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How to Enhance the Efficiency of Breslow

Intermediates for SET Catalysis

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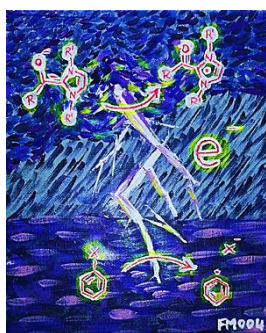
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ABSTRACT: Oxidative carbene organocatalysis, which proceeds via single electron transfer (SET) pathways, has been limited by the moderately reducing properties of deprotonated Breslow intermediates **BI**⁻ derived from thiazol-2-ylidene **1** and 1,2,4-triazolylidene **2**. Using

computational methods, we assess the redox potentials of **BI**⁻s based on ten different types of known stable carbenes and report our findings concerning the key parameters influencing the steps of the catalytic cycle. From the calculated values of the first oxidation potential of **BI**⁻s derived from carbenes **1** to **10**, it appears that apart from the diamidocarbene **7**, all the others are more reducing than thiazol-2-ylidene **1** and the 1,2,4-triazolylidene **2**. We observed that while the reducing power of **BI**⁻s significantly decreases with increasing solvent polarity, the redox potential of the oxidant can increase at a greater rate, thus facilitating the reaction. The cation, associated with the base, also plays an important role when a non-polar solvent is used; large and weakly



coordinating cations such as Cs⁺ are beneficial. The radical-radical coupling step is probably the most challenging step due to both electronic and steric constraints. Based on our results, we predict that mesoionic carbene **3** and abnormal NHC **4** are the most promising candidates for oxidative carbene organocatalysis.

While stable singlet carbenes have found numerous applications when associated with metals,¹ they also display a rich chemical reactivity on their own merits. Thiazol-2-ylidenes **1**² and 1,2,4-triazolyliidenes **2**³ have been long known to induce umpolung reactivity of carbonyl compounds, giving rise to the formation of nucleophilic Breslow intermediates (**BIs**).^{4,5} The latter allow for a variety of chemical transformations, which proceed in a well understood ionic mode, via electron-pair-transfer mechanisms. Several decades ago, it was shown that **BIs** are also involved in single-electron transfer (SET)-based catalysis during the oxidative decarboxylation of pyruvate to form acetyl-CoA.⁶ However, it is only in 2008 that Studer and coworkers⁷ developed a TEMPO-mediated biomimetic oxidation of aldehydes to TEMPO-esters. Since that time, other oxidants,

such as nitroarenes, nitroalkenes, CX₄, C₂Cl₆, sulfonic carbamate, redox-active esters, the Togni's reagent, polyfluoroalkyl halides, Katritzky pyridinium salts, oxime ester, and recently aryl iodides (*vide infra*) were also employed to achieve oxidative reactions with aldehydes.⁸

It was initially postulated that the catalytic cycle proceeded through a SET from the **BI**s leading to the radical cations **BI^{•+}** which was regarded as the key intermediates. However, mechanistic and electrochemical investigations of standard enols,⁹ as well as recent studies, showed that the active paramagnetic species is rather the corresponding neutral radical **BI[•]**.¹⁰ Moreover, we showed that the SET does not occur from the **BI**, but from their deprotonated form, **BI⁻**.¹⁰ Consequently, the catalytic cycle of the oxidative reactions of aldehydes involves six steps, which are described in Figure 1.

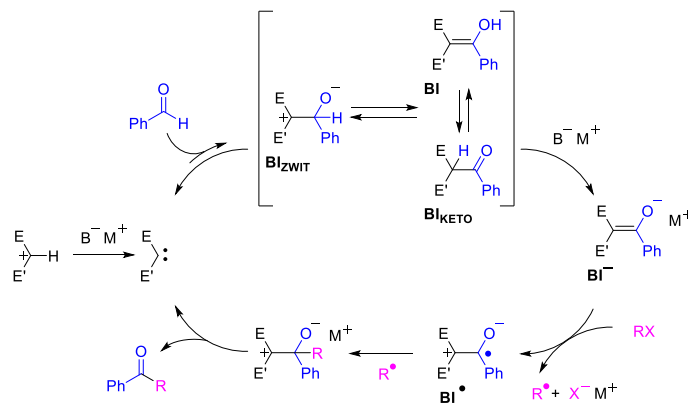


Figure 1. Catalytic cycle for carbene oxidative organocatalytic reactions.

So far, with the exception of our work¹¹ employing mesoionic carbene (MICs) **3**,¹² thiazol-2-ylidenes¹ and 1,2,4-triazolyliidenes **2**³ have been the only carbenes efficiently used in the catalytic oxidative reactions of aldehydes. Due to the moderately reducing properties of **BI⁻**s derived from **1** and **2**, the reported SET catalyzed reactions require a relatively strong oxidant (*vide supra*), which dramatically limits their synthetic applications. Motivated by the availability of a library of stable singlet carbenes with varying electronic and steric properties, we wondered if we could

predict the best candidates to promote these reactions. Obviously, one of the key factors is the reducing power of the BI^- . Since electrochemical studies can be difficult to implement and adjust to specific reaction conditions for highly reactive intermediates, we used computational methods to assess the redox potentials of BI^- s based on a variety of known stable carbenes. We also report our findings concerning each step of the catalytic cycle, including the possible pitfalls.

DFT calculations¹³ (in Jaguar 9.1)¹⁴ at the PBE/6-31G**//cc-pVTZ¹⁵ level of theory with the Poisson-Boltzmann solvation model were used for carbenes **1–10** (Fig. 2) and their related catalytic intermediates. All redox potentials are referenced to the computed ferrocene/ferrocenium couple¹⁶ and values are given in acetonitrile unless noted otherwise. A basis set and functional benchmark as well as the reproduction of experimental values, generally within experimental accuracy, validates our computational methodology (see SI).

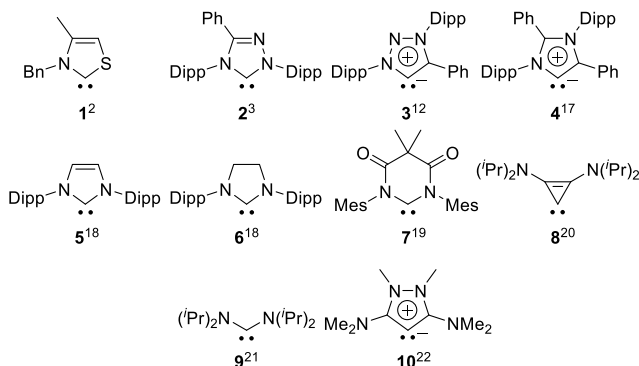


Figure 2. Carbenes considered in this manuscript.

First and second oxidation of BI^- s. We found that the first (E^1) and second (E^2) oxidation potentials of BI^- s based on carbenes **1–10** and benzaldehyde spans over a large range from -1.50 (**2**) to -2.27 V (**5**), and -0.31 (**7**) to -2.43 V (**10**), respectively (Table 1 and Fig. 3)

Because of the rather high computational expense of modeling redox potentials, we also looked into simpler predictive indicators connecting the carbenes' electronic properties and the redox

potential of their **BI**⁻s. The HOMO orbital energies of carbenes **1-10** (and further derivatives detailed in the SI) gives a rough indication of the redox potential ranking of **BI**⁻s (Pearson-*r*: -0.666), but notable outliers exist. For example, the computed redox potentials for the **BI**⁻s derived from MIC **3** (-2.22 V) and imidazol-2-ylidene **5** (-2.27 V) are predicted to be comparable, while their HOMO levels are significantly different (-4.65 and -4.94 eV, respectively). Just as for organometallic complexes, the π -accepting ability of carbenes plays a significant role. Thus, a better predictor can easily be obtained using $\frac{1}{2}(\epsilon_3^{HOMO} + \epsilon_3^{LUMO})$ which is closely related to Mulliken's electronegativity (Pearson-*r*: -0.74, R^2 : 0.55, Fig. 4).²³ Indeed, **3-BI**⁻ exhibits a lower LUMO than **5-BI**⁻ (LUMO: -2.14 and -1.23 eV, respectively) which readily explains that despite its higher HOMO, the reduction power of its **BI**⁻ is comparable to that of **5**.

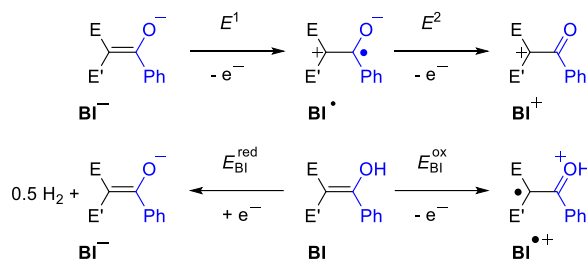


Figure 3. First and second oxidation of **BI**⁻ (top); reduction and oxidation of **BI** (bottom).

From these data, it clearly appears that MICs **3**¹² and *a*NHCs **4**,¹⁷ which lead to highly reducing **BI**⁻s, are very promising candidates than thiazol-2-ylidenes **1**² and the 1,2,4-triazolyliidenes³ that have widely been used for SET catalysis. Their strongly negative redox potential indicates that they have potential for the activating of weak oxidants.

Table 1. HOMO and LUMO energies of carbenes **1–10** and redox potentials of the corresponding BI⁻s and BIs.

	HOMO ^a	LUMO ^a	E^1 ^b	E^2 ^b	$E_{\text{BI}}^{\text{red}}$ ^b	$E_{\text{BI}}^{\text{ox}}$ ^b
1	-5.05	-1.51	-1.58	-0.72	-1.57	-0.57
2	-5.22	-2.12	-1.50	-0.93	-1.65	-0.61
3	-4.65	-2.14	-2.22	-1.12	-1.94	-0.95
4	-4.29	-2.18	-2.16	-1.59	-2.00	-1.40
5	-4.94	-1.23	-2.27	-1.10	-2.10	-0.88
6	-4.78	-1.12	-1.94	-1.05	-1.97	-0.57
7	-4.99	-2.81	-1.05	-0.31	-1.65	+0.37
8	-4.20	-0.15	-2.26	-1.43	-2.47	-1.06
9	-3.63	+0.15	-1.89	-1.14	-2.16	-0.58
10	-3.59	-0.87	-2.25 ^c	-2.43 ^c	-2.34	-1.91

^a: in eV. ^b: in V. ^c: See SI for more details.

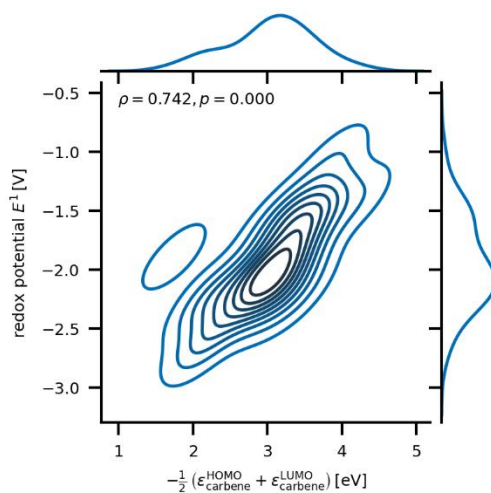


Figure 4. Distribution plot showing the correlation between E^1 and $\frac{1}{2}(\epsilon_3^{HOMO} + \epsilon_3^{LUMO})$ for all computed carbene/**BI**⁻ pairs, see SI for a full list.

Oxidation and reduction of BIs. Because of the earlier assumption that **BIs** were the active reducing agent, we also calculated their oxidation and reduction potentials. We found that the oxidation of **BIs** also covers a large range [+0.37 (**7**) to -1.91 V (**10**)], and roughly follows the order observed for **BI**⁻s. Importantly, they are on average 1.1 V less reducing than the corresponding **BI**⁻s. The resulting **BI**^{•+}s are strongly acidic as shown by the predicted very low pKa values (see SI), which readily explain the involvement of the neutral radicals **BI**[•] instead of the radical cations **BI**^{•+} in catalysis.¹⁰

A reduction process was also experimentally observed by cyclic voltammetry for a Breslow homoenol derived from **6**, in the form of an irreversible peak at -1.90 V. The outcome of this process was unclear.¹⁰ Our calculations show that the reduction of the **BI** derived from **6**, computed at -1.97 V, is coupled with a fast or concerted hydrogen evolution resulting in the formation of the corresponding **BI**⁻ (see SI). Interestingly, with some carbenes (**1**, **3-5**), the **BI**⁻ can readily reduce the corresponding **BI** giving **BI**[•], half an equivalent of H₂, and regenerating the **BI**⁻. The overall process is the electrocatalytic reduction of **BIs** into **BI**[•]s and H₂. In these cases, this competing pathway could prevent efficient oxidative catalytic processes.

Influence of the solvent and cation on the reducing properties of BI⁻s. After examining the role of the carbene, we turned our attention to the influence of the solvent and cation on the reducing properties of **BI**⁻s. We modelled solvation with a self-consistent reaction field approach (SCRf) and calculated the solvation with 25 distinct dielectric constants in the range of 1 (vacuum) to 100 (Fig. 5). Note that this model does not capture dispersion effects or explicit coordination which implies that apolar solvents may not be captured accurately. We observed that the reductant

strength power of the BI^- significantly decreases with increasing polarity of the solvent, which is a stabilizing factor for charged molecules. For example, the redox potential of the couples $\text{BI}^-/\text{BI}^\bullet$ derived from **1** and **3** shifts from -2.42 and -2.92 V in *t*BuOMe ($\epsilon = 4.5$) to -1.48 and -2.15 V in water ($\epsilon = 78.4$). Therefore, at first glance, we could assume that oxidative catalysis involving BI^- s should be favored by non-polar solvents, but this is not necessarily the case, as evidenced by recent work by Ohmiya and coworkers.²⁴ They reported the arylacylation of styrene in DMSO/H₂O, with phenyl iodide as an oxidant ($E_{\text{pa}} = -2.69$ V in CH₃CN), and thiazol-2-ylidene **1** as a catalyst, the BI^- of which has a reported $E_{1/2} = -1.43$ V in CH₃CN. To rationalize this thermodynamically unfavorable reduction, they cite the previous work by Saveant and coworkers²⁵ and wrote “the small reorganization energy of the enolate form of the Breslow intermediate and the fast mesolytic cleavage of the C(sp²)-I bond makes the pathway kinetically feasible”. Interestingly, our calculations show that although the redox potentials of BI^- s increase with solvent polarity, the redox potential of PhI (PhI \rightarrow Ph $^\bullet$ + I $^-$) increases at a higher rate. This is mainly due to the larger ion size of the BI^- compared to I $^-$; the latter being better stabilized by polar solvents. Consequently, the reaction becomes thermodynamically favorable, as shown by ΔG which decreases from -0.71 in *t*BuOMe to -12.63 kcal \cdot mol⁻¹ in water for **1** (Fig. 5, top). In the case of carbene **3**, the ΔG changes from -3.81 in *t*BuOMe to -19.35 kcal \cdot mol⁻¹ in water (Fig. 5, bottom). Due to the higher reducing power of MIC **3** compared to thiazol-2-ylidene **1**, it is not surprising that the former is able to promote the arylacylation of styrene in *t*BuOMe under milder conditions¹¹ than those reported for thiazol-2-ylidene **1** in water.²⁴

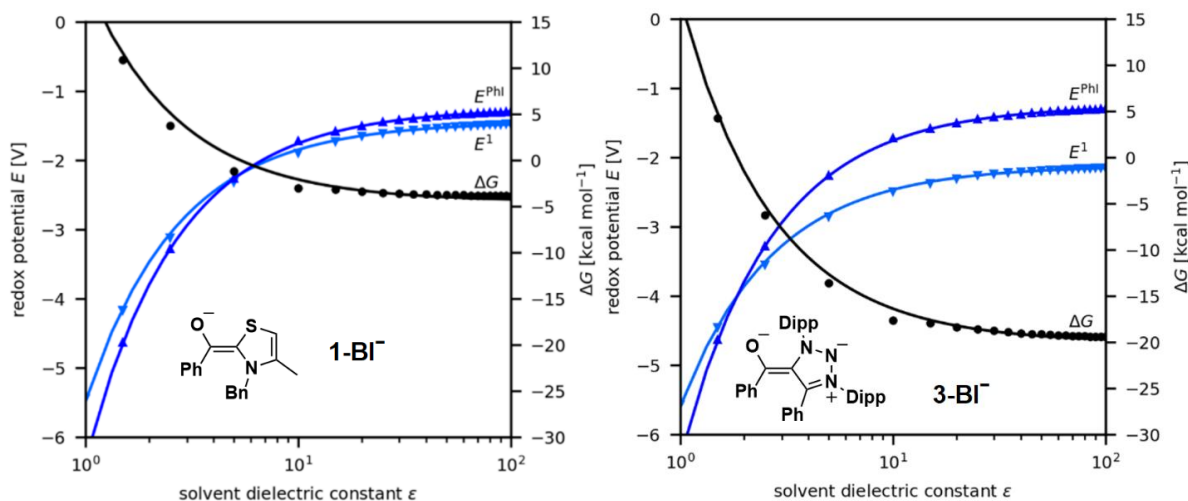


Figure 5. The thermodynamic feasibility of PhI reduction by BI^- responds differently with different carbenes which is illustrated for **1** (left) and **3** (right) with the corresponding redox potentials and the redox reaction's ΔG .

Regarding the role of the cation, we limited our study to alkali metals (Li, Na, K and Cs) because of their predominant use as counteraction of the base in oxidative organocatalysis. The salts were modelled, and a Boltzmann two-state distribution was used to predict the respective equilibrium position of the association/dissociation ($\text{BI}^- \text{M}^+ \rightleftharpoons \text{BI}^- + \text{M}^+$). We used the $1/\epsilon$ dependency of the employed solvation model to inter- and extrapolate from three explicitly computed solvation energies (in CH_3CN $\epsilon = 37.5$, THF $\epsilon = 7.6$, and $t\text{BuOMe}$ $\epsilon = 4.5$). Unsurprisingly, we found that in polar solvents, the role of the cation is minimal due to the solvent-induced BI^-/M^+ separation. In contrast, in non-polar solvents, the smaller cations significantly increase the redox potential of $\text{BI}^- \text{M}^+$ (Fig. 6). Therefore, large and weakly coordinating cations are beneficial in a non-polar medium.

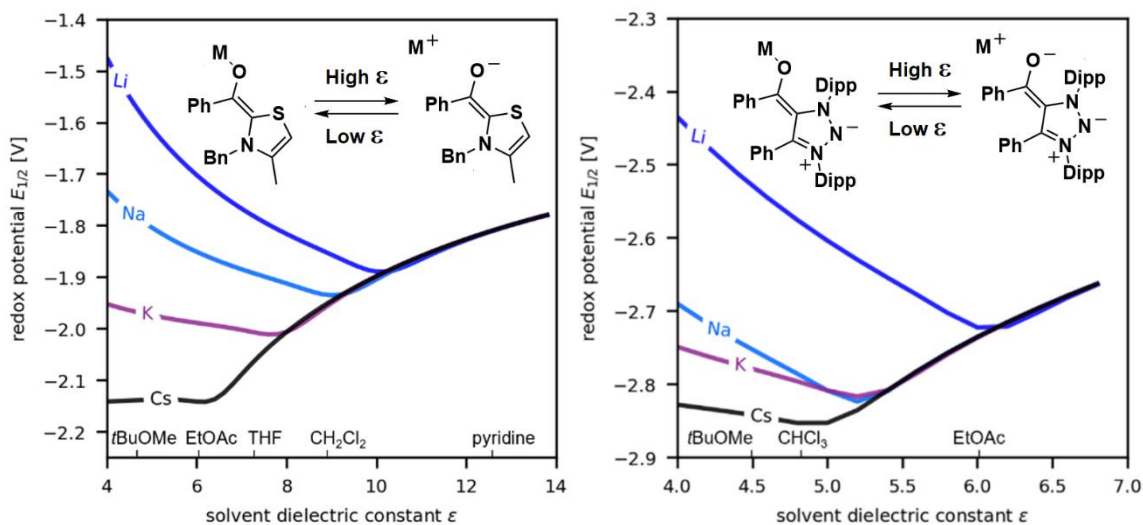


Figure 6. Influence of the cation (Li, Na, K, Cs) on the first reduction potential of **BI**⁻**M**⁺ salts derived from carbenes **1** (left) and **3** (right) with the solvent polarity.

Formation of the deprotonated Breslow Intermediate (BI⁻). The initial step of the catalytic cycle in carbene oxidative organocatalysis is the deprotonation of the carbene-conjugate acid. Our results, combined with those found in the literature, suggest that even carbonates are basic enough for all carbene precursors, provided that an aldehyde is present to shift the equilibrium.²⁴

The carbene must be nucleophilic enough to react with benzaldehyde in order to obtain the primary form zwitterionic adduct **BI_{ZWIT}**. We found this step to be endergonic with all carbenes **1–10** (ΔG s ranging from +3.7 to +18.2 kcal·mol⁻¹), but if we combine this process with the tautomerization into **BI** or **BI_{KETO}**, the free enthalpies range from -15.0 (**7**) to +11.6 kcal·mol⁻¹ (**10**), suggesting that this chemical transformation should be achievable at room temperature with all carbenes **1–10**. Note that the **BI_{KETO}** tautomer is rarely considered, although it has been observed experimentally. Berkessel and coworkers²⁶ have reported the rearrangement of **BI** to **BI_{KETO}** with NHCs of types **5** and **6**, and our group has shown that the **BI_{KETO}** tautomer was the thermodynamic product when cyclic (alkyl)(amino)carbenes²⁷ were reacted with benzaldehyde.²⁸

We calculated the ΔG for the deprotonation of any tautomer of Breslow intermediates using $t\text{BuOK}$ as a base and acetonitrile as the solvent. This process is exergonic for carbenes **1-10** (up to $\Delta G = -24.7 \text{ kcal}\cdot\text{mol}^{-1}$ for thiazol-2-ylidene **1**).

Coupling of BI \cdot with organic radicals. It is well understood that radical coupling is thermodynamically favorable when both radicals have similar singly occupied molecular orbital (SOMO) energies. We found that the SOMO levels of **BI \cdot s** generated from carbenes **1-10** lie between -4.06 (**7**) and -2.65 eV (**8**), and therefore they are electron-rich radicals (Fig. 7). The **BI \cdot s** derived from the most exploited thiazol-2-ylidene **1** and 1,2,4-triazolylidene **2** are among the least electron-rich of the series (-3.43 and -3.29 eV, respectively). Those derived from carbenes **3-5**, **8** and **9** are the most electron-rich examples (> -2.96 eV). The SOMO energy level of **BI \cdot s** readily explains the type of coupling partners which have been successfully and unsuccessfully used experimentally thus far. Tertiary alkyl radicals ($t\text{Bu}$: -3.66 eV) work very well, but phenyl radicals are far too electron-poor (-5.53 eV) to directly couple with **BI \cdot s**. However, $\text{Ph}\cdot$ can add to carbon-carbon double bonds, such as in styrene, generating a rich benzylic 1,2-diphenylethyl radical (-4.12 eV), which can couple with **BI \cdot s**. This is the concept of radical relay, which has been successfully used experimentally.^{11, 24, 8g} Based on the calculated SOMO energy levels, further promising candidates are $i\text{Pr}\cdot$ (-3.99 eV), $\text{benzyl}\cdot$ (-4.35 eV), and radicals in α -position of an heteroatom lone pair such as $\text{EtOCH}\cdot\text{CH}_3$ (-3.31 eV). Note also that it is easy to tune the redox potential of some of the **BI \cdot s**, especially those for which an electron-withdrawing group can be placed in α -position of the carbene center. A good example are the MIC-derived **BI \cdot s**. When replacing the phenyl group on the carbon atom of **3** by COOMe , the SOMO energy level decreases from -2.85 eV to -3.23 eV.

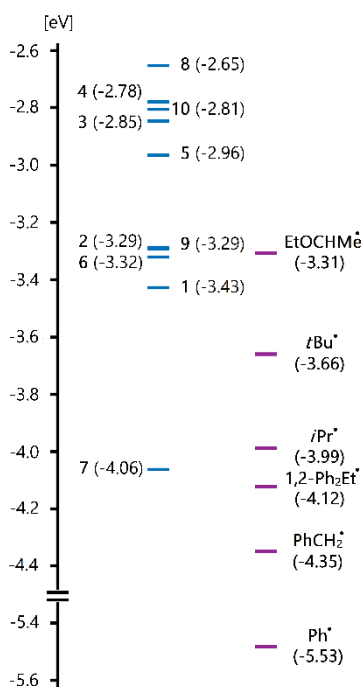


Figure 7. SOMO energy levels of **BI**[•] derived from carbenes **1-10**.

The radical-radical coupling step is also probably the most challenging step in carbene oxidative organocatalysis from a steric standpoint. We saw this e.g. in the MIC-catalyzed arylacylation of styrenes, where a Ph-substituent next to the carbene-site almost entirely suppressed the reaction.¹¹ Outside of their early discovery and affordable production, a major reason for the success of NHCs like **5** and **6** as ligands in transition metal catalysis is their large steric bulk which improves the reductive elimination step. In contrast, in carbene oxidative organocatalysis, steric bulk hampers the efficiency of the radical-radical coupling step, which can explain the superiority of **1** and **3**. To evaluate the steric demands associated with the **BI**[•]s, we computed their buried volumes (V_{bur}),²⁹ a technique usually applied to NHC transition metal complexes.³⁰ The V_{bur} was measured within a sphere of a 3.5 Å radius centered at the carbonyl carbon. Topographic steric maps show the large difference between **BI**[•]s derived from thiazol-2-ylidene **1** (**1-BI**[•]) and imidazolylidene **5** (**5-BI**[•]) in the amount of steric protection (Fig. 8). Carbenes known to promote oxidative organocatalytic

reactions lead to **BI**[•] with buried volumes below 70%. In the case of **3**, substituting the Dipp groups on N atoms with Ph groups and the Ph on the carbon atom with an H atom decreases the V_{bur} from 66 to 52 %. In this context, *a*NHC **4**, which is also stable with a hydrogen on the alpha-carbon seems particularly promising, yielding V_{bur} of 54% with Ph groups in all the other positions.

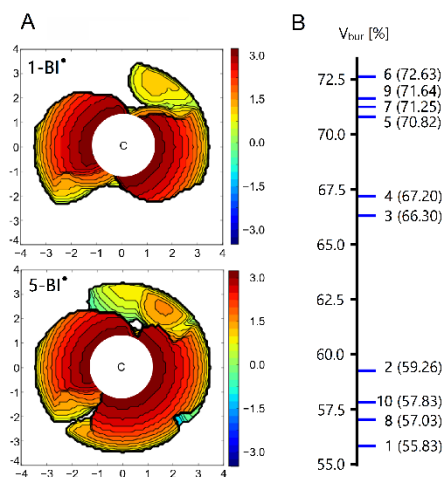


Figure 8. A: Steric maps of **1-BI**[•] and **5-BI**[•]; B: Buried volumes of **BI**[•] derived from carbenes **1-10**.

All carbenes **1-10** are nucleophilic enough to react with benzaldehyde to give the corresponding BIs. However, according to the HOMO energies, the typically used carbenes **1** and **2** are the least nucleophilic of the series, and thus the other carbenes could possibly allow for the use of less electrophilic partners than aryl aldehydes. The deprotonation of the BIs is exergonic in all cases, and thus is not a hurdle. From the calculated values of the first oxidation potential of BI[•] derived from carbenes **1-10**, it clearly appears that, apart from the diamidocarbene **7**, all the others are more reducing than thiazol-2-ylidene **1** and the 1,2,4-triazolylidene **2**. We observed that the reducing power of BI[•] significantly decreases with increasing polarity of the solvent. At first glance, this could imply that oxidative catalysis should be favored by non-polar solvents, but we found, with PhI as an example, that the redox potential of the oxidant can increase at a higher rate,

and thus can facilitate the reaction. The cation, associated with the base used to deprotonate the conjugate acid of the carbenes, also plays an important role when a non-polar solvent is used; large and weakly coordinating cations such as Cs⁺ are beneficial. The radical-radical coupling step is probably the most challenging step in carbene oxidative organocatalysis due to both electronic and steric constraints. According to the calculated SOMO energy level, all the BI[•]s derived from carbenes 1-10 are electron-rich, which readily explains the type of coupling partners which have been successfully and unsuccessfully used so far experimentally. Among radicals which have not yet been used, we found ^tPr[•], tolyl[•], and radicals in α -position of a heteroatom lone pair should work. Importantly, the range of the promising radical candidates could be expanded by tuning the redox potential of BI[•]s. This can be readily accomplished for carbenes in which an electron-withdrawing group can be placed in α -position of the carbene center; MIC **3** and aNHC **4** are excellent candidates. Steric bulk can also hamper the efficiency of the radical-radical coupling step, which can explain the superiority of **1** and **3** over imidazol-2-ylidenes **5** and imidazolin-2-ylidenes **6**, which require bulky substituents on both nitrogen atoms for their stability. In this context, MIC **3** and aNHC **4**, which are stable with a hydrogen on the carbon α to the carbene center, appear particularly promising.

ASSOCIATED CONTENT

Supporting Information. Theoretical procedures and details are included in the supporting information. This material is available free of charge via the internet at <http://pubs.acs.org>. The code for some of the data exploration and for making some of the figures can be found at: https://github.com/BaikgrpKAIST/FIGS-BIs_for_SET_catalysis.

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Author Contributions

Calculations were performed by F.F.M. The study was designed, and the manuscript was written with contributions from all authors. All authors have given approval to the final version of the manuscript.

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Notes

Any additional relevant notes should be placed here.

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REFERENCES

- 1 For recent reviews, see for examples: (a) Huynh, H. V. Electronic Properties of N-Heterocyclic Carbenes and Their Experimental Determination. *Chem. Rev.* **2018**, *118*, 9457-9492. (b) Gardiner, M. G.; Ho, C. C. Recent advances in bidentate bis(N-heterocyclic carbene) transition metal complexes and their applications in metal-mediated reactions. *Coord. Chem. Rev.* **2018**, *375*, 373-388. (c) Yong, X. F.; Thurston, R.; Ho, C. Y. Electronic Effects on Chiral NHC–Transition-Metal Catalysis. *Synthesis* **2019**, *51*, 2058-2080. (d) Liang, Q.; Song, D. Iron N-heterocyclic carbene complexes in homogeneous catalysis. *Chem. Soc. Rev.* **2020**, *49*, 1209-1032. (e) Zhao, Q.; Meng, G.; Nolan, S. P.; Szostak, M. N-Heterocyclic Carbene Complexes in C–H Activation Reactions. *Chem. Rev.* **2020**, *120*, 1981-2048. (f) Jazzar, R.; Soleilhavoup, M.; Bertrand, G. Cyclic (Alkyl) and (Aryl)(amino)carbene Coinage Metal Complexes and Their Applications. *Chem. Rev.* **2020**, *120*, 4141-4168. (g) Scattolin, T.; Nolan, S. P. Synthetic Routes to Late Transition Metal–NHC Complexes. *Trends Chem.* **2020**, *2*, 721-736. (h) Morvan, J.; Mauduit, M.; Bertrand, G.; Jazzar, R. Cyclic (Alkyl)(amino)carbenes (CAACs) in Ruthenium Olefin Metathesis. *ACS Catal.* **2021**, *11*, 1714-1748. (i) Bellotti, P.; Koy, M.; Hopkinson, M. N.; Glorius, F. Recent advances in the chemistry and applications of N- heterocyclic carbenes. *Nat. Rev. Chem.* **2021**, *5*, 711-725.

- 2 Arduengo III, A. J.; Goerlich, J. R.; Marshall, W. J. A Stable Thiazol-2-ylidene and Its Dimer. *Liebigs Ann.* **1997**, 365-374.
- 3 Enders, D.; Breuer, K.; Raabe, G.; Runsink, J.; Teles, J. H.; Melder, J. P.; Ebel, K.; Brode, S. Preparation, Structure, and Reactivity of 1,3,4-Triphenyl-4,5-dihydro-1H-1,2,4-triazol-5-ylidene, a New Stable Carbene. *Angew. Chem. Int. Ed.* **1995**, *34*, 1021-1023.
- 4 For reviews, see: (a) Pareek, M.; Yernaidu, S.; Sunoj, R. B. Tale of the Breslow intermediate, a central player in N-heterocyclic carbene organocatalysis: then and now. *Chem. Sci.* **2021**, *12*, 7973-7992. (b) Wang, M. H.; Scheidt, K. A. Cooperative Catalysis and Activation with N-Heterocyclic Carbenes. *Angew. Chem. Int. Ed.* **2016**, *55*, 14912-4922. (c) Flanigan, D. L.; Romanov-Michailidis, F.; White, N. A.; Rovis, T. Organocatalytic Reactions Enabled by N-Heterocyclic Carbenes. *Chem. Rev.* **2015**, *115*, 9307-9387. (d) Bugaut, X.; Glorius, F. Organocatalytic umpolung: N-heterocyclic carbenes and beyond. *Chem. Soc. Rev.* **2012**, *41*, 3511-3522. (e) Biju, A. T. N-Heterocyclic Carbenes in Organocatalysis. Wiley-VCH Verlag GmbH & Co. KGaA Weinheim, Germany, **2019**. (f) Chen, X.-Y.; Gao, Z.-H.; Ye, S. Bifunctional N-Heterocyclic Carbenes Derived from L-Pyroglutamic Acid and Their Applications in Enantioselective Organocatalysis. *Acc. Chem. Res.* **2020**, *53*, 690-702. (g) Ghosh, A.; Biju, A. T. Revealing the Similarities of α,β -Unsaturated Iminiums and Acylazoliums in Organocatalysis. *Angew. Chem. Int. Ed.* **2021**, *60*, 13712-13724. (h) Ishii, T.; Nagao, K.; Ohmiya, H. Recent advances in N-heterocyclic carbene-based radical catalysis. *Chem. Sci.* **2020**, *11*, 5630–5636.
- 5 (a) Breslow, R. On the Mechanism of Thiamine Action. IV. Evidence from Studies on Model Systems. *J. Am. Chem. Soc.* **1958**, *80*, 3719-3726. (b) Berkessel, A.; Elfert, S.; Yatham, V.

- R.; Neudörfl, J.-M.; Schlörer, N. E.; Teles, J. H. Umpolung by N-Heterocyclic Carbenes: Generation and Reactivity of the Elusive 2,2-Diamino Enols (Breslow Intermediates). *Angew. Chem. Int. Ed.* **2012**, *51*, 12370-12374. (c) Paul, M.; Neudörfl, J. M.; Berkessel, A. Breslow intermediates from a thiazolin-2-ylidene and fluorinated aldehydes: XRD and solution-phase NMR spectroscopic characterization. *Angew. Chem. Int. Ed.* **2019**, *58*, 10596-10600. (d) Berkessel, A.; Yatham, V. R.; Elfert, S.; Neudörfl, J.-M. Characterization of the Key Intermediates of Carbene-Catalyzed Umpolung by NMR Spectroscopy and X-Ray Diffraction: Breslow Intermediates, Homo-enolates, and Azolium Enolates. *Angew. Chem. Int. Ed.* **2013**, *52*, 11158-11162. (e) Paul, M.; Sudkaow, P.; Wessels, A.; Schlörer, N. E.; Neudörfl, J. M.; Berkessel, A. Breslow intermediates from aromatic N-heterocyclic carbenes (benzimidazolin-2-ylidenes, thiazolin-2-ylidenes). *Angew. Chem. Int. Ed.* **2018**, *57*, 8310-8315. (f) Wessels, A.; Klusmann, M.; Breugst, M.; Schlörer, N. E.; Berkessel, A. Formation of Breslow Intermediates from N-Heterocyclic Carbenes and Aldehydes Involves Autocatalysis by the Breslow Intermediate, and a Hemiacetal. *Angew. Chem. Int. Ed.* **2022**, *61*, doi.org/10.1002/ange.202117682.
- 6 Ragsdale, S. W. Pyruvate Ferredoxin Oxidoreductase and Its Radical Intermediate. *Chem. Rev.* **2003**, *103*, 2333-2346.
- 7 Guin, J.; De Sarkar, S.; Grimme, S.; Studer, A. Biomimetic Carbene-Catalyzed Oxidations of Aldehydes Using TEMPO. *Angew. Chem. Int. Ed.* **2008**, *47*, 8727-8730.
- 8 (a) White, N. A.; Rovis, T. Enantioselective N-Heterocyclic Carbene-Catalyzed β -Hydroxylation of Enals Using Nitroarenes: An Atom Transfer Reaction That Proceeds via Single Electron Transfer. *J. Am. Chem. Soc.* **2014**, *136*, 14674-14677. (b) White, N. A.;

Rovis, T. Oxidatively Initiated NHC-Catalyzed Enantioselective Synthesis of 3,4-Disubstituted Cyclopentanones from Enals. *J. Am. Chem. Soc.* **2015**, *137*, 10112-10115. (c) Zhang, Y.; Du, Y.; Huang, Z.; Xu, J.; Wu, X.; Wang, Y.; Wang, M.; Yang, S.; Webster, R. D.; Chi, Y. R. N-Heterocyclic Carbene-Catalyzed Radical Reactions for Highly Enantioselective β -Hydroxylation of Enals. *J. Am. Chem. Soc.* **2015**, *137*, 2416-2419. (d) Yang, W.; Hu, W.; Dong, X.; Li, X.; Sun, J. N-Heterocyclic Carbene Catalyzed γ -Dihalomethylenation of Enals by Single-Electron Transfer. *Angew. Chem. Int. Ed.* **2016**, *55*, 15783-15786. (e) Wu, X.; Zhang, Y.; Wang, Y.; Ke, J.; Jeret, M.; Reddi, R. N.; Yang, S.; Song, B.-A.; Chi, Y. R. Polyhalides as Efficient and Mild Oxidants for Oxidative Carbene Organocatalysis by Radical Processes. *Angew. Chem. Int. Ed.* **2017**, *56*, 2942-2946. (f) Ishii, T.; Kake-no, Y.; Nagao, K.; Ohmiya, H. N-Heterocyclic Carbene-Catalyzed Decarboxylative Alkylation of Aldehydes. *J. Am. Chem. Soc.* **2019**, *141*, 3854-3858. (g) 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. (h) Li, J.-L.; Liu, Y.-Q.; Zou, W.-L.; Zeng, R.; Zhang, X.; Liu, Y.; Han, B.; Leng, H.-J.; Li, Q.-Z. Radical Acylfluoroalkylation of Olefins through N-Heterocyclic Carbene Organocatalysis. *Angew. Chem. Int. Ed.* **2020**, *59*, 1863-1870. (i) 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. (j) Gao, Y.; Quan, Y.; Li, Z.; Gao, L.; Zhang, Z.; Zou, X.; Yan, R.; Qu, Y.; Guo, K. Organocatalytic Three-Component 1,2-Cyanoalkylacylation of Alkenes via Radical Relay. *Org. Lett.* **2021**, *23*, 183-189. (k) Chen, L.; Jin, S.; Gao, J.; Liu, T.; Shao, Y.; Feng, J.; Wang, K.; Lu, T.; Du, D. N-Heterocyclic Carbene/Magnesium Co-catalyzed Radical Relay Assembly of Aliphatic Keto Nitriles. *Org.*

- Lett.* **2021**, *23*, 394-399. (l) Yang, H.-B.; Wan, D.-H. C–C Bond Acylation of Oxime Ethers via NHC Catalysis. *Org. Lett.* **2021**, *23*, 1049-1053. (m) 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.
- 9 (a) Schmittel, M.; Baumann, U. Stability and Cyclization of Enol Radical Cations: A Mechanistic Study of One-Electron Oxidation of β,β -Dimesityl Enols. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 541-543. (b) Schmittel, M.; Röck, M. Enol cation radicals in solution. 3. Reaction of enol cation radicals in the presence of nucleophiles. *Chem. Ber.* **1992**, *125*, 1611-1620. (c) Röck, M.; Schmittel, M. Enol cation radicals in solution. 4. An improved Synthesis of 4,6,7-Trimethylbenzofurans by oxidation of β -mesityl substituted enols. *J. Prakt. Chem.* **1994**, *336*, 325-329. (d) Schmittel, M.; Gescheidt, G.; Röck, M. The First Spectroscopic Identification of an Enol Radical Cation in Solution: The Anisylidimesitylethenol Radical Cation. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1961-1963. (e) Schmittel, M.; Lal, M.; Lal, R.; Röck, M.; Langels, A.; Rappoport, Z.; Basheer, A.; Schlirf, J.; Deiseroth, H.-J.; Flörke, U.; Gescheidt, G. A comprehensive picture of the one-electron oxidation chemistry of enols, enolates and α -carbonyl radicals: oxidation potentials and characterization of radical intermediates. *Tetrahedron* **2009**, *65*, 10842-10855.
- 10 (a) 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. (b) 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.
- 11 Liu, W.; Vianna, A.; Zhang, Z.; Huang, S.; Huang, L.; Melaimi, M.; Bertrand, G.; Yan, X. Mesoionic Carbene-Breslow Intermediates as Super Electron Donors: Application to the Metal-Free Arylacylation of Alkenes. *Chem. Catal.* **2021**, *1*, 196-206.
- 12 (a) Guisado-Barrios, G.; Bouffard, J.; Donnadiou, B.; Bertrand, G. Crystalline 1H-1,2,3-Triazol-5-ylidenes: New Stable Mesoionic Carbenes (MICs). *Angew. Chem. Int. Ed.* **2010**, *49*, 4759-4762. (b) Guisado-Barrios, G.; Soleilhavoup, M.; Bertrand, G. 1H-1,2,3-Triazol-5-ylidenes: Readily Available Mesoionic Carbenes. *Acc. Chem. Res.* **2018**, *51*, 3236-3244.
- 13 Parr, R. G.; Weitao, Y. Density-Functional Theory of Atoms and Molecules; Oxford University Press, **1994**.
- 14 Bochevarov, A. D.; Harder, E.; Hughes, T. F.; Greenwood, J. R.; Braden, D. A.; Philipp, D. M.; Rinaldo, D.; Halls, M. D.; Zhang, J.; Friesner, R. A. Jaguar: A High-Performance Quantum Chemistry Software Program with Strengths in Life and Materials Sciences. *Int. J. Quantum Chem.* **2013**, *113*, 2110–2142.
- 15 (a) Perdew, J. P.; Burke, K.; Ernzerhof, M. Generalized Gradient Approximation Made Simple. *Phys. Rev. Lett.* **1996**, *77*, 3865-3868; (b) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. Self-consistent Molecular Orbital Methods. XX. A Basis Set for Correlated Wave Functions. *J. Chem. Phys.* **1980**, *72*, 650–654; (c) Dunning, T. H. Gaussian Basis Sets for Use in Correlated Molecular Calculations. I. The Atoms Boron through Neon and Hydrogen. *J. Chem. Phys.* **1989**, *90*, 1007-1023.

- 16 (a) Baik, M.-H.; Friesner, R. A. Computing Redox Potentials in Solution: Density Functional Theory as A Tool for Rational Design of Redox Agents. *J. Phys. Chem. A* **2002**, *106*, 7407-7412; (b) Roy, L. E.; Jakubikova, E.; Guthrie, M. G.; Batista, E. R. Calculation of One-Electron Redox Potentials Revisited. Is It Possible to Calculate Accurate Potentials with Density Functional Methods? *J. Phys. Chem. A* **2009**, *113*, 6745-6750.
- 17 (a) Aldeco-Perez, E.; Rosenthal, A. J.; Donnadiu, B.; Parameswaran, P.; Frenking, G.; Bertrand, G. Isolation of a C-5-Deprotonated Imidazolium, a Crystalline “Abnormal” N-Heterocyclic Carbene. *Science* **2009**, *326*, 556-559. (b) Sau, S. C.; Hota, P. K.; Mandal, S. K.; Soleilhavou, M.; Bertrand, G. Stable Abnormal N-Heterocyclic Carbenes and their Applications. *Chem. Soc. Rev.* **2020**, *49*, 1233-1252.
- 18 Arduengo, A. J., III; Krafczyk, R.; Schmutzler, R.; Craig, H. A.; Goerlich, J. R.; Marshall, W. J.; Unverzagt, M. Imidazolylidenes, imidazolinylienes and imidazolidines, *Tetrahedron* **1999**, *55*, 14523-14534.
- 19 Hudnall, T. W.; Bielawski, C. W. An N,N'-Diamidocarbene: Studies in C-H Insertion, Reversible Carbonylation, and Transition-Metal Coordination Chemistry” *J. Am. Chem. Soc.* **2009**, *131*, 16039-16040.
- 20 Lavallo, V.; Canac, Y.; Donnadiu, B.; Schoeller, W. W.; Bertrand, G. Cyclopropenylienes: From Interstellar Space to an isolated Derivative in the Laboratory. *Science* **2006**, *312*, 722-724.
- 21 Alder, R. W.; Allen, P. R.; Murray, M.; Orpen, A. G. Bis(diisopropylamino)carbene. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1121-1123.

- 22 Lavallo, V.; Dyker, C. A.; Donnadiou, B.; Bertrand, G. Synthesis and Ligand Properties of Stable Five-Membered Ring Allenes Composed of Second Row Elements. *Angew. Chem. Int. Ed.* **2008**, *47*, 5411-5414.
- 23 (a) Pearson, R. G. Absolute electronegativity and hardness correlated with molecular orbital theory. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 8440-8441; (b) 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.
- 24 Matsuki, Y.; Ohnishi, N.; Kakeno, Y.; Takemoto, S.; Ishii, T.; Nagao, K.; Ohmiya, H. Aryl radical-mediated N-heterocyclic carbene catalysis. *Nat. Commun.* **2021**, *12*, 3848.
- 25 Pause, L., Robert, M.; Savéant, J.-M. Can single-electron transfer break an aromatic carbon–heteroatom bond in one step? A novel example of transition between stepwise and concerted mechanisms in the reduction of aromatic iodides. *J. Am. Chem. Soc.* **1999**, *121*, 7158-7159
- 26 Paul, M.; Peckelsen, K.; Thomulka, T.; Martens, J.; Berden, G.; Oomens, J.; Neudorfl, J. M.; Breugst, M.; Meijer, A. J. H. M.; Schafer, M.; Berkessel, A. Breslow Intermediates (Amino Enols) and Their Keto Tautomers: First Gas-Phase Characterization by IR Ion Spectroscopy. *Chem. Eur. J.* **2021**, *27*, 2662-2669.
- 27 For reviews on CAACs see: (a) Soleilhavoup, M.; Bertrand, G. Cyclic (alkyl)(amino)carbenes (CAACs): Stable carbenes on the rise. *Acc. Chem. Res.* **2015**, *48*, 256-266. (b) Paul, U. S. D.; Radius, U. What Wanzlick did not dare to dream: cyclic

- (alkyl)(amino)carbenes (caacs) as new key players in transition-metal chemistry. *Eur. J. Inorg. Chem.* **2017**, 3362-3375. (c) Melaimi, M.; Jazzar, R.; Soleilhavoup, M.; Bertrand, G. Cyclic (alkyl)(amino)carbenes (CAACs): Recent developments. *Angew. Chem. Int. Ed.* **2017**, *56*, 10046-10068. (d) Jazzar, R.; Soleilhavoup, M.; Bertrand, G. Cyclic (alkyl)- and (aryl)-(amino)carbene coinage metal complexes and their applications. *Chem. Rev.* **2020**, *120*, 4141-4168. (e) S. K. Kushvaha, A. Mishra, H. W. Roesky and K. C. Mandal. Recent Advances in the Domain of Cyclic (Alkyl)(Amino) Carbenes. *Chem. Asian. J.* **2022**, e202101301.
- 28 Martin, D.; Canac, Y.; Lavallo, V.; Bertrand, G. Comparative Reactivity of Different Types of Stable Cyclic and Acyclic Mono- and Di-Amino Carbenes with Simple Organic Substrates. *J. Am. Chem. Soc.* **2014**, *136*, 5023-5030.
- 29 (a) Luchini, G.; Paton, R. S. DBSTEP: DFT Based Steric Parameters. <https://doi.org/10.5281/zenodo.4702097>; (b) Falivene, L.; Cao, Z.; Petta, A.; Serra, L.; Poater, A.; Oliva, R.; Scarano, V.; Cavallo, L. Towards the Online Computer-Aided Design of Catalytic Pockets. *Nat. Chem.* **2019**, *11*, 872-879.
- 30 For use of buried volume on organic compounds see the following publication and references therein: Sowndarya S. V., S.; St. John, P. C.; Paton, R. S. A quantitative metric for organic radical stability and persistence using thermodynamic and kinetic features. *Chem. Sci.* **2021**, *12*, 1315813166.