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COMMUNICATION

CAAC–IPr*: Easily Accessible, Highly Sterically-Hindered Cyclic (Alkyl)(Amino)Carbenes

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IPr* (IPr* = 1,3-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene) has emerged as a powerful highly hindered and sterically-flexible ligand platform for transition-metal catalysis. CAACs (CAAC = cyclic (alkyl)(amino)carbenes) have gained major attention as strongly electron-rich carbon analogues of NHCs (NHC = N-heterocyclic carbene) with broad applications in both industry and academia. Herein, we report a merger of CAAC ligands with highly-hindered IPr*. The efficient synthesis, electronic characterization and application in model Cu-catalyzed hydroboration of alkynes is described. The ligands are strongly electron-rich, bulky and flexible around the N-Ar wingtip. The availability of various IPr* and CAAC templates offers a significant potential to expand the existing arsenal of NHC ligands to electron-rich bulky architectures with critical applications in metal stabilization and catalysis.

The development of new catalysts represents one of the most fundamental approaches to advance the field of organic synthesis.[1,2] In this context, the isolation of N-heterocyclic carbenes by Arduengo in 1991,[3] quickly followed by extensive studies in catalysis by Herrmann and the introduction of IPr as the privileged ligand by the Nolan group (IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene) have launched expansive research on N-heterocyclic carbenes (Figure 1).[4,5] At present, NHC ligands have found ubiquitous applications in catalysis, materials science, energy research and medicinal chemistry, where the imidazole scaffold provides numerous avenues to tune the properties of the organometallic system.[6] In 2005, the Bertrand group discovered that σ-donation of NHCs can be significantly enhanced by replacing one of the nitrogen substituents with less electronegative quaternary carbon atom in CAAC ligands.[7] The presence of sp^3-hybridized carbon instead of planar nitrogen further provides sterically-differentiated

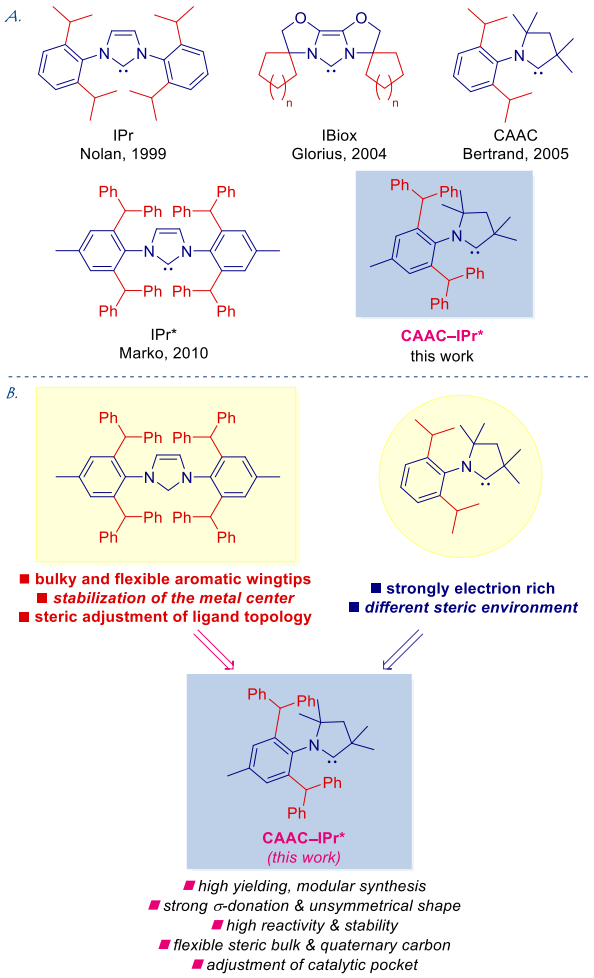

Figure 1. Sterically-demanding N-heterocyclic carbenes.

environment around the metal center,[8] making CAACs broadly popular ligands in various areas of catalysis and main metal chemistry in both academic and industrial settings.[9] Simultaneously, IPr* ligands featuring bulky and flexible aromatic wingtips have emerged as a powerful platform in transition-metal catalysis (Figure 1).[10] In these ligands, the

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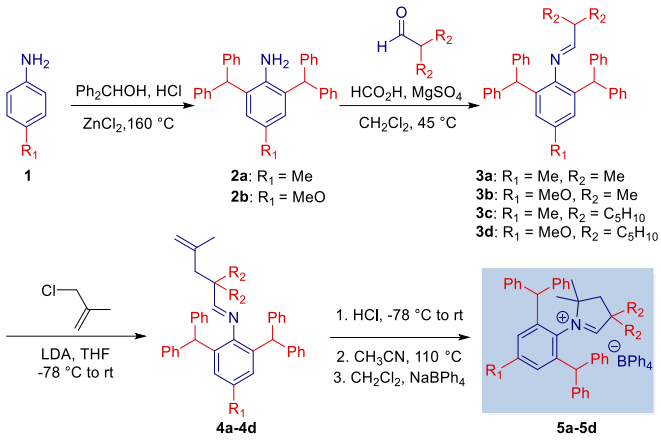
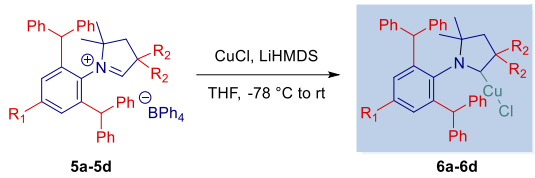


1 2a: R1 = Me 2b: R1 = MeO 3a: R1 = Me, R2 = Me 3b: R1 = MeO, R2 = Me 3c: R1 = Me, R2 = C5H10 3d: R1 = MeO, R2 = C5H10 4a-4d 5a-5d

Scheme 1. Synthesis of CAAC–IPr* Salts. Conditions: (a) **1** (1.0 equiv), Ph_2CHOH (2 equiv), $ZnCl_2$ (0.5 equiv), HCl (36% aq., 1.0 equiv), 160 °C, 15 h. **2a**: 89%; **2b**: 92%. (b) **2** (1.0 equiv), RCHO (1.5 equiv), HCO_2H (0.05 equiv), $MgSO_4$ (5 equiv), CH_2Cl_2, 45 °C, 24 h. **3a**: 70%; **3b**: 73%; **3c**: 65%; **3d**: 61%. (c) **3** (1.0 equiv), LDA (3.6 equiv), 3-chloro-2-methylprop-1-ene (6 equiv), THF, -78 °C-rt, 20 h. **4a**: 85%; **4b**: 82%; **4c**: 75%; **4d**: 72%. (d) (i) HCl (2 M in Et_2O, 1.1 equiv), hexane, -78 °C-rt, 30 min; (ii) CH_3CN, 110 °C, 24 h; (iii) $NaBPh_4$ (5 equiv), CH_2Cl_2, rt, 15 h. **5a**: 65%; **5b**: 61%; **5c**: 71%; **5d**: 74%. See SI for details.



5a-5d 6a-6d

Scheme 2. Synthesis of [Cu(IPr*–CAAC)Cl] Complexes. Conditions: **5** (1 equiv), CuCl (3 equiv), LiHMDS (3 equiv), THF, -78 °C-rt, 20 h. **6a**: 82%; **6b**: 64%; **6c**: 87%; **6d**: 69%.

extremely bulky N-aromatic wingtips provide kinetic stabilization of the metal center, while the flexibility rendered by benzhydryl substituents enables steric adjustments of the ligand topology. At present, IPr* and counterparts are among the successful successors to IPr in the rapidly growing area of N-heterocyclic carbenes.

Inspired by the elegant studies in NHC ligand development by the groups of Nolan,[11] Bertrand,[7,9,12] Glorius,[13] Marko[14] and others,[6,8,15] and following our interest in NHC ligands in catalysis,[16] we considered a merger of sterically-hindered IPr* and strongly electron-rich CAAC ligands (Figure 1B). We hypothesized that this unique class of ligands would combine the properties of both families of ligands, while providing a new strategy for the development of electron-rich, flexible and extremely bulky catalyst architectures.

The synthesis of IPr*–$CAAC^{Me}$ bearing methyl substituents at the quaternary carbon was selected as a starting point (Scheme 1, **5a**). After experimentation, we were pleased to find that a route involving condensation of 2,6-bis(diphenylmethyl)-4-toluidine with 2-methylpropanal and catalytic formic acid in CH_2Cl_2 at 45 °C afforded the product imine in 70% yield.[16f] The subsequent α-alkylation was accomplished with excess of LDA and 3-chloro-2-methylprop-1-ene in 85% yield. Finally, the intramolecular cyclization proceeded in 65% yield to give IPr*–$CAAC^{Me}$ as $HBPh_4$ salt by a sequence involving N-protonation with HCl at -78 °C to give alkenyl iminium, ring closure at 110 °C and counterion exchange with $NaBPh_4$ to facilitate purification.

It should be noted that condensation, alkylation and cyclization steps are significantly more challenging with the bulky IPr* aniline than with less hindered anilines, such as Dipp (Dipp = 2,6-diisopropylaniline) due to steric hindrance of benzhydryl substituents. The synthesis of more electron-rich analogue bearing 4-methoxy substitution at the N-Ar wingtip, IPr*^{MeO}–$CAAC^{Me}$ (**5b**) as well as analogues bearing cyclohexyl moiety that provide "flexible wall" at the quaternary carbon, IPr*–$CAAC^{Cy}$ (**5c**) and IPr*^{MeO}–$CAAC^{Cy}$ (**5d**), was successfully accomplished following the same procedures (Scheme 1), attesting to the generality of the approach.

With access to IPr*–$CAAC^{Me}$ secured, we next evaluated complexation with CuCl. [Cu(IPr*–CAAC)Cl] complexes were selected as model systems due to the predicted linear geometry and the recent advances in the use of Cu–CAACs in catalysis.[17] Complexes [Cu(IPr*–$CAAC^{Me}$)Cl] (**6a**), [Cu(IPr*^{MeO}–$CAAC^{Me}$)Cl] (**6b**), [Cu(IPr*–$CAAC^{Cy}$)Cl] (**6c**), and [Cu(IPr*^{MeO}–$CAAC^{Cy}$)Cl] (**6d**) were readily prepared by a deprotonation route with LiHMDS at -78 °C in 64-87% yields (Scheme 2). All complexes **6a**–**6d** were found to be stable to air and moisture. Complexes **6a** and **6b** were fully characterized by x-ray crystallography (Figure 2 and 3). Studies by Nolan and Cavallo demonstrated that % buried volume (%V_{bur}) and steric maps of linear NHC–metal complexes provide the best indication of steric impact of NHC ligands.[18] [Cu(IPr*–$CAAC^{Me}$)Cl] and [Cu(IPr*^{MeO}–$CAAC^{Me}$)Cl] are linear (**6a**: C–Cu–Cl, 174.45°; C–Cu, 1.864 Å; **6b**: C–Cu–Cl, 176.06°; C–Cu, 1.882 Å), making them good models for evaluating %V_{bur}. With the (%V_{bur}) of 49.5% and 49.4%, [Cu(IPr*–$CAAC^{Me}$)Cl] and [Cu(IPr*^{MeO}–$CAAC^{Me}$)Cl] represent the bulkiest $CAAC^{Me}$ ligands developed to date. These values can be compared with the (%V_{bur}) of 41.9% determined for [Cu(Dipp–$CAAC^{Me}$)Cl] (C–Cu–Cl, 173.66°; C–Cu, 1.878 Å). Note that the (%V_{bur}) of [Cu(IPr*–$CAAC^{Me}$)Cl] and [Cu(IPr*^{MeO}–$CAAC^{Me}$)Cl] approaches the (%V_{bur}) determined for imidazol-2-ylidene [Cu(IPr*)Cl] of 52.1%.

The crystallographic analysis of [Cu(IPr*–$CAAC^{Me}$)Cl] and [Cu(IPr*^{MeO}–$CAAC^{Me}$)Cl] revealed spatially-distinct unsymmetrical quadrant distribution (Figure 3). The values indicate significant steric enhancement vs. [Cu(Dipp–$CAAC^{Me}$)Cl] (SW 34%, NW 32.0%, NE 54.5%, SE 47.1%,)[17] and clearly distinguish the quaternary carbon-substituted unsymmetrical CAACs from their symmetrical imidazol-2-ylidene counterparts ([Cu(IPr*)Cl, SW 63.1%, NW 54.9%, NE 42.5%, SE 48.1%). This provides important differentiated steric quadrant distribution in combination with flexible–$CHPh_2$ aryl wingtip topology. Note that CAAC–IPr* are more sterically-bulky than IPr* (NE, SE quadrants, Figure 3), which clearly results from the presence of a quaternary center adjacent to the carbenic carbon.

We have further prepared selenourea adduct, [Se(IPr*–$CAAC^{Me}$)] (**7**), to evaluate π-backbonding from the ^{77}Se spectra (Scheme 3). The δ_{Se} value of 532.45 ppm ($CDCl_3$) for [Se(IPr*–$CAAC^{Me}$)] can be compared with Dipp–$CAAC^{Me}$ (δ_{Se} = 492 ppm), indicating enhancement of π-backbonding, as expected from the 2,6-bis(benzhydryl) substitution (IPr*: δ_{Se} = 106 ppm).[19] Furthermore, one-bond CH *J* coupling constant gives a good indication of σ-donating properties (*vide infra*). The value of 181.67 Hz for IPr*–$CAAC^{Me}$HCl (DMSO-d_6) indicates this ligand as strongly σ-donating (IPr: 223.70 Hz; Dipp–$CAAC^{Cy}$: 188.53 Hz),[20] while at the same time more sterically-demanding and flexible. The chemical shift of the iminium proton in IPr*–$CAAC^{Me}$HCl was found at 5.76 ppm ($CDCl_3$),

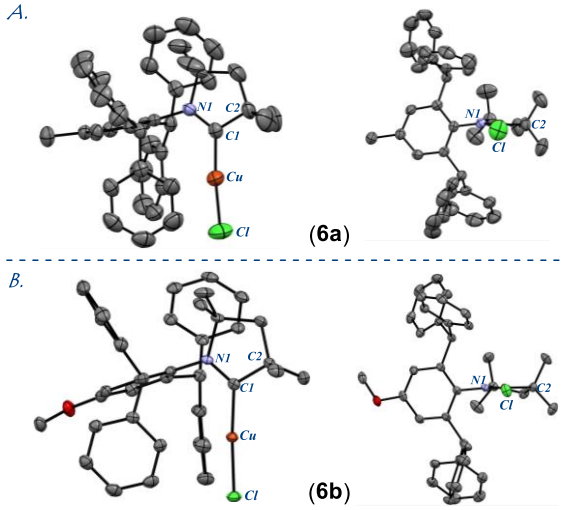


Figure 2. X-ray crystal structure of **6a**–**6b**. Two views: front (left); side (right). Hydrogen atoms have been omitted for clarity. Selected bond lengths [Å] and angles [°]: **6a**: Cu–C1, 2.0835(9); Cu–C1, 1.864(2); N1-C1, 1.300(3); N1-C9, 1.459(4); C1-C2, 1.512(4); C1–Cu–Cl, 174.45(8); C1–N1–C4, 115.4(2); C1–N1–C9, 122.7(2); C4–N1–C9, 121.8(2); Cu–C1–C2, 122.4(2); Cu–C1–N1, 128.6(2); N1–C1–C2, 122.4(2). **6b**: Cu–C1, 2.1142(5); Cu–C1, 1.882(1); N1-C1, 1.305(2); N1-C9, 1.457(2); C1-C2, 1.519(2); C1–Cu–Cl, 176.06(5); C1–N1–C4, 115.3(1); C1–N1–C9, 121.6(1); C4–N1–C9, 123.1(1); Cu–C1–C2, 122.5(1); Cu–C1–N1, 128.2(1); N1–C1–C2, 122.5(1). CCDC 2209831 (**6a**). CCDC 2209832 (**6b**).

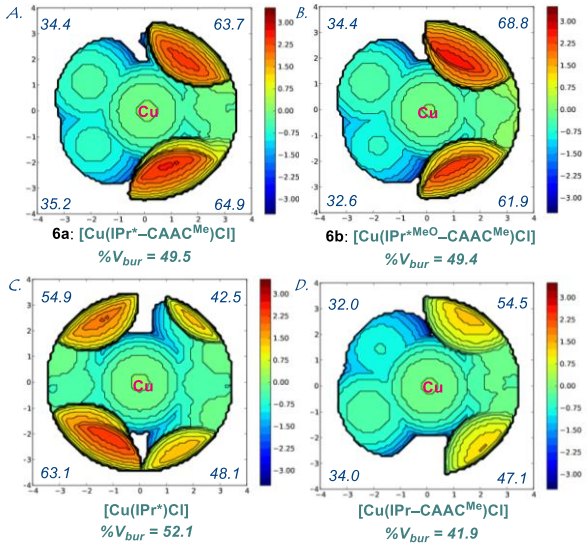
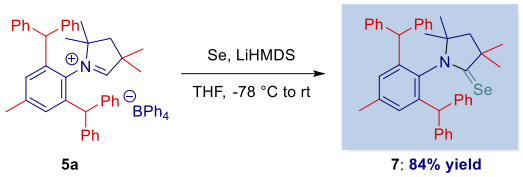


Figure 3. (A-D) Topographical steric maps of [Cu(IPr*–CAACMe)Cl] **6a**, [Cu(IPr*MeO–CAACMe)Cl] **6b**, [Cu(IPr*)Cl], [Cu(IPr-CAACMe)Cl] showing $\%V_{bur}$ per quadrant.

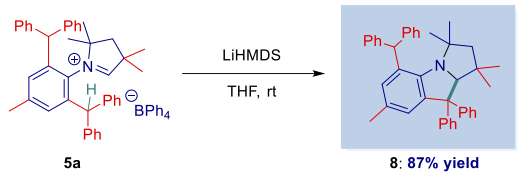
which is significantly upfield compared with imidazolium IPr* salt (13.0 ppm).[14]

Interestingly, we found that the carbene generated from IPr*–CAAC^{Me} undergoes intramolecular C–H activation at room temperature to afford benzopyrrolizidine in excellent 87% yield (Scheme 4, **8**). This reaction is driven by the steric arrangement of the carbene in the close proximity to the benzylic C–H position, providing a unique access to biologically active pyrrolizidine scaffolds.

The activity of [Cu(IPr*–CAAC)Cl] complexes was evaluated in Cu-catalyzed hydroboration of alkynes (Scheme 5). Recently, there have been major advances in Cu–CAAC-catalyzed borylcupration of alkynes, where Cu–CAACs have been identified to provide complementary regioselectivity to Cu–imidazol-2-ylidenes.[17]



Scheme 3. Synthesis of [Se(IPr*–CAAC^{Me})]

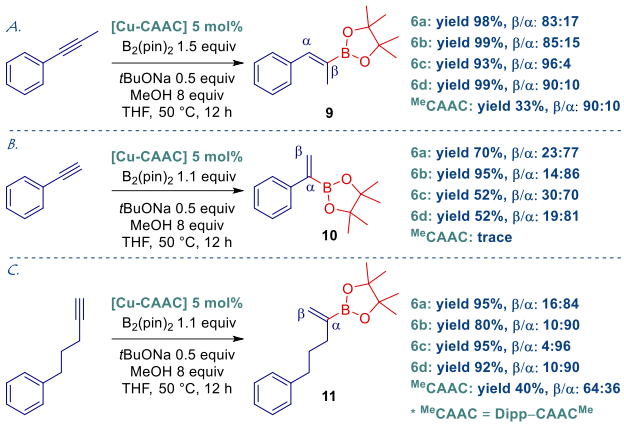


Scheme 4. Intramolecular C–H Activation

We selected this reaction as a model system vs. the parent CAAC^{Me}. All IPr*–CAAC catalysts were evaluated against the standard Dipp–CAAC^{Me} to gauge the effect of steric ligand substitution. As shown, IPr*–CAAC–Cu significantly improves the efficiency and regioselectivity of borylcupration cf. the parent CAAC^{Me}. In the hydroboration of 1-phenyl-1-propyne, the most effective is [Cu(IPr*–CAAC^{Cy})Cl] (**6c**) affording β-hydroboration product in 93% yield and 96:4 β-selectivity. All IPr*–CAAC–Cu catalysts significantly outperform the unhindered Dipp–CAAC^{Me}–Cu. In the hydroboration of phenylacetylene, the most effective is [Cu(IPr*^{MeO}–CAAC^{Me})Cl] (**6b**), affording the hydroboration product in 95% yield and 86:14 α-selectivity, while other IPr*–CAAC–Cu catalysts provide good levels of efficiency (52-70% yields). Of note, Dipp–CAAC^{Me}–Cu is completely ineffective under these conditions. Finally, in hydroboration of pent-4-yn-1-ylbenzene, the most effective is [Cu(IPr*–CAAC^{Cy})Cl] (**6c**), affording the hydroboration product in 95% yield and 96:4 α-selectivity. Again, all IPr*–CAAC–Cu catalysts significantly outperform Dipp–CAAC^{Me}–Cu.

To gain insight into the electronic properties of IPr*–CAACs, HOMO and LUMO energy levels were determined at the B3LYP 6-311++g(d,p) level (Figure 4 and SI). Most importantly, the HOMO of IPr*–CAAC^{Me} (-5.49 eV) is significantly higher than IPr (-6.01 eV), which is a model for σ-donating NHCs. This value can be compared with Dipp–CAAC^{Me} (-5.33 eV) and IPr* (-6.12 eV). Furthermore, the LUMO of IPr*–CAAC^{Me} (-0.90 eV) can be compared with Dipp–CAAC^{Me} (-5.33 eV) and IPr* (-6.12 eV). Furthermore, the LUMO of IPr*–CAAC^{Me} (-0.90 eV) can be compared with IPr (-0.48 eV, LUMO+1 due to required symmetry), Dipp–CAAC^{Me} (-0.51 eV) and IPr* (-0.90 eV). Thus, the strong σ-donation of IPr*–CAACs in combination with variable bulk makes this class of NHCs well-suited for catalysis. Note the enhancement of π-acceptance of CAAC–IPr* as a result of ortho-benzhydryl substitutents.[16f] At this stage, we have been unable to determine TEP due to facile C–H activation.[15,16f]

Furthermore, to eliminate impact from steric packing, the percent buried volume ($\%V_{bur}$) was calculated from the optimized structures of [Cu(CAAC)Cl] complexes **6a**–**6d** at the B3LYP 6-311++g(d,p) level (see SI). These studies determined the $\%V_{bur}$ of NHC in [Cu(IPr*-CAAC^{Me})Cl] (**6a**) as 47.1% (SW, 31.8%; NW, 34.7%; NE, 62.3%; SE, 59.7%); [Cu(IPr*^{MeO}-CAAC^{Me})Cl] (**6b**) as 47.1% (SW, 31.8%; NW, 35.0%; NE, 61.9%; SE, 59.6%); [Cu(IPr*-CAAC^{Cy})Cl] (**6c**) as 47.3% (SW, 32.1%; NW, 34.9%; NE, 62.5%; SE, 59.8%); and in [Cu(IPr*^{MeO}-CAAC^{Cy})Cl] (**6d**) as 47.3% (SW, 32.1%; NW, 35.4%; NE, 62.0%; SE, 59.8%). The unsymmetrical geometry rendered by the quaternary carbon provides unique steric environment of these strongly σ-donating NHC ligands.



Scheme 5. Hydroboration of Alkynes Catalyzed by [Cu(IPr*–CAAC)Cl]. Catalyst (0.05 equiv), B_2Pin_2 (1.5 or 1.1 equiv), *t*BuONa (0.5 equiv), MeOH (8 equiv), THF, 50 °C, 12 h.

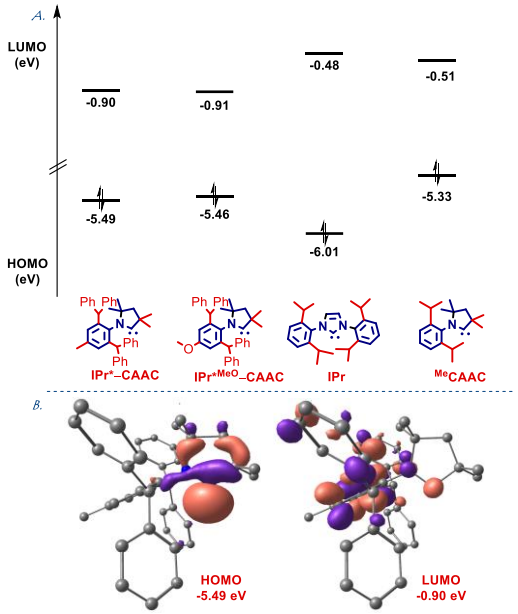


Figure 4. (A) HOMO and LUMO energy levels (eV). (B) HOMO (σ-donating orbital) and LUMO (π-accepting orbital) of IPr*–CAAC **5a**. B3LYP 6-311++g(d,p) level. See SI.

In conclusion, we have developed a unique family of highly-hindered CAAC ligands derived from IPr*. These ligands represent a merger of highly hindered and sterically-flexible IPr* with strongly electron-rich, quaternary carbon-substituted CAACs. These novel characteristics and availability of various IPr* and CAAC templates offer a significant potential to expand the arsenal of NHC ligands to electron-rich bulky architectures with key applications in metal stabilization and catalysis. Future studies are directed toward the synthesis of chiral ligands and the expansion to other metal complexes.

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