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Letter

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

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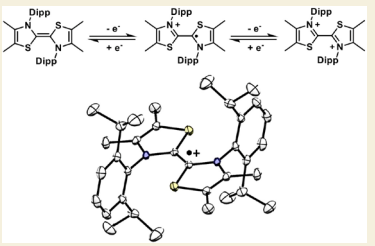
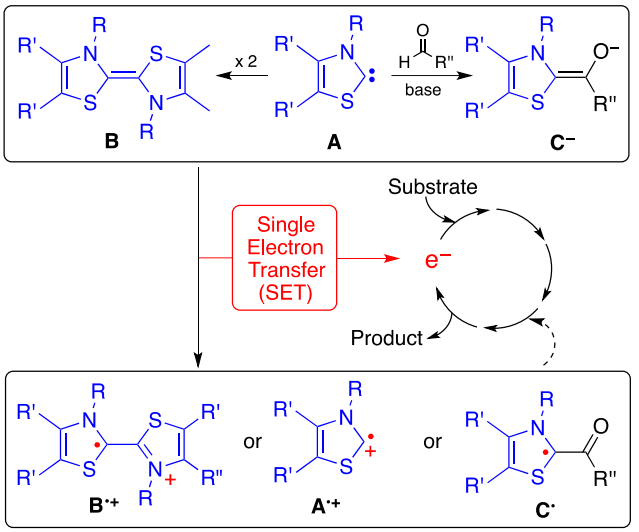
ABSTRACT: We report the isolation and study of dimers stemming from popular thiazol-2-ylidene organocatalysts. The model featuring 2,6-di(isopropyl)phenyl (Dipp) N-substituents was found to be a stronger reducing agent (E_{ox} = −0.8 V vs SCE) than bis(thiazol-2-ylidenes) previously studied in the literature. 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 α-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 cofactor.[1] These stabilized N-heterocyclic carbenes (NHCs) have been used for decades as efficient organocatalysts.[2−7] 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.[8,9] 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.[10−12] 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.[13−22]

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



In addition to ionic-type (2-electron) mechanisms, thiazol-2-ylidenes have also recently become privileged organocatalysts for radical transformations of aldehydes.[23−58] In these reactions, the Breslow-type enolates 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_{ox} > −1.6 V vs SCE).[59−62] In the absence of aldehydes, free NHCs are milder reducing reactants. For instance, imidazol-2-ylidenes perform stoichiometric reduction of the ferrocenium cation[63] (E = +0.38 V vs SCE) and the trityl cation[64] (E = +0.27 V vs SCE).[65] Wang and co-workers recently proposed that thiazol-2-ylidenes **A** could

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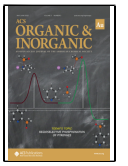

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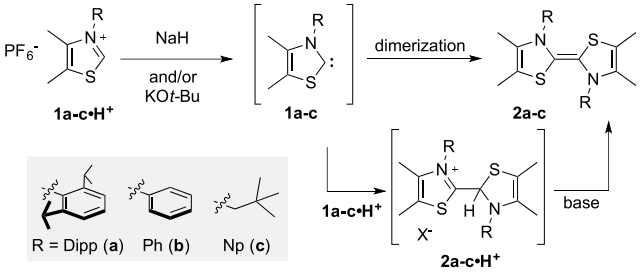
promote radical transformations in the absence of aldehydes via SET to α-bromocarbonyl compounds and transient formation of radical $\mathbf{A}^{\bullet+}$.[66−69]

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.[70−72] In addition, electrochemical studies have been limited to electron-poor derivatives with benzo-fused or electron-withdrawing R-substituents.[73−76] 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,[59−62] 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.[77]

We synthesized NHC **1a** as previously reported by Arduengo et al.[8] 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 $\mathbf{1b,c{\cdot}H^+}PF_6^-$ 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 $\mathbf{1{\cdot}H^+}$ to afford protonated dimers $\mathbf{2{\cdot}H^+}$, followed by a second deprotonation. As a matter of fact, when applying this protocol to the Dipp-substituted thiazolium $\mathbf{1a{\cdot}H^+}$, the hexafluorophosphate salt of $\mathbf{2a{\cdot}H^+}$ 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°).[8] 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

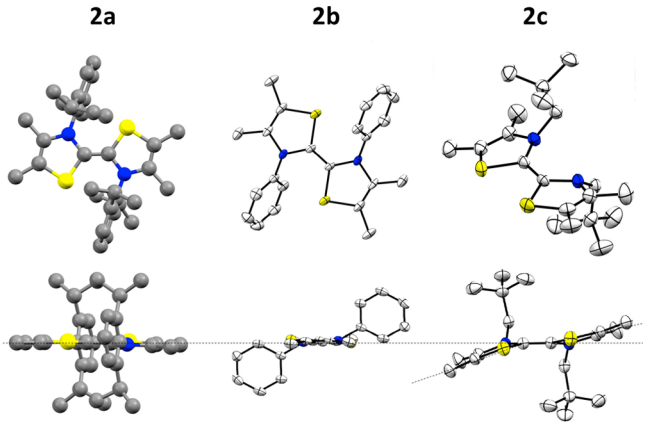


Figure 1. Solid-state structures of dimers **2a−c**. The structure of **2a** is depicted with a ball-and-stick representation as CCDC 100053 (ref 8) does not provide for thermal factors. Thermal ellipsoids for **2b,c** are set at 50% probability. Selected sides views are also shown. Hydrogen atoms are 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)[78,79] and a methyl N-substituted bis(thiazol-2-ylidene).[8] 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[80] 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^{-1}. 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 $\mathbf{2a-c}^{\bullet+}$ and dications $\mathbf{2a-c}^{2+}$, respectively (Figure 2). The three dimers are better electron donors (E_{ox} < −0.5 V vs SCE) than previously measured for other dithiadiazafulvalenes ($E_{ox} \in [+0.4; -0.5\ V]$).[73−76] Olefin **2a** is by far the strongest reducing agent of the series. We attributed its remarkably low oxidation potential of −0.8 V to

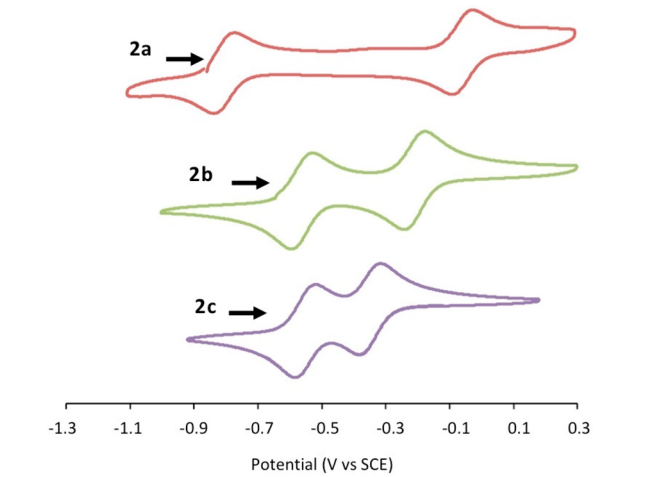


Figure 2. Cyclic voltammograms of **2a−c**; 1 mM of each compound in 0.1 M ^{n}Bu$_4$NPF$_6$ acetonitrile electrolyte at 100 mV·s^{-1} rates.

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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.[81] 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**: ΔE = 0.74 V; **2b**: ΔE = 0.35 V; **2c**: ΔE = 0.21 V).

We attempted the quantitative electrolysis of **2a**−**c** in acetonitrile. The formation of the corresponding radicals **2a**−**c**$^{\bullet+}$ could be characterized by UV−vis (see Supporting Information (SI)) and EPR spectroscopies (Figure 3a). As

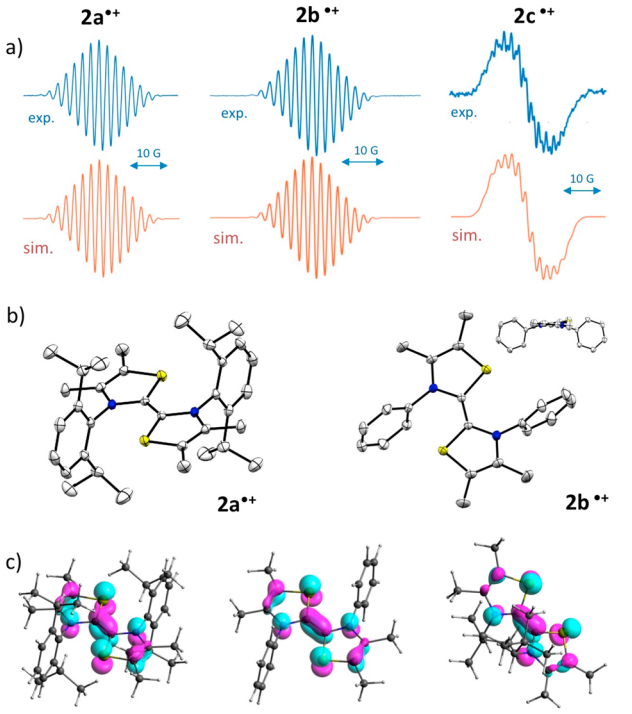


Figure 3. (a) Experimental X-band EPR spectra of **2a**−**c**$^{\bullet+}$ in acetonitrile at room temperature and respective simulated spectra.[82] (b) Solid-state structures of [**2a**$^{\bullet+}$]PF_6 and [**2b**$^{\bullet+}$]PF_6 with thermal ellipsoids set at 50% probability. Hydrogen atoms, PF_6^- anions, and cocrystallized solvent molecule(s) are omitted for clarity. (c) Representations of SOMO of **2a**−**c**$^{\bullet+}$.

expected from the geometry of dimers and ΔE values,[81] **2c**$^{\bullet+}$ slowly decomposes. Radicals **2a,b**$^{\bullet+}$ could be synthesized through one-electron oxidation of **2a,b** with $NOPF_6$ in dichloromethane and isolated in 87 and 51% yield, respectively. Whereas **2b**$^{\bullet+}$ is highly sensitive, we found the sterically protected radical **2a**$^{\bullet+}$ remarkably air-persistent at room temperature, especially in the solid state. Dication **2a**$^{2+}$ was also synthesized from **2a** employing 2 equiv of $NOPF_6$ (see SI).

Single-crystal X-ray diffraction studies revealed fully planar dithiadiazafulvalene structures for radicals **2a,b**$^{\bullet+}$ (Figure 3b). The central C═C′ bond lengths (**2a**$^{\bullet+}$: 1.403 Å; **2b**$^{\bullet+}$: 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**$^{\bullet+}$ (Figure 3c) by removing an electron from the HOMO of **2**, while both molecular orbitals are bonding combinations of π orbitals of two thiazol-2-ylidene fragments. The DFT-optimized structure of **2c**$^{\bullet+}$ features a less conjugated π-system, with a 30° twist at the central C═C′ bond. In radicals **2a**−**c**$^{\bullet+}$, the spin density is mainly distributed among N,S and central bridging C atoms (Table 1), with the twisted structure of **2c**$^{\bullet+}$ resulting in a slight transfer of spin density from the heteroatoms to the carbon atoms.

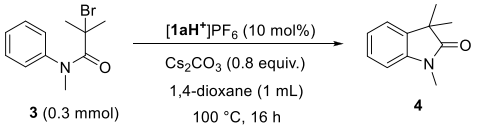
Table 1. Redox Potentials, Isotropic EPR Hyperfine Coupling Constants, and Mulliken Spin Densities of Radicals 2$^{\bullet+}$

R	Dipp	Ph	Np
$E_{1/2}$ (V)[a]			
2/**2**$^{\bullet+}$	−0.80	−0.55	−0.56
2$^{\bullet+}$/**2**$^{2+}$	−0.06	−0.20	−0.35
isotropic EPR hyperfine coupling (MHz)			
$A(^{14}Nx2)$	11.8	11.3	9.9
$A(^{1}Hx6)$	6.2	5.7	4.9
Mulliken spin density (%)[b]			
on N (x2)	32	31	27
S (x2)	28	29	28
$C_{central}$ (x2)	23	23	29

[a]E in acetonitrile vs SCE. [b]Computed at the B3LYP-D3BJ/def2-SVP level of theory.

The large potential gap between the first and second oxidations of **2a** (ΔE = 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(**2a**$^{\bullet+}$/**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 α-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.[66]

Table 2. Organocatalyzed Oxindole Synthesis[a]



3 (0.3 mmol) 4

entry	variation from the standard conditions	conv.[b]
1	none	62%
2	**1b**·H^+	49%
3	**1c**·H^+	4%
4	**2a** (5 mol %); 0.7 equiv of Cs_2CO_3	80%
5	**2b** (5 mol %); 0.7 equiv of Cs_2CO_3	38%
6	**2c** (5 mol %); 0.7 equiv of Cs_2CO_3	16%
7	[**2a**$^{\bullet+}$]PF_6 (5 mol %); 0.7 equiv of Cs_2CO_3	90%
8	[**2b**$^{\bullet+}$]PF_6 (5 mol %); 0.7 equiv of Cs_2CO_3	60%

[a]Standard reaction conditions: **3** (0.3 mmol), precatalyst [**1a**·H^+]PF_6 (0.03 mmol), Cs_2CO_3 (0.24 mmol), 1,4-dioxane (1.0 mL), Ar atmosphere, 100 °C (oil bath), 16 h. [b]Estimated from ^{1}H NMR with 1,3,5-trimethoxybenzene (TMB) as internal standard.

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In order to evaluate the reducing ability of thiazol-2-ylidenes, we considered their precursors **1a−c•H**$^+$. Their cyclic voltammograms feature an irreversible reduction wave around −1.5 V, which corresponds to an EC process[83,84] generating free carbenes **1**, through the formation of radical **1·H**$^•$, followed by the fast loss of H$^•$. The reoxidation wave allowed thiazol-2-ylidenes **1a−c** to feature oxidation potentials E_p^{ox} (**1**/**1**$^{•+}$) 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[66] employing [**1a·H**$^+$]PF_6 as a precatalyst (entry 1). Oxindole **4** was formed in 62% conversion (reported: 63%). Phenyl N-substituted **1b•H**$^+$ was less performant (entry 2) and **1c•H**$^+$ 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 α-bromoisobutyrate **5**, which is electronically similar to **3**, is reported to be E_p^{red} (**5**/**5**$^{•−}$) = −0.77 V in DMSO.[35] This value would support a spontaneous SET from **2a** (E_{ox} = −0.80 V) to **5**. However, α-bromoisobutyryl derivatives may be in fact more challenging to reduce than previously proposed. Indeed, we found a different value, E_p^{red} (**5**/**5**$^{•−}$) = −1.89 V in acetonitrile (see SI), which prompted us to measure E_p^{red} (**3**/**3**$^{•−}$) which was found at to be −1.94 V vs SCE in acetonitrile. Even more, we tested hexafluorophosphate salts of **2a,b**$^{•+}$ 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**$^{•+}$. 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 α-bromoisobutyramides, we unexpectedly found that radical **2a**$^{•+}$ 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.

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, ^{1}H and ^{13}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, 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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Author Contributions

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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