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Ludivine Delfau, Nadhrata Assani, Samantha Nichilo, Jacques Pecaut, Christian Philouze, et al..  
On the Redox Properties of the Dimers of Thiazol-2-ylidenes That Are Relevant for Radical Catal-  
ysis. ACS Organic & Inorganic Au, 2023, 3 (3), pp.136-142. 10.1021/acsorginorgau.3c00008 . hal-  
04234462

**HAL Id: hal-04234462**

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Submitted on 10 Oct 2023

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

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Cite This: *ACS Org. Inorg. Au* 2023, 3, 136–142

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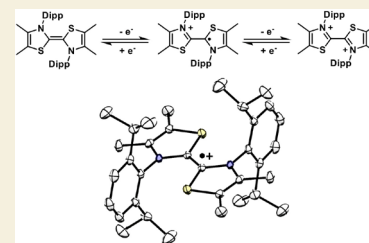
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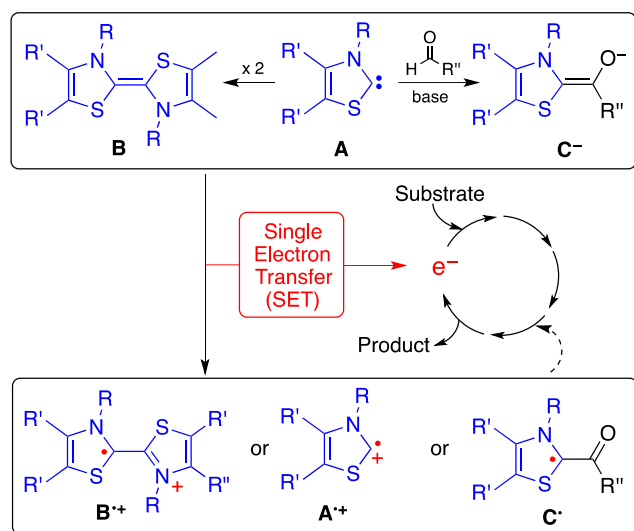
**ABSTRACT:** We report the isolation and study of dimers stemming from popular thiazol-2-ylidene organocatalysts. The model featuring 2,6-di(isopropyl)phenyl (Dipp) N-substituents was found to be a stronger reducing agent ( $E_{\text{ox}} = -0.8$  V vs SCE) than bis(thiazol-2-ylidenes) previously studied 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>

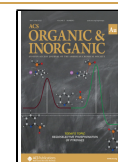
In addition to ionic-type (2-electron) mechanisms, thiazol-2-ylidenes have also recently become privileged organocatalysts for radical transformations of aldehydes.<sup>23–38</sup> In these reactions, the Breslow-type enolates  $C^-$ , which result from the condensation of aldehydes with NHCs in basic 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

Received: February 28, 2023

Revised: March 23, 2023

Accepted: March 23, 2023

Published: March 27, 2023

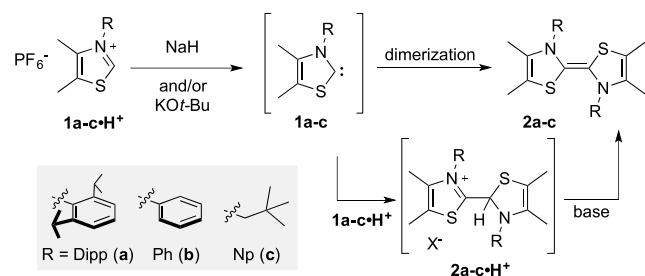


promote radical transformations in the absence of aldehydes via SET to  $\alpha$ -bromocarbonyl compounds and transient formation of radical  $A^{\bullet+}$ .<sup>66–69</sup>

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

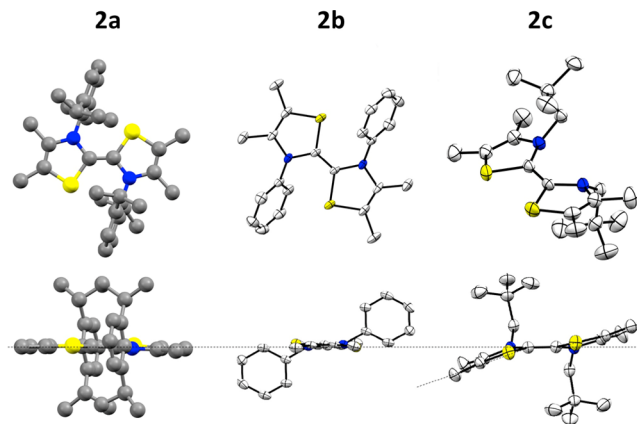
### Scheme 2. Synthesis of Carbene Dimers 2a–c



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<sup>+</sup>**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<sup>+</sup>** to afford protonated dimers **2-H<sup>+</sup>**, followed by a second deprotonation. As a matter of fact, when applying this protocol to the Dipp-substituted thiazolium **1a-H<sup>+</sup>**, the hexafluorophosphate salt of **2a-H<sup>+</sup>** was formed and isolated in 21% yield.

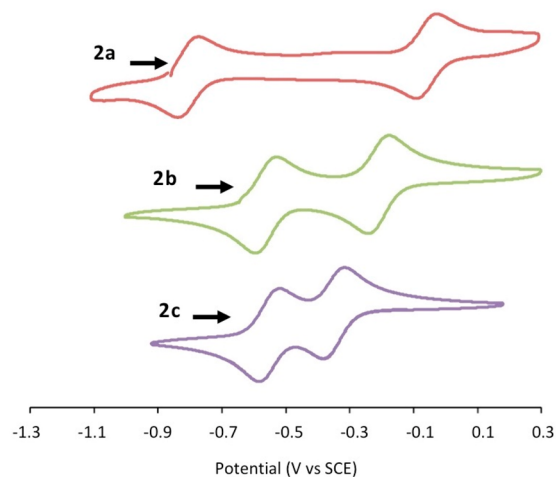
All new products were fully characterized. We obtained suitable single crystals of dimers **2b,c** (Figure 1). A previous X-ray diffraction study showed that **2a** features an almost planar structure in the solid state with a N–C–C–N dihedral angle of 177° and negligible pyramidalization around N atoms (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).

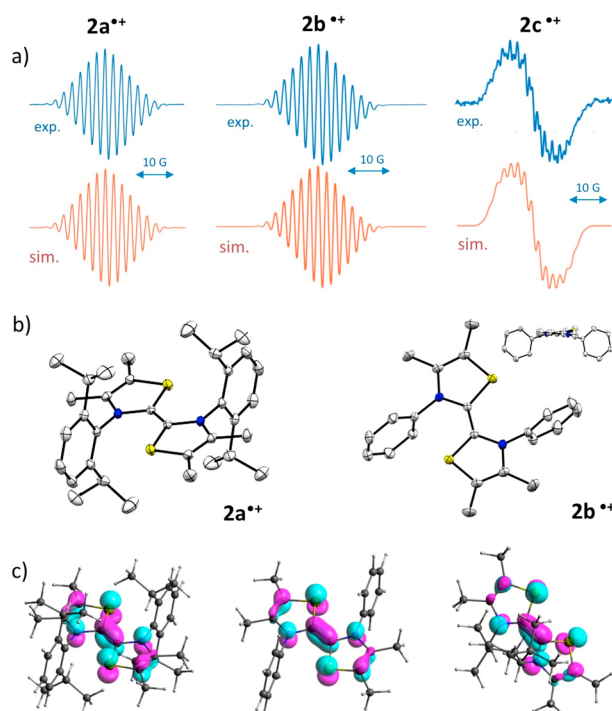
Cyclic voltammograms of **2a–c** feature two consecutive reversible oxidations, which were attributed to the formation of the corresponding radical cations **2a–c<sup>•+</sup>** and dications **2a–c<sup>2+</sup>**, respectively (Figure 2). The three dimers are better electron donors ( $E_{\text{ox}} < -0.5$  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.

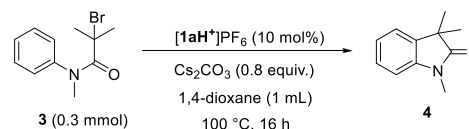
**Table 1.** Redox Potentials, Isotropic EPR Hyperfine Coupling Constants, and Mulliken Spin Densities of Radicals **2**<sup>•+</sup>

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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### 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).

### Funding

This work was funded by the French National Agency for Research (ANR-20-CE07-0010). We acknowledge the CNRS and the University of Grenoble Alpes for a frictionless environment in the context of the Labex Arcane and CBHEUR-GS (ANR-17-EURE-0003).

## Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

We thank the CECCIC centre of Grenoble for computer resources and the ICMG analytic platform (FR 2607), especially P. Girard, D. Gatineau, R. Sanahuges, and N. Altounian for their outstanding service.

## REFERENCES

- (1) Breslow, R. On the Mechanism of Thiamine Action. IV.1 Evidence from Studies on Model Systems. *J. Am. Chem. Soc.* **1958**, *80*, 3719–3726.
- (2) Enders, D.; Niemeier, O.; Henseler, A. Organocatalysis by N-Heterocyclic Carbenes. *Chem. Rev.* **2007**, *107*, 5606–5655.
- (3) Bugaut, X.; Glorius, F. Organocatalytic umpolung: N-heterocyclic carbenes and beyond. *Chem. Soc. Rev.* **2012**, *41*, 3511–3522.
- (4) De Sarkar, S.; Biswas, A.; Samanta, R. C.; Studer, A. Catalysis with N-Heterocyclic Carbenes under Oxidative Conditions. *Chem.—Eur. J.* **2013**, *19*, 4664–4678.
- (5) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An overview of N-heterocyclic carbenes. *Nature* **2014**, *510*, 485–496.
- (6) Flanigan, D. M.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115*, 9307–9387.
- (7) Wang, M. H.; Scheidt, K. A. Cooperative Catalysis and Activation with N-Heterocyclic Carbenes. *Angew. Chem., Int. Ed.* **2016**, *55*, 14912–14922.
- (8) Arduengo, A. J., III; Goerlich, J. R.; Marshall, W. J. A Stable Thiazol-2-ylidene and Its Dimer. *Liebigs Ann./Recueil* **1997**, *1997*, 365–374.
- (9) For the natural carbene stemming from thiamine, see: Meyer, D.; Neumann, P.; Ficner, R.; Tittmann, K. Observation of a stable carbene at the active site of a thiamin enzyme. *Nat. Chem. Biol.* **2013**, *9*, 488–490.
- (10) Alder, R. W.; Blake, M. E.; Chaker, L.; Harvey, J. N.; Paolini, F.; Schütz, J. When and How Do Diaminocarbenes Dimerize? *Angew. Chem., Int. Ed.* **2004**, *43*, 5896–5911.
- (11) Graham, D. C.; Cavell, K. J.; Yates, B. F. Dimerization mechanisms of heterocyclic carbenes. *J. Phys. Org. Chem.* **2005**, *18*, 298–309.
- (12) Arduengo, A. J., III; Harlow, R. L.; Kline, M. A stable crystalline carbene. *J. Am. Chem. Soc.* **1991**, *113*, 361–363.
- (13) Castells, J.; Lopez-Calahorra, F.; Geijo, F.; Perez-Dolz, R.; Bassetas, M. The Benzoin Condensation Catalysis By Bis(azolin-2-ylidene)s and Bis(azolidin-2-ylidene)s and its Interpretation Within the Context of Nucleophilic Carbene Chemistry. *J. Heterocycl. Chem.* **1986**, *23*, 715–720.
- (14) Castells, J.; Lopez-Calahorra, F.; Domingo, L. Postulation of bis(thiazolin-2-ylidene)s as the catalytic species in the benzoin condensation catalyzed by a thiazolium salt plus base. *J. Org. Chem.* **1988**, *53*, 4433–4436.
- (15) Van Den Berg, H.J.; Challa, G.; Pandit, U.K. Polymer-bound thiamine models: Part I. The kinetics of thiazolium salt catalyzed benzoin formation. *J. Mol. Catal.* **1989**, *51*, 1–12.
- (16) Chen, Y.-T.; Jordan, F. Reactivity of the thiazolium C2 ylide in aprotic solvents: novel experimental evidence for addition rather than insertion reactivity. *J. Org. Chem.* **1991**, *56*, 5029–5038.
- (17) Castells, J.; Domingo, L.; Lopez-Calahorra, F.; Marti, J. New evidence supporting bis(thiazolin-2-ylidene)s as the actual catalytic species in the benzoin condensation. *Tetrahedron Lett.* **1993**, *34*, 517–520.
- (18) Chen, Y.-T.; Barletta, G. L.; Haghjoo, K.; Cheng, J. T.; Jordan, F. Reactions of Benzaldehyde with Thiazolium Salts in Me<sub>2</sub>SO: Evidence for Initial Formation of 2-(a-Hydroxybenzyl)thiazolium by Nucleophilic Addition and for Dramatic Solvent Effects on Benzoin Formation. *J. Org. Chem.* **1994**, *59*, 7714–7722.
- (19) Lopez-Calahorra, F.; Rubires, R. A kinetic study by NMR of the benzoin condensation catalyzed by thiazolium salts in mild basic conditions: a second order process in both aldehyde and pre-catalyst. *Tetrahedron* **1995**, *51*, 9713–9728.
- (20) Miyashita, H.; Kamatani, J. Organic light emitting element, display device, image information processing device, lighting device, image forming device, exposure device, and organic photoelectric conversion element. U.S. Patent Appl. 2017/0012215 A1, 2017.
- (21) Breslow, R.; Kim, R. The thiazolium catalyzed benzoin condensation with mild base does not involve a “dimer” intermediate. *Tetrahedron Lett.* **1994**, *35*, 699–702.
- (22) Breslow, R.; Schmuck, C. The mechanism of thiazolium catalysis. *Tetrahedron Lett.* **1996**, *37*, 8241–8242.
- (23) Selected reviews and highlights: (a) Zhao, K.; Enders, D. Merging N-Heterocyclic Carbene Catalysis and Single Electron Transfer: A New Strategy for Asymmetric Transformations. *Angew. Chem., Int. Ed.* **2017**, *56*, 3754–3756.
- (24) Song, R.; Chi, Y. R. N-Heterocyclic Carbene Catalyzed Radical Coupling of Aldehydes with Redox-Active Esters. *Angew. Chem., Int. Ed.* **2019**, *58*, 8628–8630.
- (25) Ishii, T.; Nagao, K.; Ohmiya, H. Recent advances in N-heterocyclic carbene-based radical catalysis. *Chem. Sci.* **2020**, *11*, 5630–5636.
- (26) Ishii, T.; Kakeno, Y.; Nagao, K.; Ohmiya, H. N-Heterocyclic Carbene-Catalyzed Decarboxylative Alkylation of Aldehydes. *J. Am. Chem. Soc.* **2019**, *141*, 3854–3858.
- (27) Ishii, T.; Ota, K.; Nagao, K.; Ohmiya, H. N-Heterocyclic Carbene-Catalyzed Radical Relay Enabling Vicinal Alkylacylation of Alkenes. *J. Am. Chem. Soc.* **2019**, *141*, 14073–14077.
- (28) Kim, I.; Im, H.; Lee, H.; Hong, S. N-Heterocyclic carbene-catalyzed deaminative cross-coupling of aldehydes with Katritzky pyridinium salts. *Chem. Sci.* **2020**, *11*, 3192–3197.
- (29) Li, J.-L.; Liu, Y.-Q.; Zou, W.-L.; Zeng, R.; Zhang, X.; Liu, Y.; et al. Radical Acylfluoroalkylation of Olefins through N-Heterocyclic Carbene Organocatalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 1863–1870.
- (30) Zhang, B.; Peng, Q.; Guo, D.; Wang, J. NHC-Catalyzed Radical Trifluoromethylation Enabled by Togni Reagent. *Org. Lett.* **2020**, *22*, 443–447.
- (31) Ota, K.; Nagao, K.; Ohmiya, H. N-Heterocyclic Carbene-Catalyzed Radical Relay Enabling Synthesis of  $\delta$ -Ketocarboxyls. *Org. Lett.* **2020**, *22*, 3922–3925.
- (32) Kakeno, Y.; Kusakabe, M.; Nagao, K.; Ohmiya, H. Direct Synthesis of Dialkyl Ketones from Aliphatic Aldehydes through Radical N-Heterocyclic Carbene Catalysis. *ACS Catal.* **2020**, *10*, 8524–8529.
- (33) Liu, M.-S.; Shu, W. Catalytic, Metal-Free Amide Synthesis from Aldehydes and Imines Enabled by a Dual-Catalyzed Umpolung Strategy under Redox-Neutral Conditions. *ACS Catal.* **2020**, *10*, 12960–12966.
- (34) Yang, H.-B.; Wang, Z.-H.; Li, J.-M.; Wu, C. Modular synthesis of  $\alpha$ -aryl  $\beta$ -perfluoroalkyl ketones via N-heterocyclic carbene catalysis. *Chem. Commun.* **2020**, *56*, 3801–3804.
- (35) Ishii, T.; Nagao, K.; Ohmiya, H. Radical N-heterocyclic carbene catalysis for  $\beta$ -ketocarbonyl synthesis. *Tetrahedron* **2021**, *91*, 132212.
- (36) Kusakabe, M.; Nagao, K.; Ohmiya, H. Radical Relay Trichloromethylacylation of Alkenes through N-Heterocyclic Carbene Catalysis. *Org. Lett.* **2021**, *23*, 7242–7247.
- (37) Matsuki, Y.; Ohnishi, N.; Kakeno, Y.; Takemoto, S.; Ishii, T.; Nagao, K.; Ohmiya, H. Aryl radical-mediated N-heterocyclic carbene catalysis. *Nature Commun.* **2021**, *12*, 3848.
- (38) Gao, Y.; Quan, Y.; Li, Z.; Gao, L.; Zhang, Z.; Zou, X.; et al. Organocatalytic Three-Component 1,2-Cyanoalkylacylation of Alkenes via Radical Relay. *Org. Lett.* **2021**, *23*, 183–189.
- (39) Chen, L.; Jin, S.; Gao, J.; Liu, T.; Shao, Y.; Feng, J.; et al. N-Heterocyclic Carbene/Magnesium Cocatalyzed Radical Relay Assembly of Aliphatic Keto Nitriles. *Org. Lett.* **2021**, *23*, 394–399.
- (40) Yang, H. B.; Wan, D.-H. C-C Bond Acylation of Oxime Ethers via NHC Catalysis. *Org. Lett.* **2021**, *23*, 1049–1053.

- (41) Gao, Y.; Quan, Y.; Li, Z.; Gao, L.; Zhang, Z.; Zou, X.; Yan, R.; Qu, Y.; Guo, K. Organocatalytic Three-Component 1,2-Cyanoalkylation of Alkenes via Radical Relay. *Org. Lett.* **2021**, *23*, 183–189.
- (42) Chen, L.; Lin, C.; Zhang, S.; Zhang, X.; Zhang, J.; Xing, L.; Guo, Y.; Feng, J.; Gao, J.; Du, D. 1,4-Alkylcarbonylation of 1,3-Enynes to Access Tetra-Substituted Allenyl Ketones via an NHC-Catalyzed Radical Relay. *ACS Catal.* **2021**, *11*, 13363–13373.
- (43) Ren, S.-C.; Lv, W.-X.; Yang, X.; Yan, J.-L.; Xu, J.; Wang, F.-X.; Hao, L.; Chai, H.; Jin, Z.; Chi, Y. R. Carbene-Catalyzed Alkylation of Carboxylic Esters via Direct Photoexcitation of Acyl Azolium Intermediates. *ACS Catal.* **2021**, *11*, 2925–2934.
- (44) Jin, S.; Sui, X.; Haug, G. C.; Nguyen, V. D.; Dang, H. T.; Arman, H. D.; Larionov, O. V. N-Heterocyclic Carbene-Photocatalyzed Tricomponent Regioselective 1,2-Diacylation of Alkenes Illuminates the Mechanistic Details of the Electron Donor-Acceptor Complex-Mediated Radical Relay Processes. *ACS Catal.* **2022**, *12*, 285–294.
- (45) Liu, M.-S.; Min, L.; Chen, B.-H.; Shu, W. Dual Catalysis Relay: Coupling of Aldehydes and Alkenes Enabled by Visible-Light and NHC-Catalyzed Cross-Double C-H Functionalizations. *ACS Catal.* **2021**, *11*, 9715–9721.
- (46) Zhang, Z.; Zou, X.; Li, Z.; Gao, Y.; Qu, Y.; Quan, Y.; Zhou, Y.; Li, J.; Sun, J.; Guo, K. N-Heterocyclic carbene-catalyzed radical ring-opening acylation of oxime esters with aldehydes. *Org. Chem. Front.* **2021**, *8*, 6074–6079.
- (47) Cai, Y.; Chen, J.; Huang, Y. N-Heterocyclic Carbene-Catalyzed 1,4-Alkylacylation of 1,3-Enynes. *Org. Lett.* **2021**, *23*, 9251–9255.
- (48) Li, Q.-Z.; Zeng, R.; Fan, Y.; Liu, Y.-Q.; Qi, T.; Zhang, X.; Li, J.-L. Remote C(sp<sup>3</sup>)-H Acylation of Amides and Cascade Cyclization via N-Heterocyclic Carbene Organocatalysis. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202116629.
- (49) Li, Q.-Z.; Liu, Y.-Q.; Kou, X.-X.; Zou, W.-L.; Qi, T.; Xiang, P.; Xing, J.-D.; Zhang, X.; Li, J.-L. Oxidative Radical NHC Catalysis: Divergent Difunctionalization of Olefins through Intermolecular Hydrogen Atom Transfer. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202207824.
- (50) Man, Y.; Zeng, X.; Xu, B. Synthesis of Thioesters from Aldehydes via N-Heterocyclic Carbene (NHC) Catalyzed Radical Relay. *Chem.—Eur. J.* **2022**, *29*, e202203716.
- (51) Liu, W.-D.; Lee, W.; Shu, H.; Xiao, C.; Xu, H.; Chen, X.; Houk, K. N.; Zhao, J. Diastereoselective Radical Aminoacylation of Olefins through N-Heterocyclic Carbene Catalysis. *J. Am. Chem. Soc.* **2022**, *144*, 22767–22777.
- (52) Liu, Y.-Q.; Li, Q.-Z.; Kou, X.-X.; Zeng, R.; Qi, T.; Zhang, X.; Peng, C.; Han, B.; Li, J.-L. Radical Acylalkylation of 1,3-Enynes To Access Allenic Ketones via N-Heterocyclic Carbene Organocatalysis. *J. Org. Chem.* **2022**, *87*, S229–S241.
- (53) Han, Y.-F.; Huang, Y.; Liu, H.; Gao, Z.-H.; Zhang, C.-L.; Ye, S. Photoredox cooperative N-heterocyclic carbene/palladium-catalysed alkylacylation of alkenes. *Nature Commun.* **2022**, *13*, 5754.
- (54) Zhang, B.; Qi, J.-Q.; Liu, Y.; Li, Z.; Wang, J. Visible-Light-Driven Bisfunctionalization of Unactivated Olefins via the Merger of Proton-Coupled Electron Transfer and Carbene Catalysis. *Org. Lett.* **2022**, *24*, 279–283.
- (55) Chen, L.; Wang, J.; Lin, C.; Zhu, Y.; Du, D. CF<sub>2</sub>Br<sub>2</sub> as a Source for Difluoroolefination of 1,3-Enynes via N-Heterocyclic Carbene Catalysis. *Org. Lett.* **2022**, *24*, 7047–7051.
- (56) She, K.; Liang, F.; Tian, S.; Wang, H.; Tsui, G. C.; Wang, Q. Organocatalytic Three-Component Acyldifluoromethylation of Vinylarenes via N-Heterocyclic Carbene-Catalyzed Radical Relay. *Org. Lett.* **2022**, *24*, 4840–4844.
- (57) Man, Y.; Liu, S.; Xu, B.; Zeng, X. N-Heterocyclic-Carbene-Catalyzed C-H Acylation via Radical Relay. *Org. Lett.* **2022**, *24*, 944–948.
- (58) Zhang, B.; Wang, J. Acyldifluoromethylation Enabled by NHC-Photoredox Cocatalysis. *Org. Lett.* **2022**, *24*, 3721–3725.
- (59) Regnier, V.; Romero, E. A.; Molton, F.; Jazzar, R.; Bertrand, G.; Martin, D. What Are the Radical Intermediates in Oxidative N-Heterocyclic Carbene Organocatalysis? *J. Am. Chem. Soc.* **2019**, *141*, 1109–1117.
- (60) Delfau, L.; Nichilo, S.; Molton, F.; Broggi, J.; Tomás-Mendivil, E.; Martin, D. Critical Assessment of the Reducing Ability of Breslow-type Derivatives and Implications for Carbene-Catalyzed Radical Reactions. *Angew. Chem., Int. Ed.* **2021**, *60*, 26783–26789.
- (61) Rehbein, J.; Ruser, S. M.; Phan, J. NHC-Catalyzed Benzoin Condensation - Is It All Down to the Breslow Intermediate? *Chem. Sci.* **2015**, *6*, 6013–6018.
- (62) Phan, J.; Ruser, S. M.; Zeitler, K.; Rehbein, J. NHC-stabilized radicals in the formal hydroacylation of alkynes. *Eur. J. Org. Chem.* **2018**, 2–3, 557–561.
- (63) Rammial, T.; McKenzie, I.; Gorodetsky, B.; Tsang, E. M. W.; Clyburne, J. A. C. Reactions of N-heterocyclic carbenes (NHCs) with one-electron oxidants: possible formation of a carbenecation radical. *Chem. Commun.* **2004**, 1054–1055.
- (64) Dong, Z.; Pezzato, C.; Sienkiewicz, A.; Scopelliti, R.; Fadaei-Tirani, F.; Severin, K. SET processes in Lewis acid-base reactions: the tritylation of N-heterocyclic carbenes. *Chem. Sci.* **2020**, *11*, 7615–7618.
- (65) Connelly, N. G.; Geiger, W. E. Chemical Redox Agents for Organometallic Chemistry. *Chem. Rev.* **1996**, *96*, 877–910.
- (66) Wang, C.; Liu, L. NHC-catalyzed oxindole synthesis via single electron transfer. *Org. Chem. Front.* **2021**, *8*, 1454–1460.
- (67) Su, L.; Sun, H.; Liu, J.; Wang, C. Construction of Quaternary Carbon Center via NHC Catalysis Initiated by an Intermolecular Heck-Type Alkyl Radical Addition. *Org. Lett.* **2021**, *23*, 4662–4666.
- (68) Liu, L.; Zhou, C.-Y.; Wang, C. Construction of highly congested quaternary carbon centers by NHC catalysis through dearomatization. *Green Synth. Catal.* **2022**, DOI: 10.1016/j.gresc.2022.05.010.
- (69) Li, Q.; Zhou, C.-Y.; Wang, C. Divergent Construction of Heterocycles by SOMophilic Isocyanide Insertion under N-Heterocyclic Carbene Catalysis. *Org. Lett.* **2022**, *24*, 7654–7658.
- (70) Lorcy, D.; Bellec, N. Dithiadiazafulvalenes: Promising Precursors of Molecular Materials. *Chem. Rev.* **2004**, *104*, 5185–5202.
- (71) Doni, E.; Murphy, J. A. Evolution of neutral organic super-electron-donors and their applications. *Chem. Commun.* **2014**, *50*, 6073–6087.
- (72) Broggi, J.; Terme, T.; Vanelle, P. Organic electron donors as powerful single-electron reducing agents in organic synthesis. *Angew. Chem., Int. Ed.* **2014**, *53*, 384–413.
- (73) Tormos, G. V.; Bakker, M. G.; Wang, P.; Lakshmikantham, V.; Cava, M. P.; Metzger, R. M. Dithiadiazafulvalenes - New Strong Electron Donors. Synthesis, Isolation, Properties, and EPR Studies. *J. Am. Chem. Soc.* **1995**, *117*, 8528–8535.
- (74) Olivier, C.; Toplak, R.; Guerro, M.; Carlier, R.; Lorcy, D. Novel route to crown ether annelated dithiadiazafulvalenes. *C. R. Chimie* **2005**, *8*, 235–242.
- (75) Bellec, N.; Guerin, D.; Lorcy, D.; Robert, A.; Carlier, R.; Tallec, A.; Shono, T.; Toftlund, H. Chemical and Electrochemical Investigations on Thiazolium Salts: a Route to Powerful Donors in the Dithiadiazafulvalene Series. *Acta Chem. Scand.* **1999**, *53*, 861–866.
- (76) Koizumi, T.; Bashir, N.; Kennedy, A. R.; Murphy, J. A. Diazadithiafulvalenes as electron donor reagents. *J. Chem. Soc., Perkin Trans. I* **1999**, 3637–3643.
- (77) Kakeno, Y.; Kusakabe, M.; Nagao, K.; Ohmiya, H. Direct Synthesis of Dialkyl Ketones from Aliphatic Aldehydes through Radical N-Heterocyclic Carbene Catalysis. *ACS Catal.* **2020**, *10*, 8524–8529.
- (78) Borden, W. T. Pyramidalized alkenes. *Chem. Rev.* **1989**, *89*, 1095–1109.
- (79) Hitchcock, P. B. Effect of N-Aryl Substituents on the Reactivity of Electron-rich Olefins as Precursors of Transition-metal-Carbene Complexes. The Crystal and Molecular Structure of NN'N''N'''-Tetraphenyl bis(1,3-imidazolidin-2-ylidene), and its n-Electron Distribution. *J. Chem. Soc., Dalton Trans.* **1979**, 1314–1317.
- (80) DFT calculations were performed with the Gaussian09 software package: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.;

Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; et al. *Gaussian 09*, revision D.01; Gaussian Inc.: Wallingford, CT, 2009.

(81) Messelberger, J.; Grünwald, A.; Goodner, S. J.; Zeilinger, F.; Pinter, P.; Miehl, M. E.; Heinemann, F. W.; Hansmann, M. M.; Munz, D. Aromaticity and sterics control whether a cationic olefin radical is resistant to disproportionation. *Chem. Sci.* **2020**, *11*, 4138–4149.

(82) Experimental values for isotropic hyperfine constants were extracted from EPR spectra by fitting with the EasySpin simulation package: Stoll, S.; Schweiger, A. EasySpin, a comprehensive software package for spectral simulation and analysis in EPR. *J. Magn. Reson.* **2006**, *178*, 42–55.

(83) Ogawa, K. A.; Boydston, A. J. Electrochemical Characterization of Azolium Salts. *Chem. Lett.* **2014**, *43*, 907–909.

(84) Schotten, C.; Bourne, R. A.; Kapur, N.; Nguyen, B. N.; Willans, C. E. Electrochemical Generation of N-Heterocyclic Carbenes for Use in Synthesis and Catalysis. *Adv. Synth. Catal.* **2021**, *363*, 3189–3200.

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