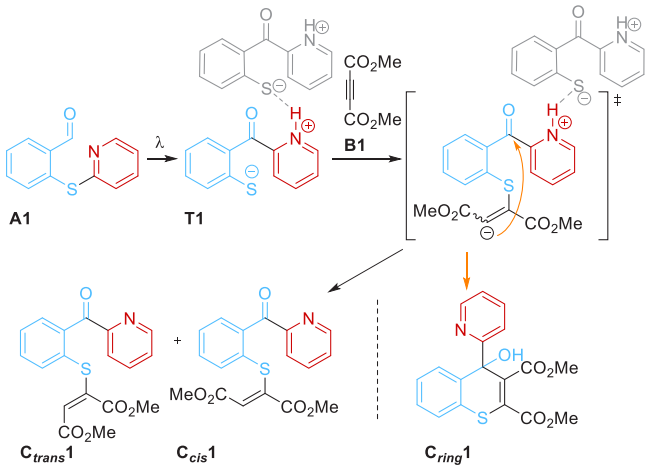
Scheme 2. Mechanism and Isomers[a]



[a]Mechanism of the self-catalyzed thiol-Michael addition. Possible isomers resulting from the reaction of the free thiol **T1** and DMAD **B1**. C_{ring}**1** depicts the structural isomer formed upon ring closure while C_{cis}**1** and C_{trans}**1** represent the *cis* and *trans* stereoisomers, respectively.

to side reactions (SI, Figure S73). The mechanism of the light-induced irreversible rearrangement of *o*TPyB relies on the formation of a new carbon−carbon bond between the original aldehyde carbon and the pyridine ring. Zeng and co-workers proposed a Minisci-type radical mechanism for the rearrangement in a similar system based on *ortho*-heteroaryloxybenzaldehydes.[35] In contrast to our system, their rearrangement product is a phenol with both lower basicity and lower nucleophilicity, hampering consecutive reactions. We hypothesize that the herein reported thiol-Michael addition is self-catalyzed by the pyridine moiety deprotonating the photochemically generated thiophenol (Scheme 2). The newly formed thiolate subsequently reacts highly efficiently with electron deficient alkenes or alkynes.

In a thiol-Michael addition the thiol anion typically attacks the electron deficient double/triple bond in the β-position, generating a carbon-centered resonance-stabilized carbanion in α-position (Scheme 2). This intermediate is planar, prochiral, and can be attacked by an electrophile from two trajectories,

Table 2. Substrate Screening[a]

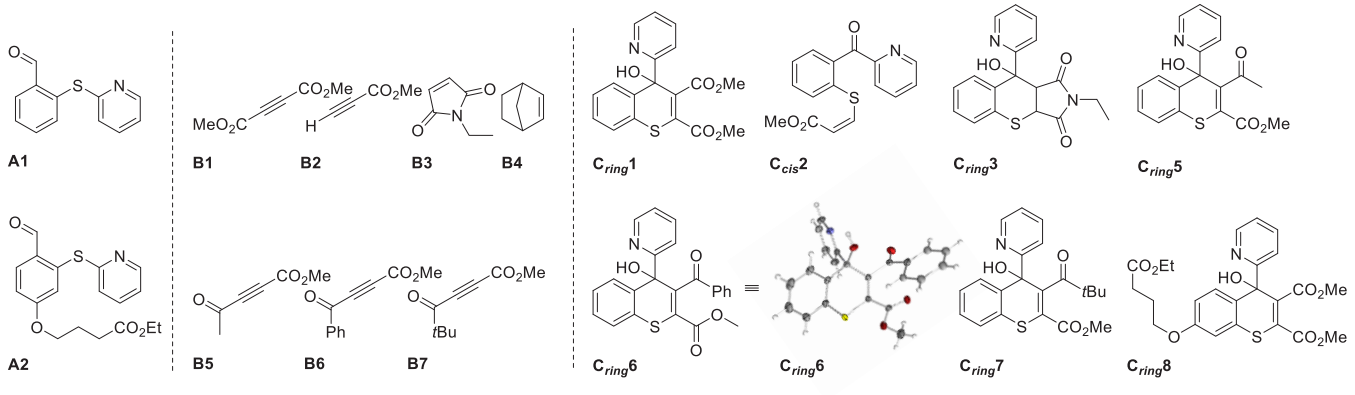
no.	*o*TPyB	alkyne/ alkene	*t* [min]	λ_{max} [nm]	$C_{cis}/C_{trans}/C_{ring}$	Y^D [%]
1	**A1**	**B1**	15	385	16:23:61	98.2[b]
2	**A1**	**B1**	60	415	28:38:34	90.6[b]
3	**A1**	**B2**	15	385	82:18:0	94.5[b]
4	**A1**	**B3**	15	385	0:12:88	91.1[b]
5	**A1**	**B4**	15	385		0
6	**A1**	**B5**	15	385	37:11:52	94.8[b]
7	**A1**	**B6**	15	385	0:0:100	96.6
8	**A1**	**B7**	15	385	0:0:100	94.9
9	**A2**	**B1**	20	385	21:24:55	89.7[b]

[a]Batch photoligation experiments in ACN (refer to substrates depicted in Scheme 3) using *o*TPyB **A1**, **A2** (5 mmol L^{-1}, 1.00 equiv), and alkynes/alkenes **B1**−**B7** (5.25 mmol L^{-1}, 1.05 equiv), irradiation time (*t*), irradiation wavelength λ_{max}, Y^D isolated yield. $C_{cis}/C_{trans}/C_{ring}$ ratio of the three isomers (refer to Scheme 2). [b]Combined yield of all isomers.

e.g., both diastereotopic sides to form C_{cis} and C_{trans} isomers. However, because of the presence of an electrophilic carbonyl group, the nucleophilic attack of the carbon centered anion affords a third ring-closed isomer C_{ring}. To highlight the broad substrate scope of our system, two different *o*TPyBs, **A1** and **A2**, were reacted with a variety of alkenes/alkynes **B1**−**B7** (Scheme 3, SI, section 2.2).[36] *o*TPyB **A2** offers a functional handle after hydrolysis to the respective carboxylic acid (SI, Figures S10−S11), suitable for linking payload molecules and therefore unlocks a variety of future applications. The experiments summarized in Table 2 were conducted in a batch reactor (SI, Figure S1), and the respective products were purified *via* HPLC to give the isolated yield (Table 2, SI, Figures S14−S40).

Entries 1 and 2 of Table 2 compare the ligation reaction of **A1** and **B1** at different wavelengths. The excellent yields (both >90%) indicate that the reaction is very efficient, not only in the UV-regime but also under visible light, similar to the results of the screening experiments (Table 1, entries 1 and 2). Additionally, **B1** was used as a model reaction partner for the linker **A2** (entry 9) presenting comparable results to **A1**, confirming that the functional handle does not undermine the rearrangement. When using **B1** or **B5** as the reaction partner

Scheme 3. Overview of the Substrates and Major Isomers Obtained in the Experiments Summarized in Table 2[a]



[a]Overview of the *o*TPyB **A1**, **A2**, and the alkynes/alkenes **B1**−**B7** used in the batch reactions. Main isomers of the isolated and characterized photoligation products **C1**−**8** are depicted. The asymmetric unit of the triclinic crystal structure (ellipsoids with 50% probability) of C_{ring}**6** is presented.

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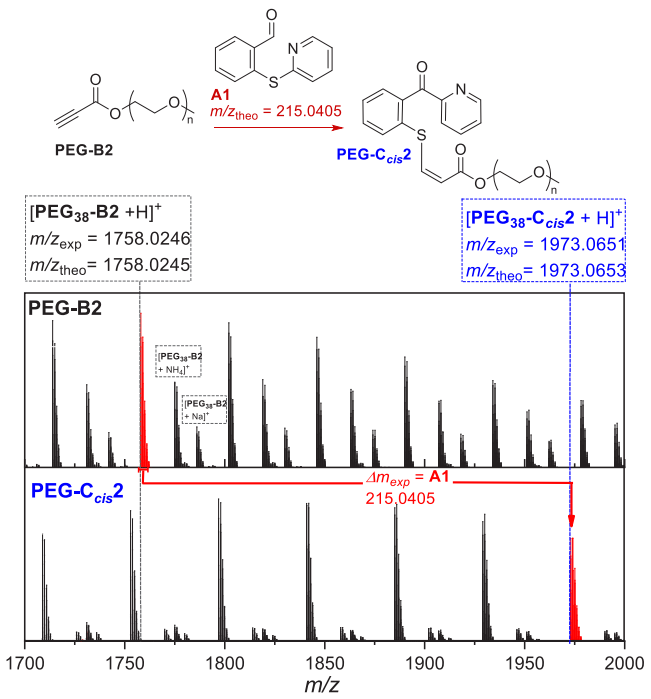

Figure 2. Polymer end group modification of **PEG-B2** (25 mmol L^{-1}, 1.00 equiv) with **A1** (30 mmol L^{-1}, 1.20 equiv) at 385 nm for 10 min, yielding **PEG-C_{cis}2**. SEC-MS spectra of **PEG-B2** and **PEG-C_{cis}2** are compared as well as the experimental and theoretical m/z values.

(entries 1, 2, 6, 9), with either *o*TPyB **A1** or **A2**, the results indicate that the $C_{cis}/C_{trans}/C_{ring}$ ratio averages between 10 and 60% each, with no clear trend evident. This is presumably due to the symmetric nature of **B1** and relatively small functional groups of both **B1** and **B5**. Interestingly, an obviously different result was observed when using the alkynes **B6** and **B7** (entries 7 and 8), where the $C_{cis}/C_{trans}/C_{ring}$ ratio is 0/0/100. We speculate that alkynes with sterically demanding substituents such as phenyl (**B6**) or *tert*-butyl (**B7**) exclusively yield the ring closed isomer. Additionally, the presence of functional groups stabilizing the carbon-centered anion in the α-position (Scheme 2) are decisive for the intramolecular nucleophilic attack, forming C_{ring}. Therefore, in the reaction between **A1** and the terminal alkyne **B2** (entry 3), no ring closure was observed. If the alkyne/alkene has no electron withdrawing groups, *e.g.*, norbornene **B4**, the thiol-Michael addition does not occur (entry 5), further confirming the addition proceeds *via* an ionic and not a radical mechanism.

The translation from small-molecule reactions to polymer modifications can be challenging and requires quantitative yields and high selectivity due to emerging difficulties associated with purification.[37,38] Therefore, the applicability of our ligation system in polymeric materials was investigated using alkyne end group containing polyethylene glycol **PEG-B2**.[39] The respective acid of the terminal alkyne **B2** was used for the end group modification because it is commercially available, stable, and can be easily tethered to the polyethylene glycol *via* a simple esterification. The ligation of **PEG-B2** and **A1** was monitored *via* size exclusive chromatography mass spectrometry (SEC-MS) and ^{1}H NMR (SI, Figures S81−S84). In Figure 2, the SEC-MS spectrum of **PEG-B2** and **PEG-C_{cis}2** are compared and the mass increase of **A1** after irradiation is representatively indicated in red, confirming the efficient polymer end group modification. Additionally, comparing the double-bond resonances in the ^{1}H NMR spectrum of **PEG-C2** with those of **C2** enables the assignments of the respective C_{cis}/C_{trans} isomers, confirming high clicking efficiency.

In conclusion, we pioneer an additive free light-induced thiol-Michael reaction. The highly efficient ligation system is based on a light-induced rearrangement of *o*-thiopyrinidyl-benzaldehyde (*o*TPyB) affords a free thiol moiety. The system self-catalyzes the deprotonation of the photochemically generated thiophenol and allows for a thiol-Michael addition under very mild conditions. We demonstrated that the ligation tolerates a range of solvents, can be triggered by both UV and visible light, and allows for a wide range of electron-deficient alkynes/alkenes. Additionally, a functional linker of *o*TPyB that contains a carboxylic acid as a handle to easily attach payload molecules was synthesized. Finally, the system was applied to efficiently functionalize polymer end groups. We believe our versatile self-catalyzed photochemical system will unlock a range of possibilities in biological applications and advanced material synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c03213.

Materials, instrumentation, synthetic procedures, supporting spectroscopic data (PDF)

Accession Codes

CCDC 2070910 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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