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Access to benzo[e][1,3]thiazin-4-ones *via* PCy_3-mediated annulations of benzo[c][1,2]dithiol-3-ones with iso(thio)cyanates

Chengxiang Yi,[a] Mingyang Zhu,[a] Jie Ren, *[b] Weimin Zhu,[a] Chuanjun Song *[a] and Yangang Wu *[a,c]

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Herein, we describe a novel organophosphine-mediated annulation reaction of benzo[c][1,2]dithiol-3-ones with iso(thio)cyanates, which proceeds *via* an S atom to C–N unit exchange strategy. The methodology efficiently produces a variety of benzo[c][1,2]dithiol-3-one derivatives in moderate to excellent yields under straightforward reaction conditions. Other salient features of this approach include transition-metal-free process, operational simplicity, gram-scale synthesis, and capacity for late-stage modifications. Additionally, control experiments were conducted to provide new insights into the conversion mechanism of benzo[c][1,2]dithiol-3-ones.

Sulfur-containing heterocyclic compounds have found a wide range of applications in the fields of synthetic chemistry, materials science, agrochemicals, and pharmaceuticals.[1] Within this privileged chemical space, benzo[*e*][1,3]thiazin-4-ones have emerged as a particularly important class of compounds in drug discovery due to their diverse biological and pharmacological properties,[2] especially with anti-HIV,[2a] antitumor,[2b] antimicrobial,[2c] and antimalarial activities[2d] (Fig. 1). Owing to their challenging frameworks and appealing properties, considerable efforts have been devoted to developing efficient strategies for constructing such valuable molecules.

Previous methods for the preparation of benzo[*e*][1,3]thiazin-4-one compounds include directed lithiation of benzamides followed by sequential treatment with sulfur and phosgene (Scheme 1a),[3] or transition-metal-catalyzed annulation of cyclic thiourea and methyl 2-iodobenzoate,[4] and related approaches.[5] However, most of the methods suffered from the limited substrate scope, tedious synthetic procedures, harsh reaction conditions, or reliance on transition metal catalysts. In recent years, several alternative routes have been developed. For example, in 2019, the Liu group reported a Cu-catalyzed domino reaction involving aryl C–I thiolation and subsequent N,S-heterocycle formation to access 2,3-dihydro-4*H*-benzo[*e*][1,3]thiazin-4-ones (Scheme 1b).[6] Subsequently, Ge *et al.*[7] and Sun *et al.*[8] individually disclosed Selectfluor-promoted intramolecular α-C–H bond functionalization of the alkylthio group for the synthesis of benzo[*e*][1,3]thiazin-4-one derivatives in the presence of HI/NaI or Ag_2O (Scheme 1c). Very recently, Song *et al.*[9] and Zhou *et al.*[10] reported the synthesis of 2,3-dihydrobenzothiazin-4-one skeletons *via* PPh_3-catalyzed cyclization of benzo[*c*][1,2]dithiol-3-ones (Scheme 1d). Despite the great progress, efficient methods for synthesizing these compounds remain to be further developed. Consequently, new synthetic approaches need to be developed.

As bench-stable and valuable structural moieties, benzo[*c*][1,2]dithiol-3-ones are widely employed in synthetic chemistry,[11] particularly for constructing sulfur-containing compounds.[9,10,11e,f,g] Inspired by the prior literature, we herein

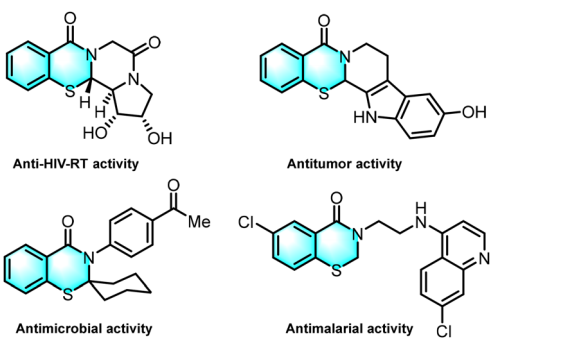
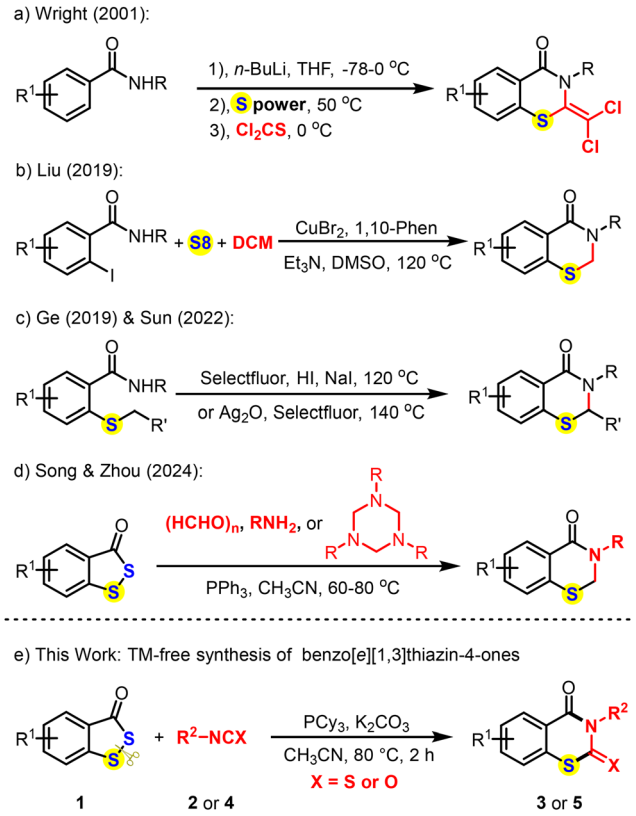


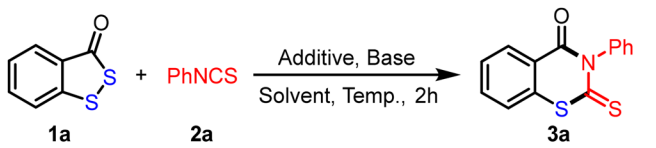
Fig. 1 Representative bioactive molecules containing the benzo[*e*][1,3]thiazin-4-one scaffold.

[a]*College of Chemistry, Pingyuan Laboratory, Zhengzhou University, No. 100 of Science Road, Henan, Zhengzhou, 450001, P. R. China. E-mail: chjsong@zzu.edu.cn, ygwu@zzu.edu.cn*
[b]*Henan International Joint Research Laboratory for Utilization of Plant Functional Components, School of Tobacco Science and Engineering, Zhengzhou University of Light Industry, No. 136 of Science Road, Henan, Zhengzhou 450002, P. R. China. E-mail: renj@zzuli.edu.cn*
[c]*School of Pharmaceutical Sciences, Zhengzhou University, No. 100 of Science Road, Henan, Zhengzhou 450001, P. R. China*



Scheme 1 Strategies to construct benzo[e][1,3]thiazin-4-ones.

Table 1 Optimization of the reaction conditions[a]



Entry	Additive	Base	Solvent	T (°C)	Yield of **3a**[b] (%)
1	PPh_3	K_2CO_3	CH_3CN	80	42
2	DPPE	K_2CO_3	CH_3CN	80	81
3	**PCy_3**	**K_2CO_3**	**CH_3CN**	**80**	**89 (87)**[c]
4[d]	TTBP	K_2CO_3	CH_3CN	80	0
5[d]	DPEPhos	K_2CO_3	CH_3CN	80	0
6[d]	—	K_2CO_3	CH_3CN	80	0
7	PCy_3	—	CH_3CN	80	29
8	PCy_3	Na_2CO_3	CH_3CN	80	65
9	PCy_3	Cs_2CO_3	CH_3CN	80	31
10	PCy_3	Li_2CO_3	CH_3CN	80	38
11	PCy_3	K_3PO_4	CH_3CN	80	51
12	PCy_3	NaOH	CH_3CN	80	42
13	PCy_3	DBU	CH_3CN	80	55
14	PCy_3	K_2CO_3	EA	80	53
15	PCy_3	K_2CO_3	DMF	80	63
16	PCy_3	K_2CO_3	1,4-Dioxane	80	67
17	PCy_3	K_2CO_3	DCE	80	35
18	PCy_3	K_2CO_3	DMSO	80	20
19[e]	PCy_3	K_2CO_3	CH_3CN	rt	Trace
20	PCy_3	K_2CO_3	CH_3CN	60	82

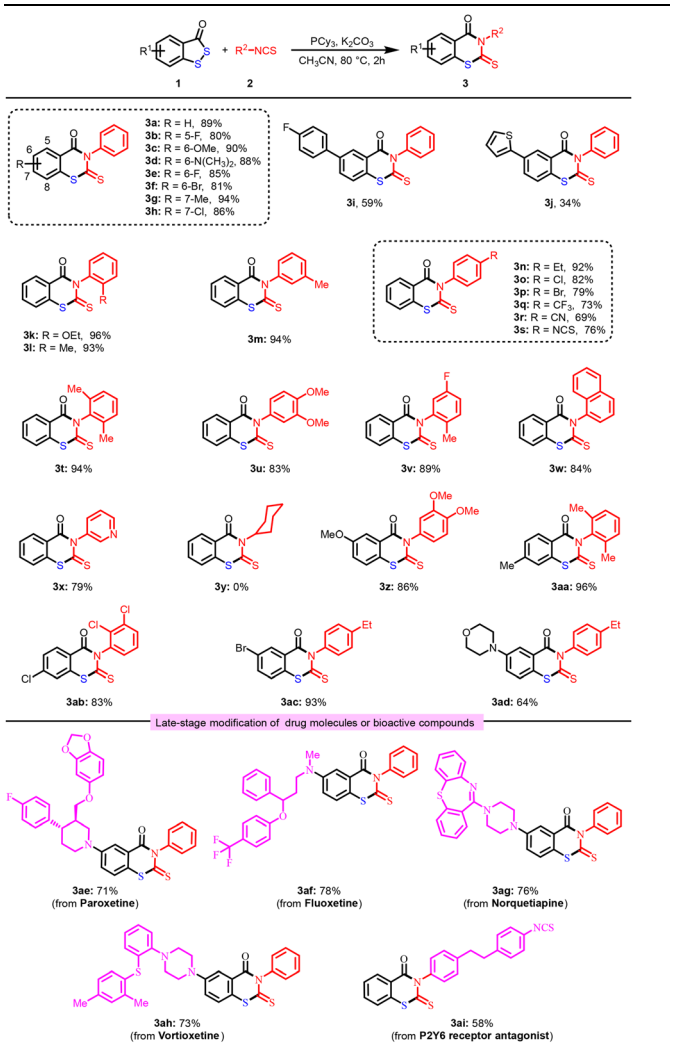
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), additive (0.3 mmol), base (0.3 mmol) and solvent (2 mL) at 80 °C for 2 h. [b] Isolated yield. [c] Yield of a gram-scale (10 mmol) reaction in parentheses. [d] No reaction. [e] Reaction gave only trace conversion.

report a cascade S–S bond cleavage/[4 + 2] cycloaddition strategy that efficiently constructs diverse benzo[*e*][1,3]thiazin-4-one derivatives from readily accessible starting materials (Scheme 1e). By applying this method to known drug molecules, we prepared several benzo[*e*][1,3]thiazin-4-one-based drug candidates.

We commenced our investigation with the reaction between benzo[*c*][1,2]dithiol-3-one (**1a**) and isothiocyanatobenzene (**2a**), and then performed extensive screening of conditions, including the additives, bases, solvents, *etc.* (Table 1). Initially, **1a** (0.2 mmol) and **2a** (0.4 mmol) were treated with PPh_3 (0.3 mmol), K_2CO_3 (0.3 mmol) and CH_3CN (2 mL) at 110 °C for 2 h, affording the desired 2-thioxo-benzo[*e*][1,3]thiazin-4-one (**3a**) in 42% yield (entry 1). Encouraged by this result, other phosphine-based additives, including 1,2-bis(diphenylphosphino)ethane (DPPE), tricyclohexylphosphine (PCy_3), tri-*tert*-butylphosphine (TTBP) and bis[2-(diphenylphosphino) phenyl] ether (DPEPhos), were screened (entries 3–5). Among these, PCy_3 exhibited the highest catalytic efficiency, affording **3a** in the highest yield (entry 3). No product formation occurred in the absence of a catalyst, confirming the necessity of the phosphine additive (entry 6). A remarkable decrease in yield was observed when the reaction was conducted in the absence of a base, revealing the acceleration effect of a base (entry 7). Subsequent screening of basic reagents demonstrated that K_2CO_3 was superior to others, such as Na_2CO_3, Cs_2CO_3, Li_2CO_3, K_3PO_4, NaOH and 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) (entry 3 *vs.* entries 8–13). Next, various solvents, such as ethyl acetate (EA), 1,4-dioxane, *N*,*N*-dimethylformamide (DMF), 1,2-dichloroethane (DCE) and dimethyl sulfoxide (DMSO), were screened. EA, DMF and 1,4-dioxane afforded moderate yields, whereas DCE and DMSO resulted in relatively poor yields (entries 14–18). The reaction failed to proceed at room temperature (entry 19) and showed reduced efficiency at 60 °C (entry 20). In particular, a 10 mmol-scale reaction of benzo[*c*][1,2]dithiol-3-one **1a** with isothiocyanatobenzene **2a** was conducted, and product **3aa** could be formed in 87% yield (entry 3).

Having established the optimal reaction conditions, we evaluated the generality of this cyclization using diverse benzo [*c*][1,2]dithiol-3-ones **1** and isothiocyanates **2** (Table 2). For benzo[*c*][1,2]dithiol-3-ones, a series of electron-donating (*e.g.*, OMe, NMe_2 and Me) and electron-withdrawing groups (*e.g.*, F, Cl, and Br) on the phenyl ring were tolerated under the standard conditions, delivering the corresponding products **3b–3h** in 81–94% yields. *para*-Fluorophenyl- and 2-thiophenyl-substituted benz[*c*][1,2]dithiole-3-ones **1i** and **1j** also smoothly participated in this cyclization process, affording the anticipated products **3i** and **3j** in 59% and 34% yields, respectively. Various aryl isothiocyanates were also identified as compatible substrates. For instance, products **3k** and **3l** could be obtained in high yields by using *ortho*-substituted isothiocyanates. *meta*-Methyl-substituted isothiocyanate also participated effectively in the reaction, affording cyclization product **3m** in 94% yield.

Table 2 Substrate scope of benzo[*c*][1,2]dithiol-3-ones and isothiocyanates[a]



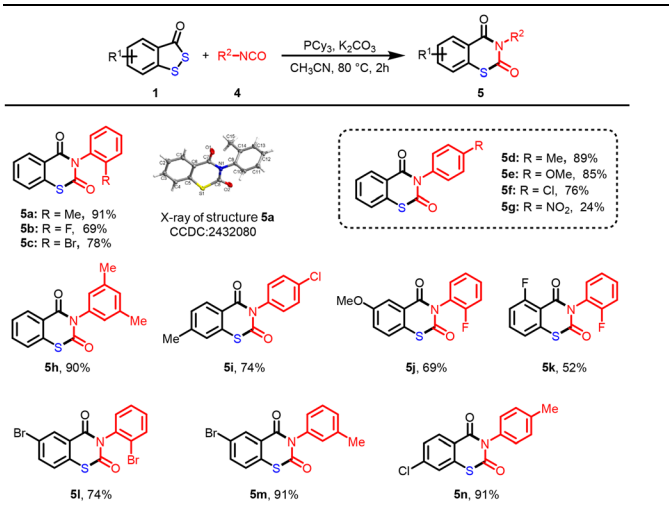
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), PCy_3 (0.3 mmol), K_2CO_3 (0.3 mmol) and CH_3CN (2 mL) at 80 °C for 2 h.

para-Substituted isothiocyanates with electron-donating groups (–Et) and electron-withdrawing groups such as –Cl, –Br, $–CF_3$, –CN and –NCS were efficiently transformed into products **3n–3s**, respectively, in yields ranging from 69% to 92%. Furthermore, disubstituted aryl isothiocyanates were compatible under the standard conditions, delivering the desired products **3t–3v** in 83–94% yields. Moreover, the reaction was also highly adaptable with heteroaryl and polycyclic substituents of isothiocyanates, affording the corresponding products **3w** and **3x** in 84% and 79% yields, respectively. Unfortunately, aliphatic isothiocyanates, such as cyclohexyl isothiocyanate, were not favorable for this conversion process, indicating that the aromatic conjugation effect may play an indispensable part in the reaction efficiency. Next, substrates **1** and **2** bearing various groups on both phenyl rings were examined, which provided products **3z–3ad** in 64%–96% yields. Critically, the applicability of the current method was further highlighted by late-stage modifications of biologically relevant molecules, such as paroxetine[12] (**3ae**), fluoxetine[13] (**3af**), norquetiapine[14] (**3ag**), bortioxetine[15] (**3ah**) and P2Y6 receptor antagonist[16] (**3ai**) derivatives, which could also be efficiently achieved in good yields. These successful applications demonstrated the potential application of this methodology in discovering diverse and promising drug derivatives.

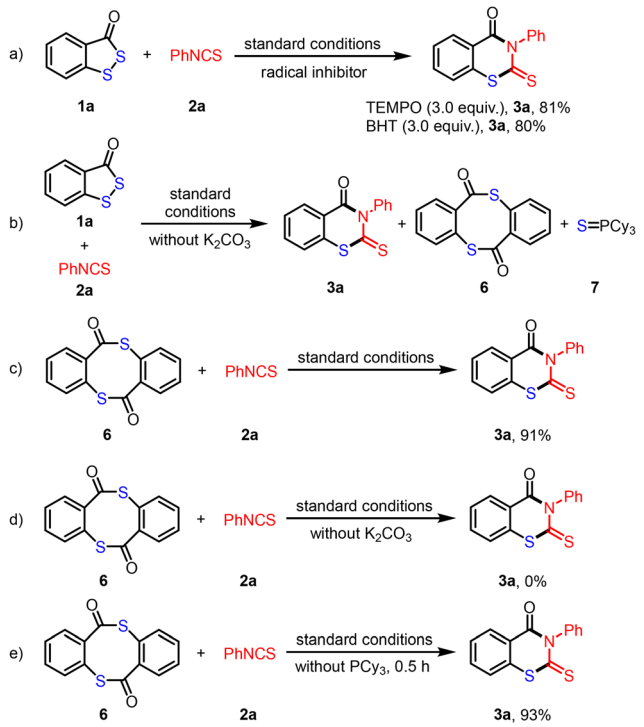
To further examine the applicability of this methodology, we turned our attention to the synthesis of benzo[*e*][1,3]thiazine-2,4-dione derivatives (Table 3). Phenyl isocyanates possessing –Me, –F and –Cl substituents at the *ortho* positions of the phenyl ring afforded benzo[*e*][1,3]thiazine-2,4-diones **5a–5c** in 78–91% yields. The defined structure of **5a** was confirmed by X-ray analysis (CCDC 2432080).[17] Similarly, *para*-substituted isocyanates bearing –Me, –OMe and –Cl substituents proved to be effective substrates, producing products **5d–5f** in good yields. However, substrates with a strong electron-withdrawing group (*e.g.*, NO_2) exhibited a decreasing yield (**5g**). Disubstituted isocyanate was also compatible, furnishing product **5h** in 90% yield. As anticipated, benzo[*c*][1,2]dithiol-3-ones **1** and isocyanates **4** with diverse substituents (Me, OMe, F, Br and Cl) on the benzene ring were found to be well suitable for the transformation, and the relevant products **5i–5n** could be isolated in moderate to good yields.

To gain further insight into the plausible reaction mechanism, several control experiments were conducted (Scheme 2). In the presence of 3 equiv. of 2,2,6,6-tetramethylpiperidinyl-1-oxide (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) under the standard conditions, the reaction efficiency remained nearly unchanged, indicating that a radical pathway was not involved in this transformation (Scheme 2a). When the model reaction was conducted without K_2CO_3, product **3a**,

Table 3 Substrate scope of benzo[*c*][1,2]dithiol-3-ones and isocyanates[a]



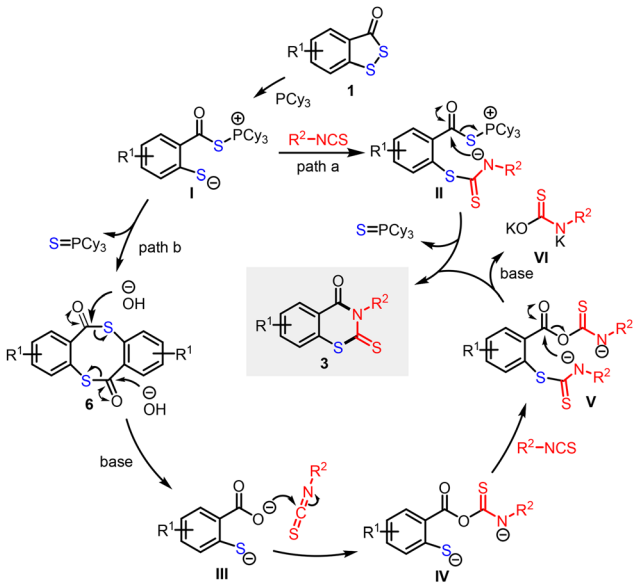
[a] Reaction conditions: **1** (0.2 mmol), **4** (0.4 mmol), PCy_3 (0.3 mmol), K_2CO_3 (0.3 mmol) and CH_3CN (2 mL) at 80 °C for 2 h.



Scheme 2 Control experiments.

dimeric compound **6** and tricyclohexylphosphine sulfide **7** were obtained as the main products (Scheme 2b). Subsequently, dimeric compound **6** could be further transformed into product **3a** in 91% yield under the standard conditions (Scheme 2c), suggesting that **6** may serve as a potential intermediate during the transformations. It should be noted that compound **6** was generally regarded as a by-product in existing literature reports.[9,10,11f,g] Moreover, compound **6** could not undergo any reaction in the absence of K_2CO_3 (Scheme 2d), whereas it could be converted to the desired product in high yield without the addition of PCy_3 (Scheme 2e). These results illustrate that **2a** functions as a chemical catalyst in addition to being a substrate.

Based on the experimental studies and literature reports,[9,10,11a,f,g,18] a plausible mechanism for the developed transformation was proposed, as shown in Scheme 3. Firstly, the zwitterionic intermediate **I** is generated *in situ* by cleavage of the S–S bond of benzo[*c*][1,2]dithiolan-3-ones **1** in the presence of PCy_3. Intermediate **I** is then converted to products **3** *via* two possible paths a or b. In path a, attack of isothiocyanates **2** with the thiolate ion in **I** generates intermediate **II**, which undergoes intramolecular cyclization to produce the desired benzo[*e*][1,3]thiazin-4-ones **3**, along with the release of tricyclohexylphosphine sulfide **7**. Alternatively, in path b, ring opening of dimeric **6** in the presence of a base provides intermediate **III**, which is then converted to intermediate **IV** by reaction with isothiocyanates **2**. Following a similar procedure to path a, attack of isothiocyanates **2** with **IV**, followed by intramolecular cyclization of the generated **V** then gives **3** along with the release of **VI**.



Scheme 3 Proposed mechanism.

Conclusions

In conclusion, we have successfully developed an annulation reaction between benzo[*c*][1,2]dithiol-3-ones and iso(thio)cyanates for the efficient synthesis of benzo[*e*][1,3]thiazin-4-one derivatives. In this transformation, the benzo[*c*][1,2]dithiol-3-ones undergo sequential S–S bond cleavage and [4 + 2] cycloaddition with iso(thio)cyanates, accompanied by S-atom extrusion to produce the final products. The transformation is scalable, powerful, and cost-effective, as it employs readily available starting materials and an inexpensive catalyst. It is facile to execute and exhibits a broad substrate scope, including substrates with adequate complexity. The practicality of this strategy has been further demonstrated through its successful application in late-stage drug modification.

Author contributions

Y.-G. W. conceived the idea, guided the project, and wrote the manuscript. C.-X. Y. carried out the reaction condition optimization, substrate screening experiments and mechanistic studies. M.-Y. Z. performed some of the substrate screening experiments. J. R., W.-M. Z., and C.-J. S. jointly completed the review & editing of the manuscript based on feedback from the other authors.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the SI.

Supplementary information is available. See DOI: https://doi.org/10.1039/d5qo01013f.

CCDC 2432080 contains the supplementary crystallographic data for this paper.[17]

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