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# On the Redox Properties of the Dimers of Thiazol-2-ylidenes That Are Relevant for Radical Catalysis

Ludivine Delfau, Nadhrata Assani, Samantha Nichilo, Jacques Pecaut, Christian Philouze, Julie Broggi, David Martin,\* and Eder Tomás-Mendivil\*

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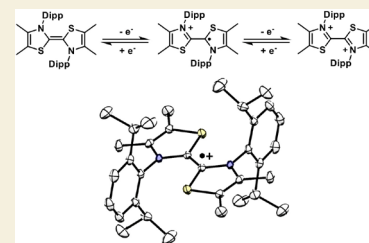
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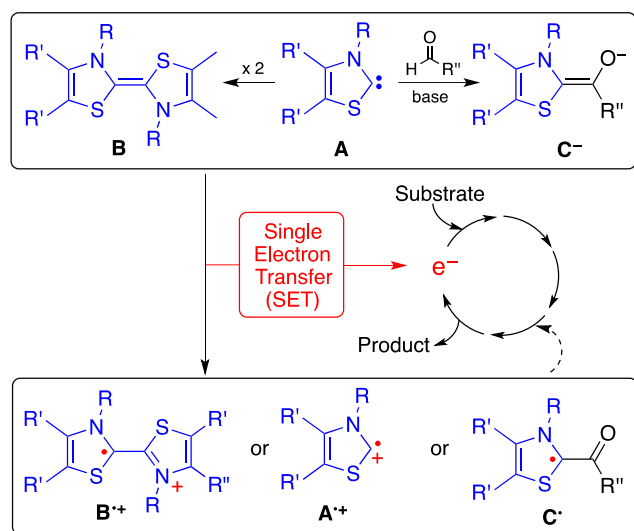
**ABSTRACT:** We report the isolation and study of dimers stemming from popular thiazol-2-ylidene organocatalysts. The model featuring 2,6-di(isopropyl)phenyl (Dipp) N-substituents was found to be a stronger reducing agent ( $E_{\text{ox}} = -0.8$  V vs SCE) than bis(thiazol-2-ylidenes) previously studied in the literature. In addition, a remarkable potential gap between the first and second oxidation of the dimer also allows for the isolation of the corresponding air-persistent radical cation. The latter is an unexpected efficient promoter of the radical transformation of  $\alpha$ -bromoamides into oxindoles.



**KEYWORDS:** Organocatalysis, N-Heterocyclic Carbenes, Reduction, Radical, Electrochemistry

Thiazol-2-ylidenes **A** (Scheme 1) are synthetic models for the active form of thiamine, a well-known enzymatic

## Scheme 1. Thiazol-2-ylidenes **A** and Their Derivatives as Possible One-Electron Transfer Agents in Radical Catalysis or Chain Reactions



cofactor.<sup>1</sup> These stabilized N-heterocyclic carbenes (NHCs) have been used for decades as efficient organocatalysts.<sup>2–7</sup> They are generated in situ from the reaction of a base and a thiazolium salt. Indeed they cannot usually be isolated, as they readily dimerize. Arduengo et al. reported that the bulky 2,6-di(isopropyl)phenyl (Dipp) N-substituent slows down the dimerization for several hours at room temperature, thus

allowing for the first isolation and characterization of such NHCs, including an X-ray diffraction study.<sup>8,9</sup> The carbene is already too short-lived for isolation with a slightly smaller 2,4,6-trimethylphenyl N-substituent but could be observed by NMR spectroscopy at 0 °C. Furthermore, traces of Bronsted or Lewis acids catalyze fast dimerization, even for thiazol-2-ylidenes with a high steric hindrance.<sup>10–12</sup> Therefore, dimers **B** are far more likely to accumulate than carbenes **A** in catalytic processes. Importantly, they react with aldehydes similarly to **A** to afford the key Breslow intermediates. They could be either resting-state reservoirs for **A** or catalysts on their own. Data exist in support and against these hypotheses for the benzoin condensation.<sup>13–22</sup>

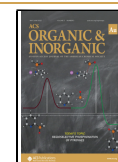
In addition to ionic-type (2-electron) mechanisms, thiazol-2-ylidenes have also recently become privileged organocatalysts for radical transformations of aldehydes.<sup>23–38</sup> In these reactions, the Breslow-type enolates  $\text{C}^-$ , which result from the condensation of aldehydes with NHCs in basic conditions, are able to undergo spontaneous single-electron transfer (SET) to challenging substrates ( $E_{\text{ox}} > -1.6$  V vs SCE).<sup>59–62</sup> In the absence of aldehydes, free NHCs are milder reducing reactants. For instance, imidazol-2-ylidenes perform stoichiometric reduction of the ferrocenium cation<sup>63</sup> ( $E = +0.38$  V vs SCE) and the trityl cation<sup>64</sup> ( $E = +0.27$  V vs SCE).<sup>65</sup> Wang and co-workers recently proposed that thiazol-2-ylidenes **A** could

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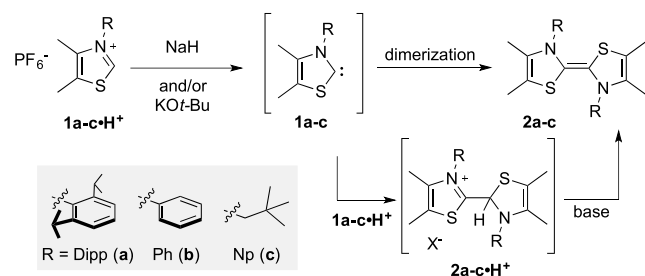


promote radical transformations in the absence of aldehydes via SET to  $\alpha$ -bromocarbonyl compounds and transient formation of radical  $A^{\bullet+}$ .<sup>66–69</sup>

Curiously, there is no consideration in the literature of the possible role of dimers **B** in redox NHC-catalyzed processes, although they belong to the large family of dithiadiazafulvalenes, which are known mild electron donors.<sup>70–72</sup> In addition, electrochemical studies have been limited to electron-poor derivatives with benzo-fused or electron-withdrawing R-substituents.<sup>73–76</sup> No data are available for a model that is relevant for catalysis. Thus, as part of ongoing efforts to establish a finer mechanistic comprehension of radical NHC catalysis,<sup>59–62</sup> we underwent the synthesis, isolation, and electrochemical study of dimers **B** of catalytically relevant NHC **A**.

Thiazol-2-ylidenes featuring the 2,6-di(isopropyl)phenyl (Dipp) N-substituent, such as **1a** (Scheme 2), stand out as

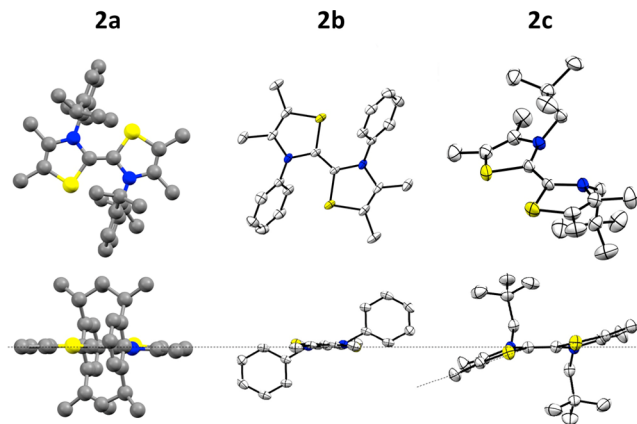
### Scheme 2. Synthesis of Carbene Dimers 2a–c



polyvalent and efficient organocatalysts for the radical transformation of aldehydes. Therefore, our primary focus was on the dimer **2a** of parent NHC **1a**. We also considered dimer **2b** with a smaller phenyl group in order to probe steric effects and dimer **2c** because thiazol-2-ylidene with a neopentyl (Np) N-substituent found a niche application in radical catalysis for the activation of challenging aliphatic aldehydes.<sup>77</sup>

We synthesized NHC **1a** as previously reported by Arduengo et al.<sup>8</sup> After 2 days at room temperature in pentane, an orange precipitate was recovered by filtration, washed with pentane, extracted with toluene, and dried under vacuum, affording olefin **2a** in 18% yield. Thiazolium salts **1b,c·H+PF<sub>6</sub><sup>-</sup>** were mixed with an excess of NaH and 10% potassium *tert*-butoxide to afford the desired electron-rich olefins **2b,c** in 52 and 28% yield, respectively. The fast reaction likely involves a two-step process including the attack of transient carbene **1** on thiazoliums **1·H+** to afford protonated dimers **2·H+**, followed by a second deprotonation. As a matter of fact, when applying this protocol to the Dipp-substituted thiazolium **1a·H+**, the hexafluorophosphate salt of **2a·H+** was formed and isolated in 21% yield.

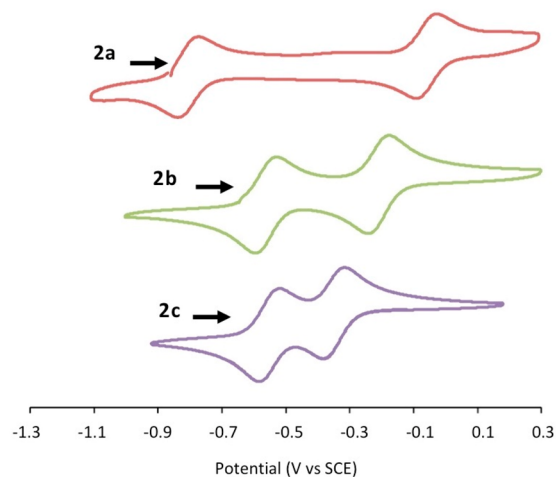
All new products were fully characterized. We obtained suitable single crystals of dimers **2b,c** (Figure 1). A previous X-ray diffraction study showed that **2a** features an almost planar structure in the solid state with a N–C–C–N dihedral angle of 177° and negligible pyramidalization around N atoms (average sum of angles: 359.6°).<sup>8</sup> In the case of phenyl N-substituted **2b**, the planarity of the olefin pattern is absolute (N–C–C–N dihedral angle: 180°), but lower steric bulk allows a pronounced pyramidalization at the nitrogen atoms (sum of angles: 350.9°). Dimer **2c** also features pyramidalization at nitrogen atoms (sum of angles: 349°) but also a marked trans-bending of the central alkene pattern. It is worth



**Figure 1.** Solid-state structures of dimers **2a–c**. The structure of **2a** is depicted with a ball-and-stick representation as CCDC 100053 (ref 8) does not provide for thermal factors. Thermal ellipsoids for **2b,c** are set at 50% probability. Selected sides views are also shown. Hydrogen atoms are omitted for clarity; N atoms are highlighted in blue, and S atoms are in yellow.

mentioning that such distortion is not uncommon among NHC dimers: they have been reported for a bis(imidazolidin-2-ylidene)<sup>78,79</sup> and a methyl N-substituted bis(thiazol-2-ylidene).<sup>8</sup> Importantly, NMR spectra of the crude products showed the presence of only one isomer. However, whereas **2a,b** are *E*, the *Z*-isomer of **2c** was observed in the solid state. Accordingly, DFT calculations<sup>80</sup> at the B3LYP-D3BJ/def2-SVP level of theory indicated a slight preference for the *Z* over the *E* configuration for **2c** by 2 kcal·mol<sup>-1</sup>. Note that the variety of geometrical situations does not significantly affect the central C=C' bond length, which remains almost unchanged within the series (**2a**: 134.4 pm; **2b**: 134.6 pm; **2c**: 134.5 pm).

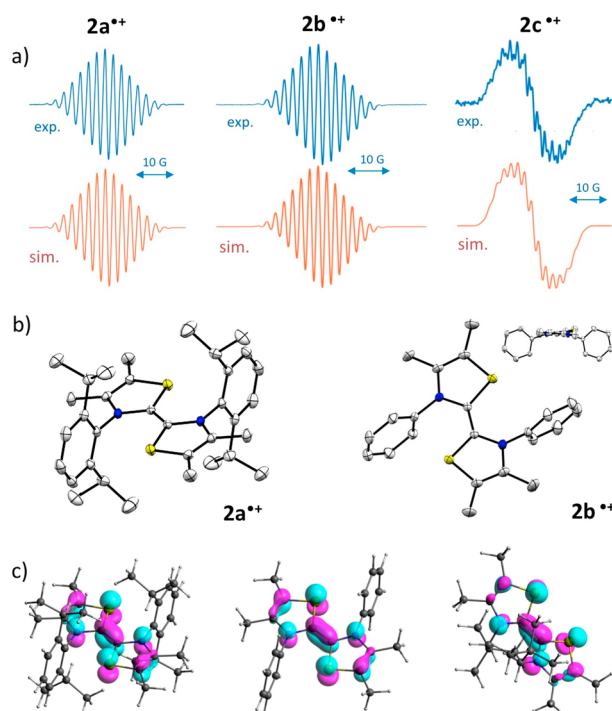
Cyclic voltammograms of **2a–c** feature two consecutive reversible oxidations, which were attributed to the formation of the corresponding radical cations **2a–c·<sup>•+</sup>** and dication **2a–c<sup>2+</sup>**, respectively (Figure 2). The three dimers are better electron donors ( $E_{\text{ox}} < -0.5$  V vs SCE) than previously measured for other dithiadiazafulvalenes ( $E_{\text{ox}} \in [+0.4; -0.5$  V]).<sup>73–76</sup> Olefin **2a** is by far the strongest reducing agent of the series. We attributed its remarkably low oxidation potential of  $-0.8$  V to



**Figure 2.** Cyclic voltammograms of **2a–c**; 1 mM of each compound in 0.1 M <sup>n</sup>Bu<sub>4</sub>NPF<sub>6</sub> acetonitrile electrolyte at 100 mV·s<sup>-1</sup> rates.

the bulky Dipp substituent, which blocks the amino groups in a planar environment and thus forces them to act as strong +M donors. Munz and co-workers recently proposed that enforced planarity in NHC dimers must also result in radical cations with higher oxidation potentials, thus providing them for thermodynamic protection toward disproportionation.<sup>81</sup> Electrochemical data of **2a–c** obey this trend, as the separation between both redox events roughly correlates with the planarity at the N atom in the solid state (**2a**:  $\Delta E = 0.74$  V; **2b**:  $\Delta E = 0.35$  V; **2c**:  $\Delta E = 0.21$  V).

We attempted the quantitative electrolysis of **2a–c** in acetonitrile. The formation of the corresponding radicals **2a–c**<sup>•+</sup> could be characterized by UV–vis (see Supporting Information (SI)) and EPR spectroscopies (Figure 3a). As



**Figure 3.** (a) Experimental X-band EPR spectra of **2a–c**<sup>•+</sup> in acetonitrile at room temperature and respective simulated spectra.<sup>82</sup> (b) Solid-state structures of [**2a**<sup>•+</sup>]<sub>2</sub>PF<sub>6</sub> and [**2b**<sup>•+</sup>]<sub>2</sub>PF<sub>6</sub> with thermal ellipsoids set at 50% probability. Hydrogen atoms, PF<sub>6</sub><sup>−</sup> anions, and cocrystallized solvent molecule(s) are omitted for clarity. (c) Representations of SOMO of **2a–c**<sup>•+</sup>.

expected from the geometry of dimers and  $\Delta E$  values,<sup>81</sup> **2c**<sup>•+</sup> slowly decomposes. Radicals **2a,b**<sup>•+</sup> could be synthesized through one-electron oxidation of **2a,b** with NOPF<sub>6</sub> in dichloromethane and isolated in 87 and 51% yield, respectively. Whereas **2b**<sup>•+</sup> is highly sensitive, we found the sterically protected radical **2a**<sup>•+</sup> remarkably air-persistent at room temperature, especially in the solid state. Dication **2a**<sup>2+</sup> was also synthesized from **2a** employing 2 equiv of NOPF<sub>6</sub> (see SI).

Single-crystal X-ray diffraction studies revealed fully planar dithiadiazafulvalene structures for radicals **2a,b**<sup>•+</sup> (Figure 3b). The central C=C' bond lengths (**2a**<sup>•+</sup>: 1.403 Å; **2b**<sup>•+</sup>: 1.391 Å) are about 6 pm longer than in the neutral dimer counterparts **2a,b**. A simple molecular orbital analysis can account for this elongation. Indeed the oxidation process corresponds to the formation of the SOMO of **2**<sup>•+</sup> (Figure 3c)

by removing an electron from the HOMO of **2**, while both molecular orbitals are bonding combinations of  $\pi$  orbitals of two thiazol-2-ylidene fragments. The DFT-optimized structure of **2c**<sup>•+</sup> features a less conjugated  $\pi$ -system, with a 30° twist at the central C=C' bond. In radicals **2a–c**<sup>•+</sup>, the spin density is mainly distributed among N,S and central bridging C atoms (Table 1), with the twisted structure of **2c**<sup>•+</sup> resulting in a slight transfer of spin density from the heteroatoms to the carbon atoms.

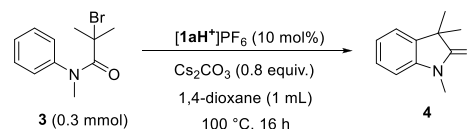
**Table 1.** Redox Potentials, Isotropic EPR Hyperfine Coupling Constants, and Mulliken Spin Densities of Radicals **2**<sup>•+</sup>

R	Dipp	Ph	Np
$E_{1/2}$ (V) <sup>a</sup>			
<b>2</b> / <b>2</b> <sup>•+</sup>	−0.80	−0.55	−0.56
<b>2</b> <sup>•+</sup> / <b>2</b> <sup>2+</sup>	−0.06	−0.20	−0.35
isotropic EPR hyperfine coupling (MHz)			
$A(^{14}\text{N} \times 2)$	11.8	11.3	9.9
$A(^1\text{H} \times 6)$	6.2	5.7	4.9
Mulliken spin density (%) <sup>b</sup>			
on N (x2)	32	31	27
S (x2)	28	29	28
C <sub>central</sub> (x2)	23	23	29

<sup>a</sup> $E$  in acetonitrile vs SCE. <sup>b</sup>Computed at the B3LYP-D3BJ/def2-SVP level of theory.

The large potential gap between the first and second oxidations of **2a** ( $\Delta E = 0.74$  V) indicates that it must behave as an efficient one-electron donor. It also stands out among bis(thiazol-2-ylidenes) as a remarkably strong reducing olefin ( $E(\mathbf{2a}^{\bullet+}/\mathbf{2a}) = -0.80$  V vs SCE). Overall, these data suggest that dimer **2a** might not be innocent in radical transformations allegedly involving the popular NHC **1a** as a catalyst. For instance, recent works from Wang et al. attracted our attention. Methodological studies showed that  $\alpha$ -bromoisobutyramides, such as **3** (see Table 2) can be activated with NHC radical catalysis to afford oxindoles, and free thiazol-2-ylidene **1a** was proposed as a key single-electron donor.<sup>66</sup>

**Table 2.** Organocatalyzed Oxindole Synthesis<sup>a</sup>



entry	variation from the standard conditions	conv. <sup>b</sup>
1	none	62%
2	<b>1b</b> ·H <sup>+</sup>	49%
3	<b>1c</b> ·H <sup>+</sup>	4%
4	<b>2a</b> (5 mol %); 0.7 equiv of Cs <sub>2</sub> CO <sub>3</sub>	80%
5	<b>2b</b> (5 mol %); 0.7 equiv of Cs <sub>2</sub> CO <sub>3</sub>	38%
6	<b>2c</b> (5 mol %); 0.7 equiv of Cs <sub>2</sub> CO <sub>3</sub>	16%
7	[ <b>2a</b> <sup>•+</sup> ] <sub>2</sub> PF <sub>6</sub> (5 mol %); 0.7 equiv of Cs <sub>2</sub> CO <sub>3</sub>	90%
8	[ <b>2b</b> <sup>•+</sup> ] <sub>2</sub> PF <sub>6</sub> (5 mol %); 0.7 equiv of Cs <sub>2</sub> CO <sub>3</sub>	60%

<sup>a</sup>Standard reaction conditions: **3** (0.3 mmol), precatalyst [**1a**·H<sup>+</sup>]<sub>2</sub>PF<sub>6</sub> (0.03 mmol), Cs<sub>2</sub>CO<sub>3</sub> (0.24 mmol), 1,4-dioxane (1.0 mL), Ar atmosphere, 100 °C (oil bath), 16 h. <sup>b</sup>Estimated from <sup>1</sup>H NMR with 1,3,5-trimethoxybenzene (TMB) as internal standard.

In order to evaluate the reducing ability of thiazol-2-ylidenes, we considered their precursors **1a–c•H<sup>+</sup>**. Their cyclic voltammograms feature an irreversible reduction wave around  $-1.5$  V, which corresponds to an EC process<sup>83,84</sup> generating free carbenes **1**, through the formation of radical **1•H<sup>•</sup>**, followed by the fast loss of H<sup>•</sup>. The reoxidation wave allowed thiazol-2-ylidenes **1a–c** to feature oxidation potentials  $E_p^{ox}$  (**1/1<sup>•+</sup>**) higher than  $-0.2$  V vs SCE (see SI).

Not only is thiazol-2-ylidene **1a** a very weak reducing agent, but the NHC is also prone to fast dimerization in the reaction conditions. Therefore, we naturally hypothesized that olefin **2a** was the relevant electron donor in the transformation of **3** into oxindole **4**, and we ran a few control experiments (Table 2). We first reproduced results from the literature<sup>66</sup> employing [**1a•H<sup>+</sup>**]PF<sub>6</sub> as a precatalyst (entry 1). Oxindole **4** was formed in 62% conversion (reported: 63%). Phenyl N-substituted **1b•H<sup>+</sup>** was less performant (entry 2) and **1c•H<sup>+</sup>** barely promoted the reaction (4% conversion, entry 3). As expected, the corresponding dimers **2a–c** gave similar or higher conversions (entries 4–6).

The reduction potential of ethyl  $\alpha$ -bromoisobutyrate **5**, which is electronically similar to **3**, is reported to be  $E_p^{red}$  (**5/5<sup>•-</sup>**) =  $-0.77$  V in DMSO.<sup>35</sup> This value would support a spontaneous SET from **2a** ( $E_{ox}$  =  $-0.80$  V) to **5**. However,  $\alpha$ -bromoisobutyryl derivatives may be in fact more challenging to reduce than previously proposed. Indeed, we found a different value,  $E_p^{red}$  (**5/5<sup>•-</sup>**) =  $-1.89$  V in acetonitrile (see SI), which prompted us to measure  $E_p^{red}$  (**3/3<sup>•-</sup>**) which was found at to be  $-1.94$  V vs SCE in acetonitrile. Even more, we tested hexafluorophosphate salts of **2a,b<sup>•+</sup>** as catalysts (entries 7 and 8). Surprisingly, the radical cations were more efficient than the corresponding electron-donating olefins **2a,b**. These data suggest that the hypothesis of a simple SET process is not valid.

In conclusion, bis(thiazol-2-ylidene) **2a**, stemming from the popular NHC organocatalyst **1a**, presents three stable redox states. The bulky Dipp N-substituent forces planar geometries, thus resulting in an unusually low oxidation potential and a comparatively high second oxidation potential, allowing for the isolation of air-persistent radical **2a<sup>•+</sup>**. Olefin **2a** is not strong enough to compete as a reducing agent with Breslow-type enolates. However, it remains a potential electron donor, which can interfere in radical reactions that are allegedly catalyzed by **1a** and does not involve aldehyde derivatives as substrates. In the specific case of the activation of  $\alpha$ -bromoisobutyramides, we unexpectedly found that radical **2a<sup>•+</sup>** is the most efficient redox form as a catalyst. This surprising result suggests that the NHC derivatives are unlikely to promote this radical reaction through a simple SET, as initially proposed. We are actually undergoing further experimental and theoretical studies, in an attempt to decipher and better understand such process.

## ■ ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsorginorgau.3c00008>.

Experimental procedures, X-ray crystallographic data, computational details, <sup>1</sup>H and <sup>13</sup>C NMR spectra of all new compounds (PDF)

### Accession Codes

CCDC 2244590–2244591 and 2244593–2244596 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto: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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CRedit: Ludivine Delfau investigation (lead), writing-original draft (supporting), writing-review & editing (supporting); Nadhrata Assani investigation (supporting); Samantha Nichilo investigation (supporting); Jacques Pecaut investigation (supporting); Christian Philouze investigation (supporting); Julie Broggi conceptualization (equal), funding acquisition (equal), supervision (equal), writing-review & editing (supporting); David Martin conceptualization (equal), funding acquisition (equal), investigation (supporting), supervision (equal), writing-review & editing (equal); Eder Tomás-Mendivil conceptualization (equal), investigation (supporting), supervision (equal), writing-original draft (lead), writing-review & editing (equal).

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## Notes

The authors declare no competing financial interest.

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