Communication

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Bicyclic (Alkyl)(amino)carbenes (BICAACs): Stable Carbenes more Ambiphilic than CAACs

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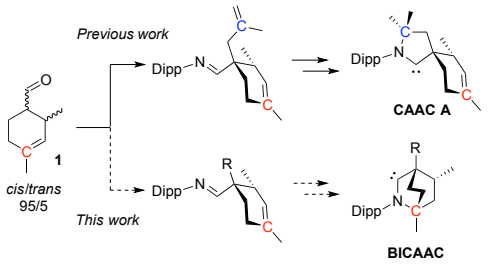
Supporting Information Placeholder

ABSTRACT: A straightforward strategy allows for the synthesis of storable bicyclic (alkyl)(amino)carbenes (BICAACs), which feature enhanced σ-donating and π-accepting properties compared to monocyclic (alkyl)(amino)carbenes (CAACs). Due to the bicyclo[2.2.2]octane skeleton, the steric environment around the carbene center is different from that of CAACs, and similar to that observed in classical NHCs. The different electronic properties of BICAACs as compared to CAACs allow for ligand exchange reactions not only at a metal center, but also at main group elements.

In 2005, our group reported the synthesis of stable cyclic (alkyl)(amino)carbenes (CAACs)[1,2] which result from the replacement of one of the two amino substituents of classical NHCs[3] by a quaternary carbon atom. This modification increases both the nucleophilicity and electrophilicity of the carbene center,[4] thereby allowing CAACs to outperform NHCs for the stabilization of paramagnetic species,[5,6] and the activation of small molecules and enthalpically strong bonds.[7] Additionally, CAAC-metal bonds are stronger than in NHC complexes, which allowed for promoting difficult transition metal catalyzed reactions under very demanding conditions.[8] Herein we report the preparation of stable bicyclic (alkyl)(amino)carbenes (BICAACs) and show that this modification of the CAAC skeleton leads to a geometry similar to that of NHCs. Moreover, this novel family of carbenes displays enhanced σ-donating and π-accepting properties compared to those of CAACs, and thus NHCs. We present computational and experimental evidence for this claim. Of particular interest we found that ligand exchange between BICAACs and CAACs occurred not only at a transition metal center, but also at a main group element.

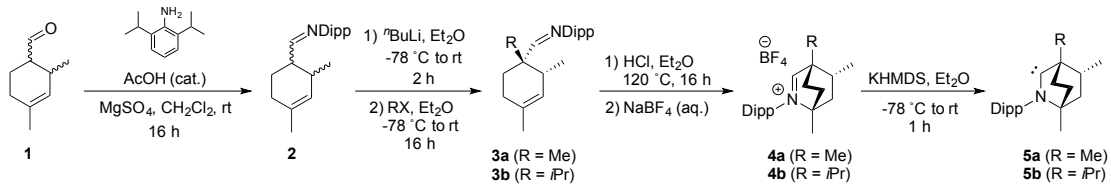
The synthetic strategy to access BICAACs is derived from that used for the preparation of the spirocyclic CAAC **A**[9] (Scheme 1). In our previous work, starting from the commercially available 2,4-dimethyl-3-cyclohexene carboxaldehyde (trivertal) (*cis*/*trans* isomers, racemate) **1**, a common fragrance and flavor material produced in bulk quantities,[10] we prepared in two steps the corresponding alkenyl-aldimine as a single diastereomer. Under acidic conditions, an intramolecular 5-*exo* cyclization reaction led to the corresponding five-membered ring iminium salt (commercially available), which can be deprotonated to give the free stable carbene **A**. In this process, the C-C double bond of the cyclohexenyl functionality remained untouched. With this in mind, we envisaged that replacement of the 2-methyl-2-propenyl group by a saturated R substituent, the acid promoted rearrangement would involve the endocyclic double bond of the cyclohexene, and would lead to a bicyclic iminium salt via a 6-*endo* cyclization. Subsequent deprotonation would generate a cyclic (alkyl)(amino)carbene (CAAC) with the bicyclo[2.2.2]octane framework that we named BICAACs.

Scheme 1. Inspiration for the synthesis of BICAACs.



Condensation of 2,6-di*iso*propylaniline and trivertal **1** under acidic conditions quantitatively led to imine **2** (Scheme 2). Deprotonation of **2** with *n*-butyl lithium followed by alkylation with iodomethane diastereoselectively afforded **3a** [*i.e.* the facial selectivity is controlled by the methyl group being in equatorial position (see SI for further details)]. The 6-*endo* cyclization of **3a** took place in a sealed flask at 120 ºC in the presence of excess HCl in diethyl ether. Anion exchange from chloride to tetrafluoroborate in aqueous medium gave iminium salt **4a**. Lastly, deprotonation with KHMDS generated free BICAAC **5a** as a racemic mixture of a single diastereomer in moderate overall yield. The overall synthetic route is also compatible with the introduction of a secondary R group as shown with the *iso*propyl BICAAC **5b**. Carbenes **5a,b** can indefinitely be stored in the solid state at room temperature under inert atmosphere, without any decomposition. The ^{13}C NMR spectra of both **5a** and **5b** show a singlet at 334.4 and 336.0 ppm, respectively, for the carbene carbon nucleus, which is slightly deshielded compared to that of **A** (320 ppm). Single-crystals of **5a** and **5b** were obtained from a pentane solution at -40 ºC, and X-ray diffraction studies confirmed the diastereoselectivity of the alkylation step. The C1-N1 [**5a**: 1.343(6), **5b**: 1.3154(15) Å] and C1-C2 [**5a**: 1.523(7), **5b**: 1.5304(15) Å] distances are in the range of those observed in CAACs, and the

Scheme 2. Synthesis of BICAACs 5a,b.



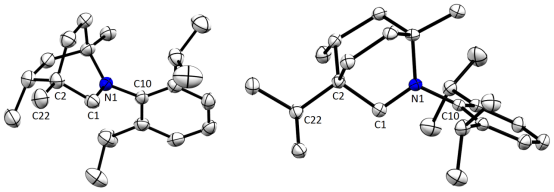
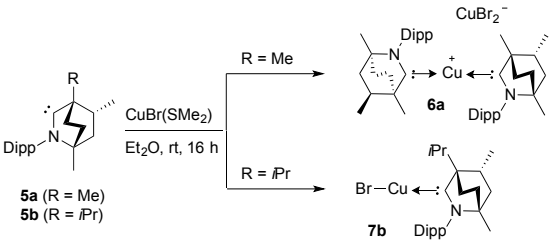


Figure 1. Solid-state structures of **5a** (left) and **5b** (right) viewed from two different orientations with ellipsoids at 50% level of probability. One enantiomer is shown. H-atoms are omitted for clarity. Selected bond lengths [Å] and angles [°]. **5a**: C1-N1 1.343(6), C1-C2 1.523(7), N1-C1-C2 108.3(4), C10-N1-C1-C2 175.883, N1-C1-C2-C22 178.986. **5b**: C1-N1 1.3154(15), C1-C2 1.5304(15), N1-C1-C2 109.17(9), C10-N1-C1-C2 176.218, N1-C1-C2-C22 178.575.

N1-C1-C2 angle [**5a**: 108.3(4), **5b**: 109.17(9) º] is significantly wider [CAACs: 106.54(18) º]. Very importantly, C10, N1, C1, C2 and C22 are coplanar with the lone pair, leading to a geometry similar to that observed in classical NHCs, but different to that of CAACs such as **A**.

The reaction of $(SMe_2)CuBr$ with methyl- and isopropyl-BICAACs **5a** and **5b** nicely illustrates the steric tunability of these carbenes (Scheme 3). With the less hindered carbene **5a**, a mixture of meso and racemic homoleptic [bis(BICAAC)Cu][$CuBr_2$] **6a** was obtained. In contrast, with the more sterically demanding carbene **5b**, the heteroleptic (**5b**)CuBr **7b** was selectively formed. The molecular structures of **6a** and **7b** were unambiguously confirmed by single crystal X-ray diffraction studies (Figure 2).

Scheme 3. Synthesis of copper complexes 6a and 7b.



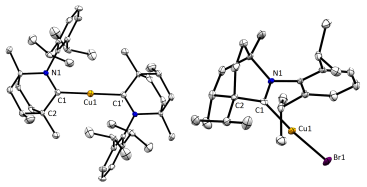
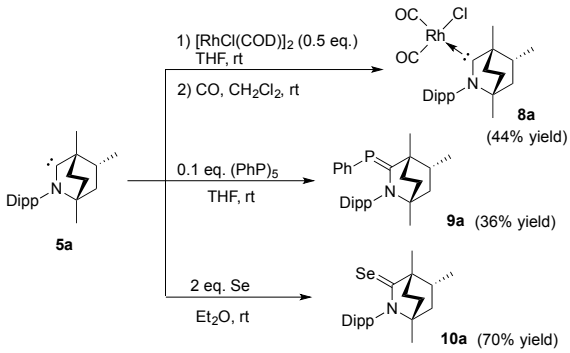


Figure 2. Solid-state structures of **6a** (left) and **7b** (right) with ellipsoids at 50% level of probability. One enantiomer is shown. H-atoms and [$CuBr_2$] in **6a** are omitted for clarity. Selected bond lengths [Å] and angles [°]. **6a**: C1-Cu1 1.919(4), N1-C1-C2 111.5(4), C1-Cu1-C1' 180. **7b**: C1-Cu1 1.902(3), Cu1-Br1 2.2351(6), N1-C1-C2 112.3(3), C1-Cu1-Br1 174.64(10).

To compare the electronic properties of BICAACs **5** with CAACs, the *cis*-[(**5a**)$Rh(CO)_2Cl$] complex **8a** was prepared as shown in Scheme 4. The IR spectrum of **8a** in dichloromethane solution shows two absorptions for C-O bond stretching at 1990 and 2074 cm^{-1}, (ν^{av}_{CO} = 2032 cm^{-1}), suggesting that BICAAC **5a** is an overall better donor than classic CAAC ligands (ν^{av}_{CO} = 2036 cm^{-1}).[11] To differentiate between the σ-donation and the π-accepting ability of the carbene, the phosphinidene adduct **9a** was prepared by reacting **5a** with $(PhP)_5$.[12] The ^{31}P NMR signal appeared at +90 ppm, substantially downfield shifted compared to anagolous adducts of monocyclic CAACs (+56 to +69 ppm), and even diamidocarbenes (DACs) (+ 83 ppm), one of the most electrophilic carbenes known so far.[13] To verify the surprising electrophilic character of **5a**, the selenium adduct **10a** was also synthesized.[14] As expected, the ^{77}Se NMR of **10a** shows a signal at lower field (+645 ppm) than CAACs (+492 ppm)[15] but surprisingly at higher field than DACs (+847 ppm),[14b,16] which means that the electrophilicity scales based on phosphinidene and selenium adducts do not always correlate. Nevertheless, these data clearly suggest that BICAACs have higher π-accepting ability than CAACs, and when combined with the TEP values, it can be concluded that BICAACs are also more σ-donating.

Scheme 4. Synthesis of rhodium complex, phosphinidene and selenium-adducts of 5a.



To confirm these conclusions, we performed DFT calculations at the B3LYP/def2-TZVPP level of theory. Indeed, we found that the HOMO and LUMO of the model BICAAC are higher and lower in energy, respectively, than those of CAACs (Figure 3). This is further supported by a significant decrease of the singlet-triplet gap from 49.2 kcal/mol (CAAC) to 45.7 kcal/mol (BICAAC).[17] The increased σ-donation and π-acceptance of BICAACs compared to CAACs might be correlated to the wider carbene bond angle (110.2 º *vs* 106.9 º, values from DFT).[12a,18]

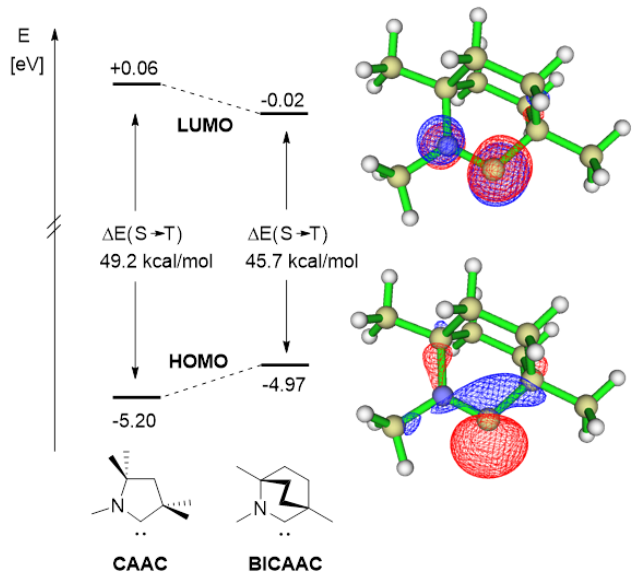
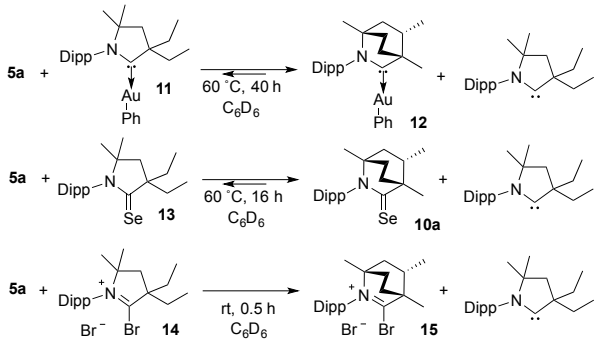


Figure 3. Frontier molecular orbital comparison between CAAC and BICAAC at the B3LYP/def2-TZVPP level.

Based on these results, one can expect that BICAACs would lead to even stronger metal-carbon bonds than CAACs. As a proof of principle, we reacted **5a** with one equivalent of (CAAC)AuPh complex **11**, and after 40 h at 60 °C, we reached an equilibrium containing a 65/35 ratio of (BICAAC)AuPh complex **12** (along with free CAAC) and (CAAC)AuPh **11** (along with **5a**) (Scheme 5). Carbene exchange at a metal center is a very classical reaction, but we wondered if a similar phenomenon could also occur at main group elements.[19] Indeed, the reaction between the CAAC-Se adduct **13** and BICAAC **5a** reached an equilibrium after 16 h at 60 ºC; a 70/30 ratio of **10a** and **13** was observed together with the corresponding amount of the free carbenes. Lastly, the bromo-iminium **14** cleanly reacted at room temperature with **5a** quantitatively affording the corresponding BICAAC-Br adduct **15** along with the free CAAC.

Scheme 5. Ligand exchange reactions at metal and main group element centers.



In summary, a straightforward strategy allows for the synthesis of bicyclic (alkyl)(amino)carbenes (BICAACs) from abundant and cheap trivertal. The steric bulk around the carbene center is easily tunable, and the bicyclo[2.2.2]octane skeleton confers to BICAACs a fan-like geometry which is different than that of CAACs, but similar to that observed in classical NHCs. These novel carbenes are more electrophilic and nucleophilic than monocyclic CAACs, and of course NHCs as shown by exchange reactions at metal centers but also main group elements. Of particular importance, BICAACs can be stored in the solid state at room temperature over a year.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/xxx. CCDC 1548015 (**5a**), CCDC 1548016 (**5b**), CCDC 1548017 (**6a**), CCDC 1548018 (**7b**), CCDC 1548019 (**10a**) and CCDC 1548020 (**13**) contain the crystallographic data.

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Notes

The authors declare no competing financial interests.

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REFERENCES

[1] For the synthesis of CAACs, see: (a) Lavallo, V.; Canac, Y.; Präsang, C.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 5705. (b) Jazzar, R.; Dewhurst, R. D.; Bourg, J. B.; Donnadieu, B.; Canac, Y.; Bertrand, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 2899. (c) Jazzar, R.; Bourg, J. B.; Dewhurst, R. D.; Donnadieu, B.; Bertrand, G. *J. Org. Chem.* **2007**, *72*, 3492. (d) Zeng, X.; Frey, G. D.; Kinjo, R.; Donnadieu, B.; Bertrand G. *J. Am. Chem. Soc.* **2009,** *131*, 8690.

[2] For reviews on CAACs, see: (a) Soleilhavoup, M.; Bertrand, G. *Acc. Chem. Res.* **2015**, *48*, 256. (b) Melaimi, M.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem. Int. Ed.* **2010,** *49*, 8810. (c) Roy, S.; Mondal, K. C.; Roesky, H. W. *Acc. Chem. Res.* **2016**, *49*, 357. (d) Melaimi, M.; Jazzar, R.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem. Int. Ed.* **2017,** *56*, DOI: 10.1002/anie.201702148.

[3] For thematic issues and books on NHCs, see: (a) Rovis, T.; Nolan, S. P. *Synlett* **2013**, *24*, 1188. (b) Arduengo, A. J.; Bertrand, G. *Chem. Rev.* **2009**, *109*, 3209. (c) Díez-González, S. *N-Heterocyclic Carbenes : From Laboratory Curiosities to Efficient Synthetic Tools*, Royal Society of Chemistry: Cambridge, **2016**; (d) Nolan, S. P. *N-Heterocyclic Carbenes: Effective Tools for Organometallic Synthesis*; Wiley-VCH: Weinheim, **2014**.

[4] (a) Lavallo, V.; Canac, Y.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *Angew. Chem. Int. Ed.* **2006**, *45*, 3488. (b) Droege, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 6940. (c) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. *Nature* **2014**, *510*, 485. (d) Vatsadze, S. Z.; Loginova, Y. D.; dos Passos Gomes, G.; Alabugin, I. V. *Chem. Eur. J.* **2017**, *23*, 3225.

[5] For reviews, see: (a) Martin, C. D.; Soleilhavoup, M.; Bertrand, G. *Chem. Sci.* **2013**, *4*, 3020. (b) Mondal, K. C.; Roy, S.; Roesky, H. W. *Chem. Soc. Rev.* **2016**, *45*, 1080.

[6] See for examples: (a) Weinberger, D. S.; Melaimi, M.; Moore, C. E.; Rheingold, A. L.; Frenking, G.; Jerabek, P.; Bertrand, G. *Angew. Chem. Int. Ed.* **2013**, *52*, 8964. (b) Singh, A. P.; Samuel, P. P.; Roesky, H. W.; Schwarzer, M. C.; Frenking, G.; Sidhu, N. S.; Dittrich, B. *J. Am. Chem. Soc.* **2013**, *135*, 7324. (c) Mondal, K. C.; Samuel, P. P.; Roesky, H. W.; Carl, E.; Herbst-Irmer, R.; Stalke, D.; Schwederski, B.; Kaim, W.; Ungur, L.; Chibotaru, L. F.; Hermann, M.; Frenking, G. *J. Am. Chem. Soc.* **2014**, *136*, 1770. (d) Ung, G.; Rittle, J.; Soleilhavoup, M.; Bertrand, G.; Peters, J. C. *Angew. Chem. Int. Ed.* **2014**, *53*, 8427. (e) Kinjo, R.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 5930. (f) Back, O.; Celik, M. A.; Frenking, G.; Melaimi, M.; Donnadieu, B.; Bertrand, G. *J. Am. Chem. Soc.* **2010**, *132*, 10262. (g) Kinjo, R.; Donnadieu, B.; Celik, M. A.; Frenking, G.; Bertrand, G. *Science* **2011**, *333*, 610. (h) Mondal, K. C.; Roesky, H. W.; Schwarzer, M. C.; Frenking, G.; Tkach, I.; Wolf, H.; Kratzer, D.; Herbst-Irmer, R.; Niepötter, B.; Stalke, D. *Angew. Chem. Int. Ed.* **2013**, *52*, 1801. (i) Abraham, M. Y.; Wang, Y.; Xie, Y.; Gilliard R. J. Jr.; Wei, P.; Vaccaro, B. J.; Johnson, M. K.; Schaefer H. F. III; Schleyer, P. v. R.; Robinson, G. H. *J. Am. Chem. Soc.* **2013**, *135*, 2486. (j) Kretschmer, R.; Ruiz, D. A.; Moore, C. E.; Rheingold, A. L.; Bertrand, G. *Angew. Chem. Int. Ed.* **2014**, *53*, 8176. (k) Roy, S.; Stückl, A. C.; Demeshko, S.; Dittrich, B.; Meyer, J.; Maity, B.; Koley, D.; Schwederski, B.; Kaim, W.; Roesky, H. W. *J. Am. Chem. Soc.* **2015**, *137*, 4670. (l) Martin, D.; Moore, C. E.; Rheingold, A. L.; Bertrand, G. *Angew. Chem. Int. Ed.* **2013**, *52*, 7014. (m) Li, Y.; Mondal, K. C.; Samuel, P. P.; Zhu, H.; Orben, C. M.; Panneerselvam, S.; Dittrich, B.; Schwederski, B.; Kaim, W.; Mondal, W. T.; Koley, D.; Roesky, H. W. *Angew. Chem. Int. Ed.* **2014**, *53*, 4168. (n) Munz, D.; Chu, J.; Melaimi, M.; Bertrand, G. *Angew. Chem Int. Ed.* **2016**, *55*, 12886. (o) Mahoney, J. K.; Martin, D.; Moore, C. E.; Rheingold, A. L.; Bertrand, G. *J. Am. Chem. Soc.* **2013**, *135*, 18766. (p) Mahoney, J. K.; Martin, D.; Thomas, F.; Moore, C. E.; Rheingold, A. L.; Bertrand, G.; *J. Am. Chem. Soc.* **2015**, *137*, 7519.

[7] (a) Frey, G. D.; Lavallo, V.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. *Science* **2007**, *316*, 439. (b) Frey, G. D.; Masuda, J. D.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 9444. (c) Martin, D.; Canac, Y.; Lavallo, V.; Bertrand, G. *J. Am. Chem. Soc.* **2014**, *136*, 5023. (d) Paul, U. S. D.; Radius, U. *Chem. Eur. J.* **2017**, *23*, 3993. (e) Würtemberger-Pietsch, S.; Schneider, H.; Marder, T. B.; Radius, U. *Chem. Eur. J.* **2016**, *22*, 13032. (f) Mohapatra, C.; Samuel, P. P.; Li, B.; Niepötter, B.; Schürmann, C. J.; Herbst-Irmer, R.; Stalke, D.; Maity, B.; Koley, D.; Roesky, H. W. *Inorg. Chem.* **2016**, *55*, 1953. (g) Turner, Z. R.; Buffet, J.-C. *Dalton. Trans.* **2015**, *44*, 12985. (h) Turner, Z. R. *Chem. Eur. J.* **2016**, *22*, 11461.

[8] See for exemples: (a) Lavallo, V.; Frey, G. D.; Donnadieu, B.; Soleilhavoup, M.; Bertrand, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 5224. (b) Kinjo, R; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.* **2011**, *50*, 5560. (c) Zeng, X.; Soleilhavoup, M.; Bertrand, G. *Org. Lett.* **2009**, *11*, 3166. (d) Zeng, X.; Frey, G. D.; Kousar, S.; Bertrand, G. *Chem. Eur. J.* **2009**, *15*, 3056. (e) Zeng, X.; Kinjo, R.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.* **2010**, *49*, 942.

[9] Zeng, X.; Frey, G. D.; Kinjo, R.; Donnadieu, B.; Bertrand, G. *J. Am. Chem. Soc.* **2009**, *131*, 8690.

[10] *Common Fragrance and Flavor Materials: Preparation, Properties and Uses, 6th Edition* Ed.: Surburg, H.; Panten, P. Wiley-VCH, Weinheim, **2016.**

[11] Lavallo, V.; Canac, Y.; Dehope, A.; Donnadieu, B.; Bertrand, G. *Angew. Chem. Int. Ed.* **2005**, *44*, 7236.

[12] (a) Back, O.; Henry-Ellinger, M.; Martin, C. D.; Martin, D.; Bertrand, G. *Angew. Chem. Int. Ed.* **2013**, *52*, 2939. (b) Rodrigues, R. R.; Dorsey, C. L.; Arceneaux, C. A.; Hudnall, T. W. *Chem. Commun.* **2014**, *50*, 162.

[13] (a) Moerdyk, J. P.; Bielawski, *Chem. Commun.* **2014**, *50*, 4551. (b) Hudnall, T. W.; Bielawski, C. W. *J. Am. Chem. Soc.* **2009**, *131*, 16039. (c) Moerdyk, J. P.; Schilter, D.; Bielawski, C. W. *Acc. Chem. Res.* **2016**, *49*, 1458.

[14] (a) Liske, A.; Verlinden, K.; Buhl, H.; Schaper, K.; Ganter, C. *Organometallics* **2013**, *32*, 5269. (b) Verlinden, K.; Buhl, H.; Frank, W.; Ganter, C. *Eur. J. Inorg. Chem.* **2015**, 2416.

[15] Tretiakov, M.; Shermolovich, Y. G.; Singh, A. P.; Samuel, P. P.; Roesky, H. W.; Niepötter, B.; Visscher, A.; Stalke, D. *Dalton Trans.* **2013**, *42*, 12940.

[16] Paul, U. S. D.; Sieck, C.; Haehnel, M.; Hammond, K.; Marder, T. B.; Radius, U. *Chem. Eur. J.* **2016**, *22*, 11005.

[17] The nitrogen substitution (Me *vs* Dipp) has little influence on the calculated S/T gap at the B3LYP-D3BJ/def2-TZVP level of theory [49.4 kcal/mol (Dipp-CAAC) and 45.3 kcal/mol (Dipp-BICAAC) instead of 49.2 kcal/mol (Me-CAAC) and 45.7 kcal/mol (Me-BICAAC).

[18] (a) Hirai, K.; Itoh, T.; Tomioka, H. *Chem. Rev.* **2009**, *109,* 3275. (b) Bourissou, D.; Guerret, O.; Gabbaï, F. P.; Bertrand, G. *Chem. Rev.* **2000**, *100,* 39.

[19] We have recently reported that CAACs can displace triphenylphosphine from a phosphinidene-PPh_3 adduct. Hansmann, M. M.; Bertrand, G. *J. Am. Chem. Soc.* **2016**, *138*, 15885.

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