

Cite this: *Chem. Sci.*, 2024, 15, 3707

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 29th August 2023

Accepted 18th January 2024

DOI: 10.1039/d3sc04543a

rsc.li/chemical-science

# Ambiphilicity of ring-expanded N-heterocyclic carbenes†

François Vermersch,<sup>‡</sup> Victor T. Wang,<sup>‡</sup> Mehdi Abdellaoui,<sup>‡</sup>  
Rodolphe Jazzar<sup>‡\*</sup> and Guy Bertrand<sup>‡\*</sup>

N-heterocyclic carbenes, such as imidazole-2-ylidenes and imidazolin-2-ylidenes, the popular class of singlet carbenes introduced by Arduengo in 1991 have not been shown to be ambiphilic owing to the two  $\sigma$ -withdrawing,  $\pi$ -donating amino groups flanking the carbene centre. However, our experimental data suggest that ring-expanded N-heterocyclic carbenes (RE-NHCs), especially the seven and eight membered rings, are significantly ambiphilic. Our results also show that the steric environment in RE-NHCs can become a determining factor for controlling the E–H bond activation.

## Introduction

Thanks to growing efforts in main group chemistry, the activation of enthalpically strong bonds and industrially relevant small molecules is no longer restricted to transition-metals.<sup>1</sup> More than a decade ago, our group discovered that cyclic (alkyl)(amino)carbenes (CAAC-5),<sup>2,3</sup> a class of highly ambiphilic carbenes, could react with carbon monoxide,<sup>4</sup> H<sub>2</sub>,<sup>5</sup> NH<sub>3</sub> (ref. 5) and P<sub>4</sub>.<sup>6</sup> More recently, it has been shown that CAAC-5s not only activate a variety of bonds (C–H, Si–H, B–H...) but also promote catalytic reactions.<sup>8</sup> In comparison, imidazole-2-ylidenes<sup>9</sup> and imidazolin-2-ylidenes,<sup>10</sup> the classical N-heterocyclic carbenes (NHC-5s), are much less ambiphilic due to their two  $\pi$ -donating amino substituents. Consequently, they are reluctant to activate small molecules, as illustrated by their lack of reactivity with CO.<sup>11,12</sup> Much less studied than NHC-5s are the so-called ring-expanded N-heterocyclic carbenes (RE-NHCs).<sup>13</sup> Herein we compare the ambiphilic nature of NHC-5 with RE-NHCs (–6,<sup>13a</sup> –7 (ref. 14) and –8 (ref. 13c)) and CAAC-5 through DFT calculations and their reactivity with small molecules.

## Results and discussion

Compared to NHC-5s, RE-NHCs display a larger N–C–N bond angle ( $\angle_{\text{carb}}$ ) which imposes greater steric constraint when used as a ligand for transition metals, a feature used to enhance catalytic activity.<sup>15</sup> Arguably less emphasized, is the larger carbene bond angle, which increases the p-character of the lone

pair, and thus the energy level of the HOMO.<sup>16</sup> Comparatively, the LUMO is less affected since ring expansion does not significantly disrupt the planarization of the  $\alpha$ -amino fragments, which leaves the mesomeric stabilization of the  $p_{\pi}$  orbital by the nitrogen lone pairs nearly identical.

The ambiphilicity of a carbene can be estimated computationally by considering the singlet-triplet gap ( $\Delta E_{\text{S-T}}$ ) (Scheme 1). As expected, our calculations indicate a correlation between the ring size and ambiphilicity of a carbene. Interestingly, the data also suggests that the ambiphilicity of NHC-7 and NHC-8 approaches that of CAAC-5.

To compare experimentally the ambiphilicity of NHCs with that of CAAC-5, we first considered the activation of sp-hybridized CH bonds which has been reported with CAACs,<sup>17</sup> but seldomly described with NHCs (one example has been reported using acetylene gas).<sup>18</sup> We first investigated the reaction of *p*-tolylacetylene [ $pK_{\text{a}}$  (DMSO) = 28.8 vs. 25 for acetylene] with NHC-5 at room temperature in benzene solution (Scheme 2). In this case, no reaction was observed within 1 hour. In marked contrast, using CAAC-5 the oxidative addition product **1a** was quantitatively obtained within minutes. Under the same conditions a rapid and clean reaction was also observed with NHC-6<sup>13a</sup> NHC-7<sup>15</sup> and NHC-8<sup>13c</sup> giving adducts **1b–d** as shown by characteristic <sup>1</sup>H NMR signals at 6.04, 5.87 and 5.64 ppm, and <sup>13</sup>C NMR signals at 72.3, 73.9 and 77.1 ppm, respectively. The structure of adduct **1c** (from NHC-7) was confirmed by X-ray crystallography. Because of the significant difference in reactivity observed between NHC-5 and the RE-NHCs, we re-evaluated the reaction of NHC-5 with *p*-tolylacetylene and observed very slow conversion to adduct **1e** upon performing the reaction at 80 °C for 4 hours.

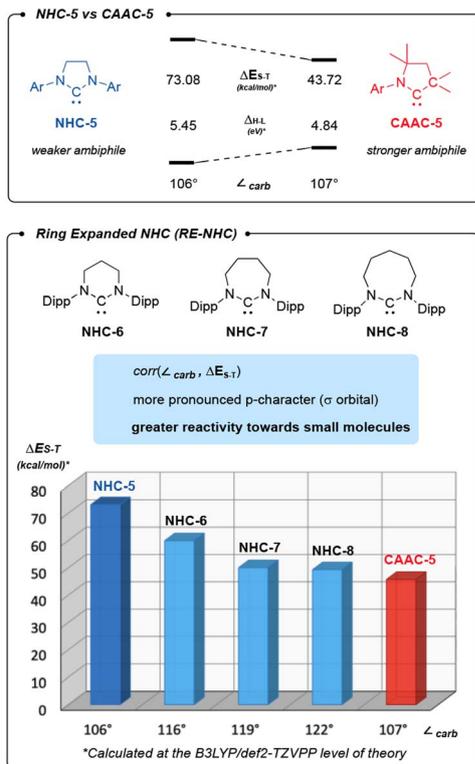
These initial results prompted us to search for more challenging molecules to activate. Examples of stable carbenes reacting with isonitriles to afford ketenimines are scarce.

UCSD-CNRS Joint Research Chemistry Laboratory (IRL 3555), Department of Chemistry and Biochemistry, University of California, La Jolla, San Diego, California 92093-0358, USA. E-mail: rjazzar@ucsd.edu; gbertrand@ucsd.edu

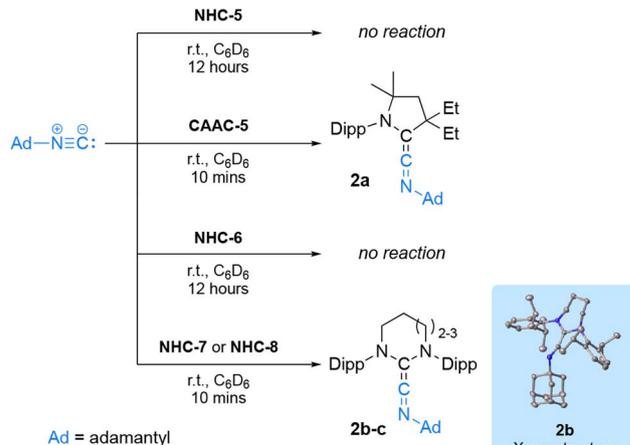
† Electronic supplementary information (ESI) available. CCDC 2291449, 2291450–2291455. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d3sc04543a>

‡ These authors contributed equally to this work.





Scheme 1 CAAC-5 is more ambiphilic than NHC-5. NHC ambiphilicity is improved in ring-expanded NHC (RE-NHCs) as shown by their decreasing singlet–triplet gap ( $\Delta E_{S-T}$ ).

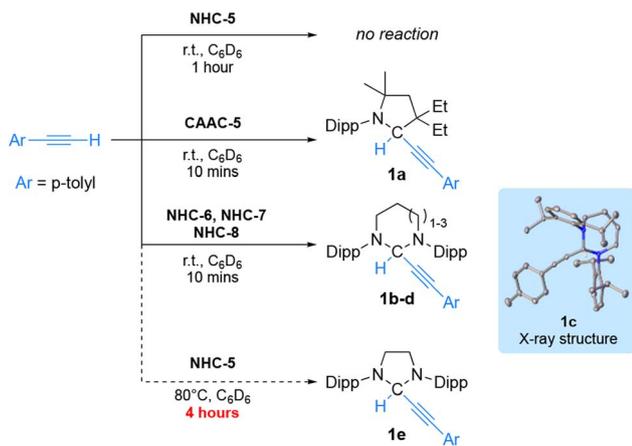


Scheme 3 Reactivity of NHC-5–8 and CAAC-5 with adamantyl isocyanide.

within minutes. With **NHC-6**, no reaction was observed even after 12 hours. However, with **NHC-7** and **NHC-8**, the quantitative formation of compound **2b** and **2c**, was observed after 10 minutes, as evidenced by the diagnostic <sup>13</sup>C NMR signal for the central carbon of ketenimines at 216.9 ppm and 211.5 ppm, respectively. We confirmed the structure of compound **2b** by X-ray crystallography. Interestingly, the solid-state structure of **2b** revealed a pronounced bent geometry ( $C_{NHC}-C-N$  angle: 158.5°) compared to that of diamido cyclohexylketenimine ( $C_{DAC}-C-N$  angle: 173.8°)<sup>20b</sup> with a longer  $C_{NHC}-C_{ket}$  bond (133.8 pm vs. 129.7 pm for DAC). This observation indicates that **NHC-7** is less electrophilic than DAC.

Collectively, the reactions with terminal alkynes and isocyanides suggest that the ambiphilicity of the carbenes is in the order **NHC-5** < **NHC-6** < **NHC-7** < **NHC-8** < **CAAC-5**, which is in agreement with their singlet–triplet gap. To deconvolute these results further, we wondered if RE-NHCs, notwithstanding their lower electrophilicity could compare with **CAAC-5** in the activation of ammonia.<sup>5</sup> Under 2 atmospheres of NH<sub>3</sub>, no reaction occurred with **NHC-5**, which was expected since several diaminocarbenes have even been generated in liquid ammonia.<sup>22</sup> (Scheme 4). In agreement with literature precedent,<sup>5</sup> under the same conditions, **CAAC-5** rapidly led to the ammonia adduct **3a**. Switching to RE-NHCs, no reaction was observed with **NHC-6** despite prolonged reaction time, while **NHC-7** led to the clean formation of product **3b** with distinctive <sup>1</sup>H and <sup>13</sup>C NMR signals at  $\delta = 5.25$  ppm and 85.8 ppm, respectively. This result was confirmed by single crystal X-ray diffraction. However, to our surprise, no reaction was observed with **NHC-8**.

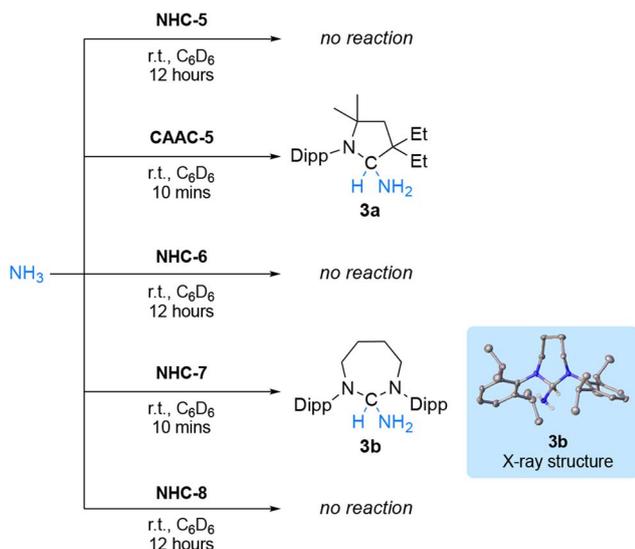
We previously reported that the steric environment of **CAAC-5** is a determining factor in controlling the reversibility of E–H bond activation (E = N–H, P–H).<sup>8</sup> Compared to **CAAC-5** ( $\angle_{carb} = 106^\circ$ ), **NHC-8** is more sterically constrained around the carbene carbon due to its large N–C<sub>NHC</sub>–N bond angle ( $\angle_{carb} = 122^\circ$ ).<sup>13c</sup> We hypothesized this could explain its lack of reactivity with ammonia despite favourable electronics. To probe this hypothesis, we prepared the *N*-Mesityl (-Mes) substituted **NHC-8** (<sup>Mes</sup>**NHC-8**) since its steric profile is significantly smaller



Scheme 2 Reactivity of NHC-5–8 and CAAC-5 with *p*-tolylacetylene.

They only include the anti-Bredt **NHC-19** and diamidocarbenes (**DAC**) **20** thanks to their enhanced electrophilicity resulting from reduced donation of the nitrogen lone-pair into the empty p-type orbital of the carbene carbon. Curious to probe the reactivity of RE-NHCs, we considered their reactivity and that of **NHC-5** or **CAAC-5** with adamantyl isocyanide (Scheme 3). **CAAC-5** cleanly afforded the ketenimine **2a** within minutes, while no reaction occurred with **NHC-5** after 12 hours at room temperature in benzene solution.<sup>21</sup> This result contrasts with **CAAC-5** which cleanly afforded the ketenimine **2a**

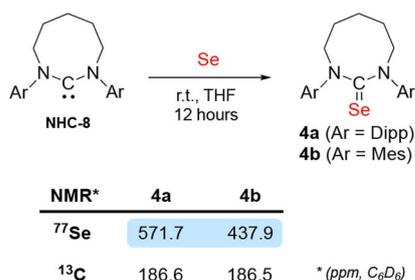




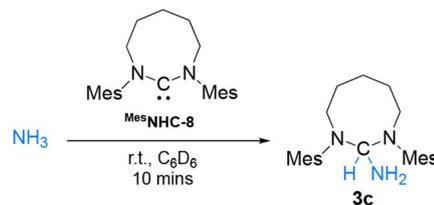
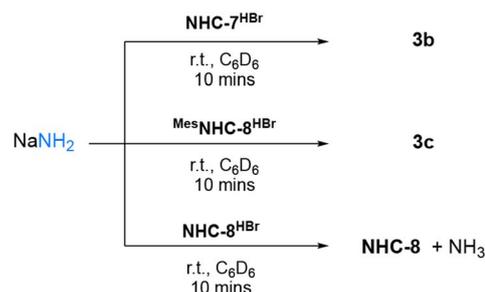
Scheme 4 Reactivity of NHC-5–8 and CAAC-5 with ammonia.

than that of the Dipp-substituted **NHC-8**. This is apparent from the solid state structures, when considering the steric maps (see ESI for details<sup>†</sup>) and percent buried volumes (% $V_{\text{bur}}$ )<sup>23</sup> around the carbene carbon. **NHC-8** (80.1%) compared to <sup>Mes</sup>**NHC-8** (77.2%) which is closer to that of **NHC-7** (78.4%). The larger steric hindrance is also apparent in solution when considering the unusual <sup>77</sup>Se NMR downfield shift of the **NHC-8**-Se adduct **4a** (571.1 ppm) compared to <sup>Mes</sup>**NHC-8**-Se adduct **4b** (437.9 ppm) (Scheme 5). Indeed, <sup>77</sup>Se NMR is a spectroscopic marker for highlighting non-classical bonding (NCB) interactions between pendant *N*-Dipp substituents and the selenium atom.<sup>24</sup> Note that when comparing the reactivity of *N*-tolyl and *N*-Dipp 8-membered NHCs with silver chloride, Cavell and co-workers discovered that in very large ring NHCs the steric environment provided by *N*-Dipp substituents can become so overwhelming that it prevents coordination.<sup>13c</sup>

Having confirmed that <sup>Mes</sup>**NHC-8** is less sterically hindered than **NHC-8** and even **NHC-7**, we evaluated its reactivity towards ammonia. Gratifyingly, rapid formation of the corresponding ammonia adduct was observed when performing the reaction in C<sub>6</sub>D<sub>6</sub> under 2 atmospheres of NH<sub>3</sub> (Scheme 6). To confirm these results, we also investigated the reactivity of the corresponding imidazolium salts with sodium amide which provided the expected adducts *via* nucleophilic addition of NH<sub>2</sub><sup>−</sup> (Scheme 7).



Scheme 5 Selenium adducts of Dipp- and Mes-substituted NHC-8.

Scheme 6 Reactivity of <sup>Mes</sup>NHC-8 with ammonia.Scheme 7 Reactivity of NHC-7, <sup>Mes</sup>NHC-8 and NHC-8 conjugate acid salts with NaNH<sub>2</sub>.

Note that under these conditions, reaction of **NHC-8**<sup>HBr</sup> with NaNH<sub>2</sub> afforded the free **NHC-8** and ammonia. Overall, these results suggest that for 8-membered ring NHCs, the activation of ammonia is controlled by steric parameters and possibly reversible.

## Conclusions

Imidazole-2-ylidenes<sup>9</sup> and imidazolin-2-ylidenes,<sup>10</sup> the popular class of singlet carbenes introduced by Arduengo, have not proven to be ambiphilic owing to the two  $\sigma$ -withdrawing,  $\pi$ -donating amino groups stabilizing the carbene centre. However, our experimental data demonstrate that ring-expanded *N*-heterocyclic carbenes, **NHC-7s** and **NHC-8s**, belong to the class of ambiphilic carbenes. Our results also show that the steric environment in RE-NHCs can become a determining factor for controlling the E–H bond activation. We anticipate these results will have far reaching implications in the design and applications of large ring singlet carbene skeletons.

## Data availability

All the data available has been provided in the ESI.<sup>†</sup>

## Author contributions

F. V. and R. J. conceptualized this work. F. V., V. T. W. and M. A. performed the synthetic work. R. J. performed X-ray diffraction analysis. The manuscript was written by R. J. and G. B. and reviewed by all the authors. R. J. and G. B. guided the project.

## Conflicts of interest

There are no conflicts to declare.



## Acknowledgements

This work was supported by the U.S. Department of Energy, Office of Science, Basic Energy Sciences, Catalysis Science Program, under Award # DE-SC0009376, and the Agence Nationale de la Recherche (ANR-20-CE07-0000-cResolu).

## References

- (a) P. P. Power, *Nature*, 2010, **463**, 171–177; (b) T. Chu and G. I. Nikonov, *Chem. Rev.*, 2018, **118**, 3608–3680; (c) D. Martin, M. Soleilhavoup and G. Bertrand, *Chem. Sci.*, 2011, **2**, 389–399.
- V. Lavallo, Y. Canac, C. Präsang, B. Donnadiou and G. Bertrand, *Angew. Chem., Int. Ed.*, 2005, **44**, 5705–5709.
- Selected reviews: (a) M. Melaimi, M. Soleilhavoup and G. Bertrand, *Angew. Chem., Int. Ed.*, 2010, **49**, 8810–8849; (b) M. Soleilhavoup and G. Bertrand, *Acc. Chem. Res.*, 2015, **48**, 256–266; (c) M. Melaimi, R. Jazzar, M. Soleilhavoup and G. Bertrand, *Angew. Chem., Int. Ed.*, 2017, **56**, 10046–10068; (d) U. S. D. Paul and U. Radius, *Eur. J. Inorg. Chem.*, 2017, **2017**, 3362–3375; (e) S. Kundu, S. Sinhababu, V. Chandrasekhar and H. W. Roesky, *Chem. Sci.*, 2019, **10**, 4727–4741; (f) R. Jazzar, M. Soleilhavoup and G. Bertrand, *Chem. Rev.*, 2020, **120**, 4141–4168; (g) R. K. Singh, T. Khan, S. Misra and A. K. Singh, *J. Organomet. Chem.*, 2021, **956**, 122133.
- V. Lavallo, Y. Canac, B. Donnadiou, W. W. Schoeller and G. Bertrand, *Angew. Chem., Int. Ed.*, 2006, **45**, 3488–3491.
- G. D. Frey, V. Lavallo, B. Donnadiou, W. W. Schoeller and G. Bertrand, *Science*, 2007, **316**, 439–441.
- J. D. Masuda, W. W. Schoeller, B. Donnadiou and G. Bertrand, *Angew. Chem., Int. Ed.*, 2007, **46**, 7052–7055.
- (a) G. D. Frey, J. D. Masuda, B. Donnadiou and G. Bertrand, *Angew. Chem., Int. Ed.*, 2010, **49**, 9444–9447; (b) A. V. Zhukhovitskiy, M. G. Mavros, K. T. Queeney, T. Wu, T. Van Voorhis and J. A. Johnson, *J. Am. Chem. Soc.*, 2016, **138**, 8639–8652; (c) S. Würtemberger-Pietsch, H. Schneider, T. B. Marder and U. Radius, *Chem.–Eur. J.*, 2016, **22**, 13032–13036; (d) A. Bakker, M. Freitag, E. Kolodzeiski, P. Bellotti, A. Timmer, J. Ren, B. Schulze Lammers, D. Moock, H. W. Roesky, H. Mönig, S. Amirjalayer, H. Fuchs and F. Glorius, *Angew. Chem., Int. Ed.*, 2020, **59**, 13643–13646; (e) G. Kaur, R. L. Thimes, J. P. Camden and D. M. Jenkins, *Chem. Commun.*, 2022, **58**, 13188–13197; (f) A. V. Zhukhovitskiy, M. G. Mavros, K. T. Queeney, T. Wu, T. V. Voorhis and J. A. Johnson, *J. Am. Chem. Soc.*, 2016, **138**, 8639–8652; (g) C. A. Smith, M. R. Narouz, P. A. Lummis, I. Singh, A. Nazemi, C.-H. Li and C. M. Crudden, *Chem. Rev.*, 2019, **119**, 4986–5056.
- (a) D. Tolentino, S. Neale, C. Isaac, S. Macgregor, M. Whittlesey, R. Jazzar and G. Bertrand, *J. Am. Chem. Soc.*, 2019, **141**, 9823–9826; (b) J. Peltier, E. Tomás-Mendivil, D. Tolentino, M. Hansmann, R. Jazzar and G. Bertrand, *J. Am. Chem. Soc.*, 2020, **142**, 18336–18340.
- A. J. Arduengo, R. L. Harlow and M. Kline, *J. Am. Chem. Soc.*, 1991, **113**, 361–363.
- A. J. Arduengo, J. R. Goerlich and W. J. Marshall, *J. Am. Chem. Soc.*, 1995, **117**, 11027–11028.
- D. A. Dixon, A. J. Arduengo III, K. D. Dobbs and D. V. Khasnis, *Tetrahedron Lett.*, 1995, **36**, 645–648.
- C. Goedecke, M. Leibold, U. Siemeling and G. Frenking, *J. Am. Chem. Soc.*, 2011, **133**, 3557.
- (a) M. Iglesias, D. J. Beetstra, J. C. Knight, L.-L. Ooi, A. Stasch, S. Coles, L. Male, M. B. Hursthouse, K. J. Cavell, A. Dervisi and I. A. Fallis, *Organometallics*, 2008, **27**, 3279–3289; (b) E. L. Kolychev, I. A. Portnyagin, V. V. Shuntikov, V. N. Khrustalev and M. S. Nechaev, *J. Organomet. Chem.*, 2009, **694**, 2454–2462; (c) W. Y. Lu, K. J. Cavell, J. S. Wixey and B. Kariuki, *Organometallics*, 2011, **30**, 5649–5655.
- J. J. Dunsford, D. S. Tromp, K. J. Cavell, C. J. Elsevier and B. M. Kariuki, *Dalton Trans.*, 2013, **42**, 7318–7329.
- (a) M. J. Page, W. Y. Lu, R. C. Poulten, E. Carter, E. A. G. Algarra, B. M. Kariuki, S. A. Macgregor, M. F. Mahon, K. J. Cavell, D. M. Murphy and M. K. Whittlesey, *Chem.–Eur. J.*, 2013, **19**, 2158–2167; (b) A. Cervantes-Reyes, F. Rominger, M. Rudolph and A. S. K. Hashmi, *Adv. Synth. Catal.*, 2020, **362**, 2523–2533; (c) J. W. Hall, D. Bouchet, M. F. Mahon, M. K. Whittlesey and C. S. J. Cazin, *Organometallics*, 2021, **40**, 1252–1261.
- (a) M. Eck, S. Würtemberger-Pietsch, A. Eichhorn, J. H. J. Berthel, R. Bertermann, U. S. D. Paul, H. Schneider, A. Friedrich, C. Kleeberg, U. Radius and T. B. Marder, *Dalton Trans.*, 2017, **46**, 3661–3680; (b) L. García, K. H. M. Al Furaiji, D. J. D. Wilson, J. L. Dutton, M. S. Hill and M. F. Mahon, *Dalton Trans.*, 2017, **46**, 12015–12018; (c) G. Kundu, R. Dixit, S. Tothadi, K. Vanka and S. S. Sen, *Dalton Trans.*, 2022, **51**, 14452–14457; (d) K. Balayan, H. Sharma, K. Vanka, S. Ravindranathan, R. G. Gonnade and S. S. Sen, *Chem. Commun.*, 2023, **59**, 8540–8543.
- Z. R. Turner, *Chem.–Eur. J.*, 2016, **22**, 11461–11468.
- A. J. Arduengo III, J. C. Calabrese, F. Davidson, H. V. Rasika Dias, J. R. Goerlich, R. Krafczyk, W. J. Marshall, M. Tamm and R. Schmutzler, *Helv. Chim. Acta*, 1999, **82**, 2348–2364.
- D. Martin, N. Lassauque, B. Donnadiou and G. Bertrand, *Angew. Chem., Int. Ed.*, 2012, **51**, 6172–6175.
- (a) M. Braun, W. Frank, G. J. Reiss and C. Ganter, *Organometallics*, 2010, **29**, 4418–4420; (b) T. W. Hudnall and C. W. Bielawski, *J. Am. Chem. Soc.*, 2009, **131**, 16039–16041; (c) V. César, S. Labat, K. Miqueu, J.-M. Sotiropoulos, R. Brousses, N. Lugan and G. Lavigne, *Chem.–Eur. J.*, 2013, **19**, 17113–17124.
- An alternative reactivity has been reported: Y. Kim, L. L. Liu and D. W. Stephan, *Chem.–Eur. J.*, 2019, **25**, 7110–7113.
- W. A. Herrmann, L. J. Gooßen and M. Spiegler, *J. Organomet. Chem.*, 1997, **547**, 357–366.
- L. Falivene, Z. Cao, A. Petta, L. Serra, A. Poater, R. Oliva, V. Scarano and L. Cavallo, *Nat. Chem.*, 2019, **11**, 872–879.
- (a) A. Liske, K. Verlinden, H. Buhl, K. Schaper and C. Ganter, *Organometallics*, 2013, **32**, 5269–5272; (b) G. P. Junor, J. Lorkowski, C. M. Weinstein, R. Jazzar, C. Pietraszuk and G. Bertrand, *Angew. Chem., Int. Ed.*, 2020, **59**, 22028–22033.

