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ItOct (ItOctyl) – pushing the limits of ItBu: highly hindered electron-rich N-aliphatic N-heterocyclic carbenes†

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ItBu (**ItBu** = 1,3-di-*tert*-butylimidazol-2-ylidene) represents the most important and most versatile *N*-alkyl *N*-heterocyclic carbene available in organic synthesis and catalysis. Herein, we report the synthesis, structural characterization and catalytic activity of **ItOct** (ItOctyl), *C*₂-symmetric, higher homologues of **ItBu**. The new ligand class, including saturated imidazolin-2-ylidene analogues has been commercialized in collaboration with MilliporeSigma: **ItOct**, 929 298; **SlfOct**, 929 492 to enable broad access of the academic and industrial researchers within the field of organic and inorganic synthesis. We demonstrate that replacement of the *t*-Bu side chain with *t*-Oct results in the highest steric volume of *N*-alkyl *N*-heterocyclic carbenes reported to date, while retaining the electronic properties inherent to *N*-aliphatic ligands, such as extremely strong σ -donation crucial to the reactivity of *N*-alkyl *N*-heterocyclic carbenes. An efficient large-scale synthesis of imidazolium **ItOct** and imidazolium **SlfOct** carbene precursors is presented. Coordination chemistry to Au(I), Cu(I), Ag(I) and Pd(II) as well as beneficial effects on catalysis using Au(I), Cu(I), Ag(I) and Pd(II) complexes are described. Considering the tremendous importance of **ItBu** in catalysis, synthesis and metal stabilization, we anticipate that the new class of **ItOct** ligands will find wide application in pushing the boundaries of new and existing approaches in organic and inorganic synthesis.

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Introduction

ItBu (**ItBu** = 1,3-di-*tert*-butylimidazol-2-ylidene) is the most useful and most general bulky *N*-alkyl *N*-heterocyclic carbene in organic synthesis and catalysis (Fig. 1A, 1).^{1–3} The importance of **ItBu** is reflected by the numerous applications in transition-metal-catalysis using an entire palette of metals and transformations. The extraordinary high utility of **ItBu** stems from the large steric volume (%*V*_{bur} = 39.6%; %*V*_{bur} = %buried volume, [Au(**ItBu**)Cl]) provided by the bulky *t*-Bu group at the *N*-wingtip.⁴ Simultaneously, the electron-donating *N*-alkyl groups engender the ligand with strong σ -donation (TEP, 2049 cm⁻¹, [Rh(**ItBu**)(CO)₂Cl]) and high π -acceptance (⁷⁷Se NMR, δ_{Se} , 183 ppm, [Se(**ItBu**)]), which supersede the values observed for *N*-aromatic NHCs.⁵ Overall, this results in a unique NHC scaffold that has become an indispensable part of the synthetic,

organometallic and inorganic toolbox, while providing direct access to novel reactivity, and is now routinely utilized in metal stabilization, reaction screening and optimization. **ItBu**

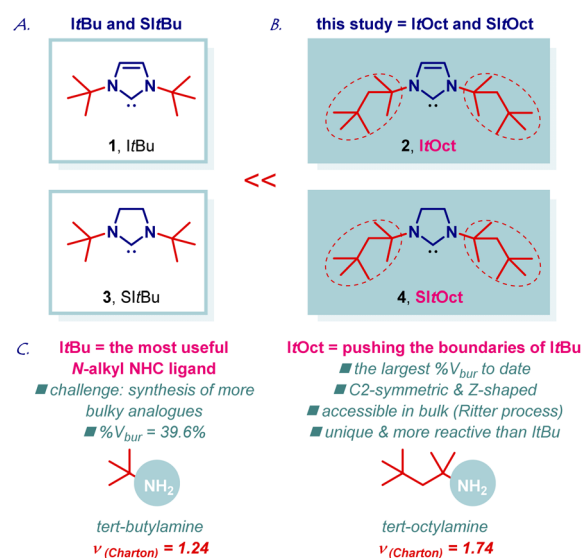


Fig. 1 (A–C) Pushing the limits of sterically-demanding *N*-alkyl-heterocyclic carbenes: moving beyond **ItBu**. **ItOct** and **SlfOct** are commercially available from MilliporeSigma: **ItOct**, 929 298; **SlfOct**, 929 492.

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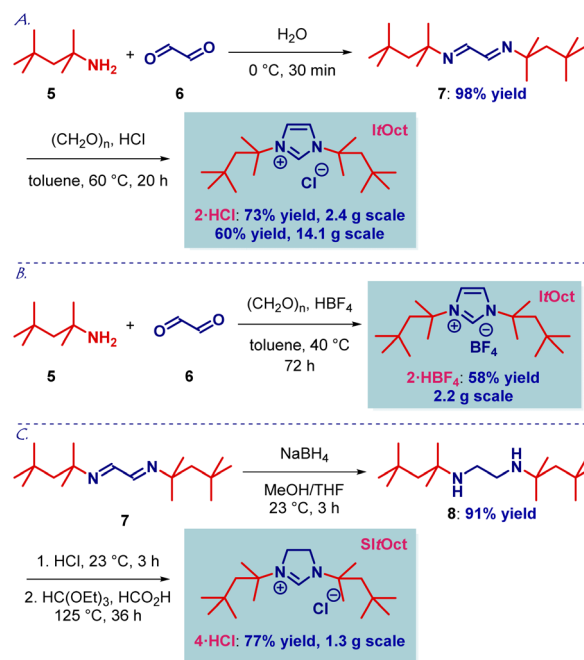
imidazolium precursor is now commercially available from several suppliers as Cl or BF₄ salts (CAS: 157197-54-1; CAS: 263163-17-3).^{6,7}

As part of our program in transition-metal-catalysis,^{8,9} herein we report the synthesis, structural characterization, and catalytic activity of **ItOct** (ItOctyl) class of ligands, which are C₂-symmetric, higher homologues of **ItBu** (Fig. 1B, 2). The new ligand class, including saturated imidazolin-2-ylidene analogue, has been commercialized in collaboration with MilliporeSigma: **ItOct**, 929 298; **SItOct**, 929 492, to enable broad access of academic and industrial researchers.¹⁰ We demonstrate that **ItBu** to **ItOct** exchange results in the highest steric volume reported to date for *N*-alkyl *N*-heterocyclic carbenes (% *V*_{bur} = 44.7%), while retaining electronic properties inherent to *N*-alkyl ligands, such as extremely strong σ-donation and π-acceptance.^{4,5} Notably, the steric volume of **ItOct** matches the values observed for the archetypal *N*-aromatic NHC ligands for the first time (IPr, %*V*_{bur} = 45.4%; IMes, %*V*_{bur} = 36.5%, [Au(NHC)Cl]). **ItOct** features a unique C₂-symmetric and Z-shape scaffold.¹¹ The saturated congener, **SItOct** (Fig. 1B, 4), is homologous to **SItBu** (Fig. 1A, 3). Large scale synthesis, coordination chemistry to Au(I), Cu(I), Ag(I) and Pd(II), structure and electronic properties of the carbene center as well as beneficial effects on catalysis using Au(I), Cu(I), Ag(I) and Pd(II) complexes are described. Considering the tremendous importance and utility of **ItBu** in catalysis, synthesis and metal stabilization¹⁻³ we anticipate that the new class of **ItOct** ligands will find wide application in pushing the limits of *N*-alkyl *N*-heterocyclic carbenes in organic and inorganic synthesis.

Results and discussion

The chemistry of *N*-bulky NHC ligands has been studied in a wide array of contexts, including catalysis, coordination chemistry and stabilization of reactive metal centers.^{11,12} We reasoned that an increase in sterics as measured by the Charton parameter (*t*-Bu, *ν* = 1.24; *t*-Oct, *ν* = 1.74, Fig. 1C) would result in an attractive new class of *N*-aliphatic bulky NHC ligands. As a key element of our design, we recognized that *tert*-octylamine is considerably cheaper than other bulky amines and readily available on kg scale by the Ritter process of the isomeric 2,2,4-trimethylpentenes,^{13,14} which are commercially produced from isobutene feedstock.

We initiated our studies by developing a flexible and robust synthesis of **ItOct** imidazolium precursor using the readily available *tert*-octylamine¹³⁻¹⁵ as the starting material (Scheme 1A). As shown in Scheme 1, the optimized synthesis of **ItOct** precursor proceeds in cost-effective, chromatography-free, and straightforward manner. Thus, condensation of *tert*-octylamine with glyoxal at room temperature and cyclization of the diimine using a combination of HCl/(CH₂O)_{*n*} in toluene at 60 °C delivered the desired **ItOct** as HCl salt after simple filtration, allowing for a routine preparation of gram quantities of the product (step 1: 98% yield, 61 mmol scale; step 2: 73% yield, 10 mmol scale). The synthesis of **ItOct** as HBF₄ salt was optimized to proceed in 82% yield (Scheme 1B), while a one-step procedure was developed using the combination of *tert*-

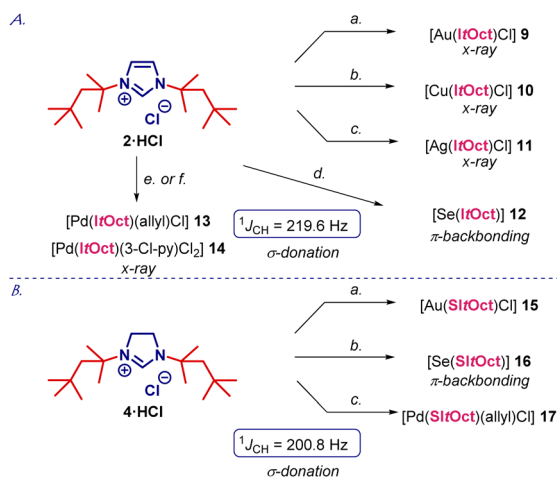


Scheme 1 Synthesis of **ItOct**, **SItOct** and precursors. Conditions: (A) **5** (1.0 equiv.), (CHO)₂ (40% aq. 0.5 equiv.), H₂O, 0 °C, then (CH₂O)_{*n*} (1.0 equiv.), HCl (4.0 M, dioxane, 1.0 equiv.), toluene, 60 °C. (B) **7** (1.0 equiv.), (CH₂O)_{*n*} (1.0 equiv.), HBF₄ (48% aq. 1.0 equiv.), toluene, 40 °C; one-step: **5** (1.2 equiv.), (CH₂O)_{*n*} (1.0 equiv.), HBF₄ (48% aq. 1.0 equiv.), toluene, 40 °C. (C) **7** (1.0 equiv.), NaBH₄ (8.0 equiv.), MeOH/THF, 23 °C, then HCl, 23 °C, HC(OEt)₃ (10.0 equiv.), HCO₂H, 125 °C.

octylamine, HBF₄/(CH₂O)_{*n*} and glyoxal in 58% yield (see ESI†). The synthesis of **SItOct** as HCl salt was accomplished by the reduction of diimine **7** to the diamine using NaBH₄ in MeOH/THF at room temperature (91% yield, 18 mmol scale) and cyclization to the imidazolium **SItOct** salt using a combination of HC(OEt)₃/HCO₂H at 125 °C (77% yield, 5 mmol scale) (Scheme 1C). It should be noted that the synthesis is highly practical and allows for the isolation of **ItOct**·HCl, **ItOct**·HBF₄ and **SItOct**·HCl by simple filtration and recrystallization from the reaction mixtures.

With facile access to **ItOct** in hand, we next focused on comprehensive evaluation of steric and electronic properties of this novel NHC ligand (Scheme 2A). As shown in Scheme 2, the gold complex [Au(**ItOct**)Cl] (**9**) was prepared using LiHMDS/THF, while the method using K₂CO₃/acetone gave lower yields.¹⁶ Moreover, [Ag(**ItOct**)Cl] (**10**) and [Cu(**ItOct**)Cl] (**11**) were prepared using Ag₂O/CuCl and K₂CO₃ in 1,4-dioxane at 80 °C.¹⁷ The selenium adduct [Se(**ItOct**)] (**12**) was synthesized using selenium/K₂CO₃ at 80 °C,¹⁸ while the Pd(II) complexes [Pd(**ItOct**)(allyl)Cl] (**13**) and [Pd(**ItOct**)(3-Cl-py)Cl₂] (**14**) were prepared from the palladium allyl dimer [{Pd(allyl)(μ-Cl)}₂] and PdCl₂/3-Cl-py in the presence of LiHMDS and K₂CO₃, respectively.^{19,20} It should be noted that NHC salts (**2**) and (**4**) as well as all products **9–14** were found to be stable to air and moisture. Complexes **9–12** and **14** were fully characterized by X-ray crystallography (Fig. 2, 3, and ESI†).²¹





Scheme 2 Synthesis of **ItOct** and **SitOct** complexes. Conditions: (A) (a) $\text{AuCl} \cdot \text{Me}_2\text{S}$ (1.0 equiv.), LiHMDS (1.1 equiv.), THF, 23 °C, 15 h, 84%. (b) CuCl (2.0 equiv.), K_2CO_3 (3.0 equiv.), dioxane, 80 °C, 15 h, 76%. (c) Ag_2O (2.0 equiv.), K_2CO_3 (3.0 equiv.), dioxane, 80 °C, 15 h, 80%. (d) Se (2.0 equiv.), K_2CO_3 (3.0 equiv.), dioxane, 80 °C, 15 h, 75%. (e) LiHMDS (1.1 equiv.), $[\text{Pd}(\text{allyl})\text{Cl}]_2$ (1.0 equiv.), THF, 23 °C, 15 h, 89%. (f) PdCl_2 (1.0 equiv.), K_2CO_3 (3.0 equiv.), 3-Cl-py, 80 °C, 15 h, 76%. (B) (a) $\text{AuCl} \cdot \text{Me}_2\text{S}$ (1.0 equiv.), LiHMDS (1.1 equiv.), THF, 23 °C, 15 h, 81%. (b) Se (2.0 equiv.), KOt-Bu (3.0 equiv.), THF, 23 °C, 15 h, 69%. (c) LiHMDS (1.1 equiv.), $[\text{Pd}(\text{allyl})\text{Cl}]_2$ (1.0 equiv.), THF, 23 °C, 15 h, 74%.

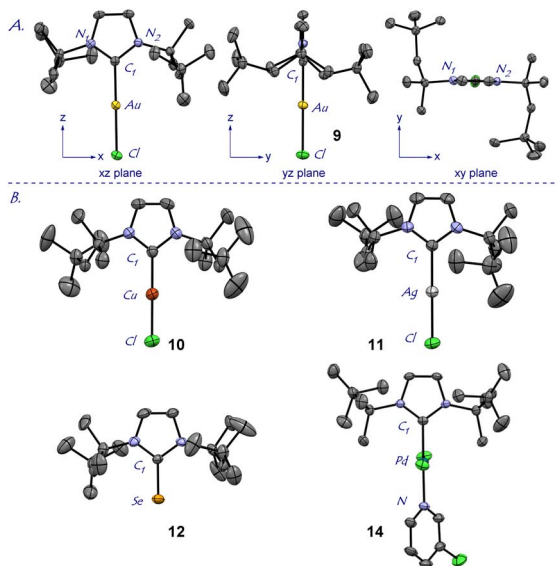


Fig. 2 X-ray crystal structures of complexes **9–12**, **14**. (A) **9**: Views along three axes are shown. (B) **10–12**, **14**. Hydrogen atoms have been omitted for clarity. See ESI† for bond lengths [Å], angles and expanded structures. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center. CCDC 2239373 (**9**); CCDC 2239374 (**10**); CCDC 2239375 (**11**); CCDC 2239376 (**12**); CCDC 2239377 (**14**).

The X-ray structure of $[\text{Au}(\text{ItOct})\text{Cl}]$ (**9**) revealed a unique C_2 -symmetric and Z-shape arrangement of *N*-alkyl substituents with a linear (C–Au–Cl, 179.9°; C–Au, 2.007 Å) geometry (Fig. 2A). The % buried volume (% V_{bur}) of $[\text{Au}(\text{ItOct})\text{Cl}]$ is 44.7%. Crucially,

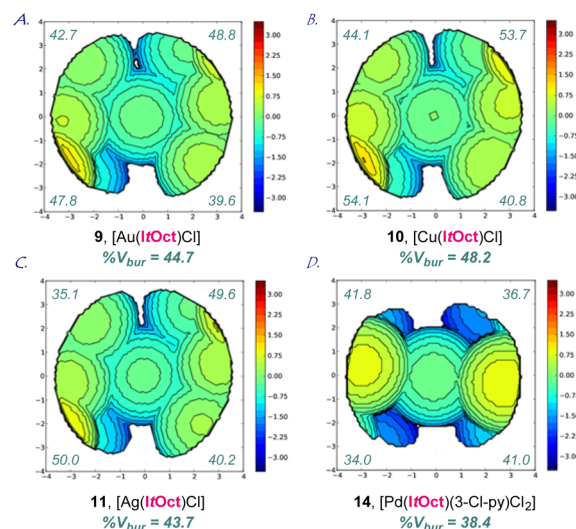


Fig. 3 (A–D) Topographical steric maps of $[\text{Au}(\text{ItOct})\text{Cl}]$ (**9**), $[\text{Cu}(\text{ItOct})\text{Cl}]$ (**10**), $[\text{Ag}(\text{ItOct})\text{Cl}]$ (**11**) and $[\text{Pd}(\text{ItOct})(3\text{-Cl-py})\text{Cl}_2]$ (**14**) showing % V_{bur} per quadrant. See ESI† for additional details.

$[\text{Au}(\text{ItOct})\text{Cl}]$ represents the most bulky *N*-alkyl NHC ligand reported to date.^{4,5} This value can be compared with the (% V_{bur}) of 39.6% determined for $[\text{Au}(\text{ItBu})\text{Cl}]$.^{4b} Furthermore, it should be noted that the gem- Me_2 substitution²² of the longer *tert*-Oct side-chain places the metal within the pocket formed by the alkyl side chain. The steric mapping of the metal center²³ in $[\text{Au}(\text{ItOct})\text{Cl}]$ is shown in Fig. 3 (see Fig. 5 and ESI† for comparison between $[\text{M}(\text{ItOct})\text{X}]$ and $[\text{M}(\text{ItBu})\text{X}]$). It should be noted that *ItOct* is large and flexible, while the % V_{bur} determined by XRD represent local minima in terms of energies.

Complexes $[\text{Ag}(\text{ItOct})\text{Cl}]$ (**10**), $[\text{Cu}(\text{ItOct})\text{Cl}]$ (**11**), $[\text{Se}(\text{ItOct})]$ (**12**) and $[\text{Pd}(\text{ItOct})(3\text{-Cl-py})\text{Cl}_2]$ (**14**) were also fully characterized by X-ray crystallography (Fig. 2, 3 and ESI†). The summary of structural parameters is presented in the ESI†. Importantly, the %buried volume (% V_{bur}) of linear $[\text{Ag}(\text{ItOct})\text{Cl}]$ (**10**), $[\text{Cu}(\text{ItOct})\text{Cl}]$ (**11**), and $[\text{Se}(\text{ItOct})]$ (**12**) of 43.7%, 48.2% and 44.1%, attests to the immense steric impact of the *ItOct* substitution. The (% V_{bur}) of square planar $[\text{Pd}(\text{ItOct})(3\text{-Cl-py})\text{Cl}_2]$ (**14**) is lower of 38.4%, which demonstrates the capacity of the *tert*-octyl side chains to adjust to the steric impact of the metal center (see ESI†).¹¹

The selenourea adduct $[\text{Se}(\text{ItOct})]$ (**12**) permits to gauge π -backbonding of *ItOct* from the ⁷⁷Se NMR spectra.¹⁸ The δ_{Se} value of 216.7 ppm for $[\text{Se}(\text{ItOct})]$ (CDCl_3) indicates that *ItOct* is more π -accepting than *ItBu* (δ_{Se} , 183 ppm, CDCl_3). Furthermore, $^1J_{\text{CH}}$ coupling constant from the ¹³C satellites of ¹H NMR spectra of 219.60 Hz for *ItOct*·HCl (CDCl_3) gives an accurate indication of σ -donation,²⁴ and indicates that this ligand is more strongly donating than *N*-aryl ligands, such as IPr ($^1J_{\text{CH}} = 223.70 \text{ Hz}$; cf. *ItBu*: $^1J_{\text{CH}} = 219.35 \text{ Hz}$).

We also performed the synthesis of representative complexes using the imidazolium precursor *SitOct* (Scheme 2B). The synthesis of $[\text{Au}(\text{SitOct})\text{Cl}]$ (**15**), $[\text{Se}(\text{SitOct})]$ (**16**) and $[\text{Pd}(\text{ItOct})(\text{allyl})\text{Cl}]$ (**17**) proceeded smoothly under the conditions developed for *ItOct*·HCl (Scheme 2A). The δ_{Se} value of 298.2 ppm and the $^1J_{\text{CH}}$ value of 200.8 Hz indicate an increased

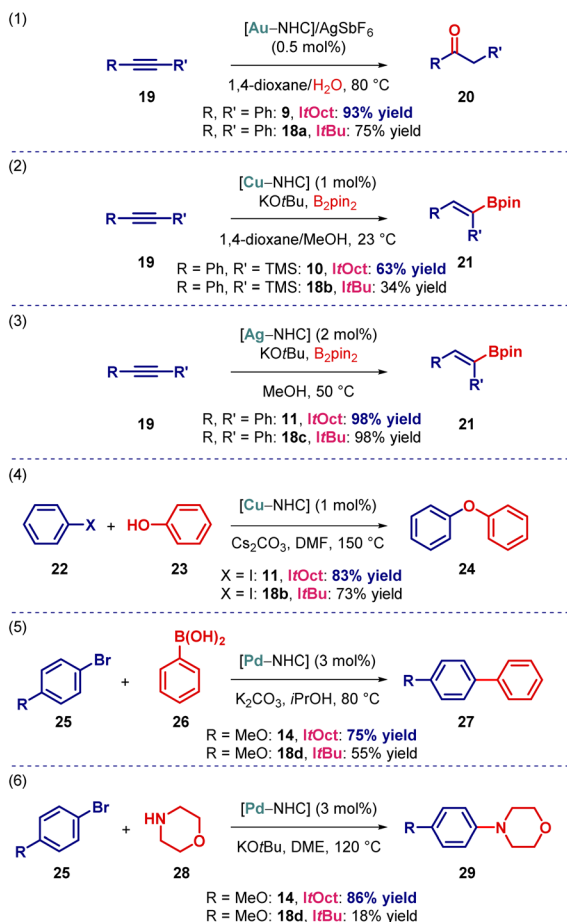


π -acceptance and σ -donation of the saturated imidazolin-2-ylidene **SIItOct**, as expected.^{4,5}

From the outset, we proposed that the increased steric bulk of the **ItOct** ligand would be beneficial on transition-metal-catalysis. To demonstrate the effect of increased steric substitution, we performed several representative reactions in Au(I), Cu(I), Ag(I) and Pd(0) catalysis (Scheme 3). For direct comparison, the corresponding [**ItBu**-M] complexes were prepared and tested in parallel. As shown, the performance of [Au(**ItOct**)Cl], [Cu(**ItOct**)Cl], [Ag(**ItOct**)Cl], [Pd(**ItOct**)(3-Cl-py)Cl₂] in Au(I)-catalyzed hydration,²⁵ Cu(I)-catalyzed hydroboration,²⁶ Ag(I)-catalyzed hydroboration,²⁷ Cu(I)-catalyzed C–O coupling²⁸ and Pd(0)-catalyzed C–C and C–N coupling²⁹ supersede the analogous [**ItBu**-M] complexes.

These highly promising preliminary studies provide a strong support for the routine addition of the **ItOct** class of ligands to the toolbox for reaction screening. Further, it is expected that the **ItOct** to **ItBu** replacement will have an even greater effect on stabilizing reactive metal centers by metal shielding.^{1–3} Studies in this direction are currently underway and will be reported in due course.

To gain further insight into the electronic structure of the **ItOct** class of ligands, we determined HOMO and LUMO energy levels at the B3LYP 6-311++g(d,p) level (Fig. 4 and ESI†). It is well



Scheme 3 Activity of [**ItOct**-M] in catalysis. See ESI† for additional details.

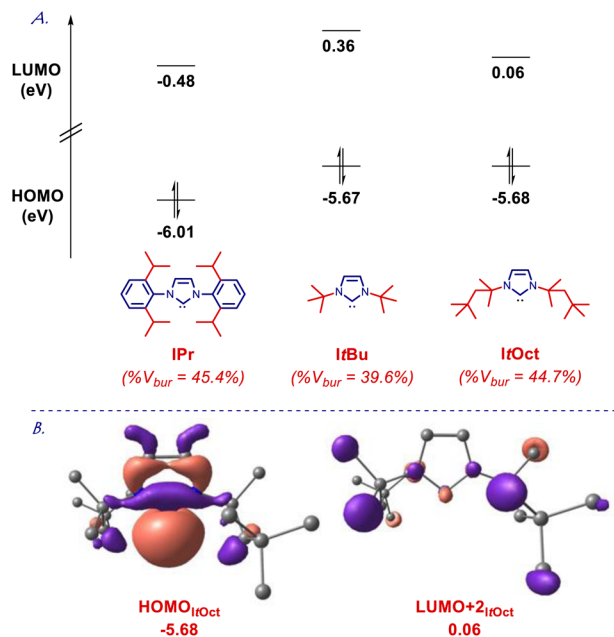


Fig. 4 (A) HOMO and LUMO energy levels (eV). (B) HOMO and LUMO+2 (eV) of **ItOct** calculated at B3LYP 6-311++g(d,p). See ESI†

established that computed HOMO and LUMO provide the most accurate estimation of nucleophilicity and electrophilicity of NHC ligands.^{5,6} The HOMO of **ItOct** (−5.68 eV) is in the same range as **ItBu** (−5.67 eV), which is much higher than for the archetypal **IPr**³⁰ (−6.01 eV). The HOMO of **SIItOct** is even higher (−5.50 eV), which can be compared with **SIItBu** (−5.46 eV). The π -accepting orbital (LUMO+2 due to required symmetry) of **ItOct** (0.06 eV) and **SIItOct** (−0.04 eV) are comparable to **ItBu** (0.36 eV) and **SIItBu** (0.14 eV), which could be compared with **IPr** (−0.48 eV). Overall, these results confirm **ItOct** as strongly σ -nucleophilic and sterically-bulky ligands with electronics matching those of **ItBu**.

Furthermore, to eliminate impact from steric packing, we have determined the (%V_{bur}) for the linear [Cu(NHC)Cl] complexes at the B3LYP 6-311++g(d,p) level (NHC = **ItOct**, **ItBu**, **SIItOct**, **SIItBu**, Fig. 5 and ESI†). The accurate determination of the computed linear geometry obviates effects from crystal packing.^{5,6} [Cu(I)-NHC] complexes were selected to facilitate

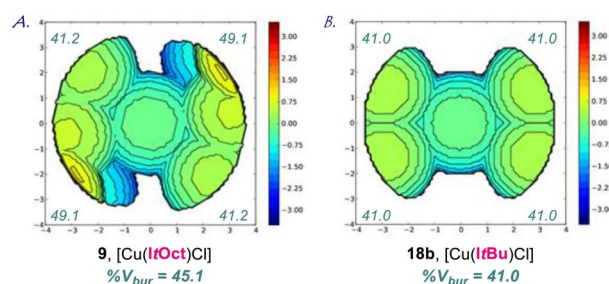


Fig. 5 (A and B) Topographical steric maps of [Cu(**ItOct**)Cl] (**9**) and [Cu(**ItBu**)Cl] (**18b**) showing %V_{bur} per quadrant determined at the B3LYP 6-311++g(d,p) level. See ESI† for additional details. Note the steric difference between the **ItOct** and **ItBu** ligands.



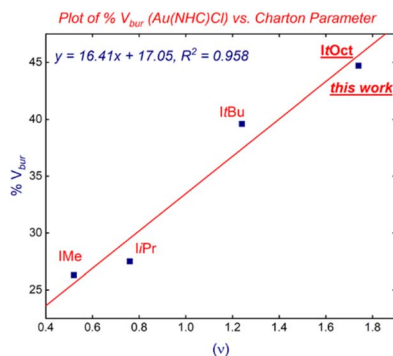


Fig. 6 Plot of % V_{bur} vs. Charton parameter in $[Au(NHC)Cl]$ complexes. Note that **ItOct** is the most sterically-demanding *N*-alkyl-NHC to date.

computations. The % V_{bur} of **ItOct** (45.1%), **ItBu** (41.0%), **SItOct** (47.1%), **SItBu** (41.7%) confirm the effects observed in the X-ray analysis and clearly demonstrate the increased steric demand and unique C_2 -symmetric Z-shape of **ItOct** ligands.

Interestingly, we found that there is a very good linear correlation between the (% V_{bur}) and the steric Charton parameter (ν)³¹ (Fig. 6) using linear $[Au(NHC)Cl]$ complexes. This finding further establishes **ItOct** as the most sterically-demanding *N*-alkyl NHC ligands. The present correlation appears to be general and can be used for the future determination of steric impact of *N*-alkyl-substituted NHC ligands. Finally, it should be noted that the expensive yet extremely useful bulky adamantyl (IAd)³² is much smaller in volume than **ItOct** (% V_{bur} = 39.8%, IAd vs. 44.7%, **ItOct**).

Conclusions

In summary, we have reported **ItOct** (ItOctyl) class of ligands that push the limits of **ItBu**, which is the most useful *N*-alkyl NHC ligand developed to date in various facets of organic and inorganic synthesis. The **ItOct** class of ligands is characterized by the highest steric volume reported to date for *N*-aliphatic NHC ligands, while exploiting extremely strong σ -donating electronic properties inherent to *N*-alkyl *N*-heterocyclic carbenes. The facile preparation of **ItOct** has been developed using *tert*-octylamine as a product of downstream conversion of feedstock isobutene, which allows for rapid and cost-effective synthesis of **ItOct** ligands. This route enables routine access and commercial availability. Further, the **ItOct** class of ligands feature a unique C_2 -symmetric Z-shaped steric architecture, making it attractive for future development of strongly σ -donating carbenes. Considering the tremendous importance of *N*-aliphatic ligands and the commercial availability of the **ItOct** ligands (MilliporeSigma: **ItOct**, 929 298; **SItOct**, 929 492),¹⁰ we anticipate that **ItOct** ligands will find wide application in pushing the boundaries of new and existing approaches in organic and inorganic synthesis.

Data availability

Experimental procedures, characterization data, crystallographic and computational details are available in the ESI.†

Author contributions

M. R. developed the ligands and performed the experiments. G. M. was involved in ligand design. E. B. and B. D. provided crystallographic analysis. R. L. was involved in crystallographic studies. R. S. performed DFT computations. M. S. conceived and directed the project and wrote the manuscript.

Conflicts of interest

The authors declare the following competing financial interests: Rutgers University has filed patents on ligands and precatalysts described in this manuscript (US 63/155492, Mar 2, 2021).

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Notes and references

- Science of Synthesis: N-Heterocyclic Carbenes in Catalytic Organic Synthesis*, ed. S. P. Nolan and C. S. J. Cazin, Thieme, Stuttgart, 2017.
- (a) M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, *Nature*, 2014, **510**, 485–496; (b) *N-Heterocyclic Carbenes*, ed. S. P. Nolan, Wiley, Weinheim, 2014; (c) G. C. Fortman and S. P. Nolan, *Chem. Soc. Rev.*, 2011, **40**, 5151–5169; (d) S. Diez-Gonzalez, N. Marion and S. P. Nolan, *Chem. Rev.*, 2009, **109**, 3612–3676; (e) *N-Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools*, ed. S. Diez-Gonzalez, RSC, Cambridge, 2016; (f) H. V. Huynh, *The Organometallic Chemistry of N-Heterocyclic Carbenes*, Wiley, Hoboken, 2017; (g) *N-Heterocyclic Carbenes in Transition Metal Catalysis*, ed. C. S. J. Cazin, Springer, New York, 2011; (h) F. Glorius, *Top. Organomet. Chem.*, 2007, **21**, 1–231; (i) S. Würtz and F. Glorius, *Acc. Chem. Res.*, 2008, **41**, 1523–1533; (j) E. A. B. Kantchev, C. J. O. O'Brien and M. G. Organ, *Angew. Chem., Int. Ed.*, 2007, **46**, 2768–2813; (k) W. A. Hermann, *Angew. Chem., Int. Ed.*, 2002, **41**, 1290–1309; (l) E. Peris, *Chem. Rev.*, 2018, **118**, 9988–10031; (m) G. Sipos and R. Dorta, *Coord. Chem. Rev.*, 2018, **375**, 13–68; (n) M. Iglesias and L. A. Oro, *Chem. Soc. Rev.*, 2018, **47**, 2772–2808; (o) D. Munz, *Organometallics*, 2018, **37**, 275–289; (p) A. A. Danopoulos, T. Simler and P. Braunstein, *Chem. Rev.*, 2019, **119**, 3730–3961; (q) Q. Zhao, G. Meng,



- S. P. Nolan and M. Szostak, *Chem. Rev.*, 2020, **120**, 1981–2048.
- 3 (a) G. Pisano and C. S. J. Cazin, *Green Chem.*, 2020, **22**, 5253–5256; (b) T. Scattolin, N. V. Tzouras, L. Falivene, L. Cavallo and S. P. Nolan, *Dalton Trans.*, 2020, **49**, 9694–9700; (c) K. B. Smith and M. K. Brown, *J. Am. Chem. Soc.*, 2017, **139**, 7721–7724; (d) K. Kubota, M. Uesugi, S. Osaki and H. Ito, *Org. Biomol. Chem.*, 2019, **17**, 5680–5683; (e) R. Guo, X. Huang, M. Zhao, Y. Lei, Z. Ke and L. Kong, *Inorg. Chem.*, 2019, **58**, 13370–13375; (f) B. Hupp, J. Nitsch, T. Schmitt, R. Bertermann, K. Edkins, F. Hirsch, I. Fischer, M. Auth, A. Sperlich and A. Steffen, *Angew. Chem., Int. Ed.*, 2018, **57**, 13671–13675; (g) Z. C. Cao, Q. Y. Luo and Z. J. Shi, *Org. Lett.*, 2016, **18**, 5978–5981; (h) J. Zhang, J. Xu, Y. Xu, H. Sun, Q. Shen and Y. Zhang, *Organometallics*, 2015, **34**, 5792–5800; (i) Y. Hoshimoto, Y. Hayashi, H. Suzuki, M. Ohashi and S. Ogoshi, *Angew. Chem., Int. Ed.*, 2012, **51**, 10812–10815; (j) M. McGraw and E. Y. X. Chen, *ACS Catal.*, 2018, **8**, 9877–9887; (k) Y. Zhang, M. Schmitt, L. Falivene, L. Caporaso, L. Cavallo and E. Y. X. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 17925–17942; (l) A. T. Papastavrou, M. Pauze, E. Gómez-Bengoia and G. C. Vougioukalakis, *ChemCatChem*, 2019, **11**, 5379–5386; (m) S. Li, Z. Tang, Y. Wang, D. Wang, Z. Wang, C. Yu, T. Li, D. Wei and C. Yao, *Org. Lett.*, 2019, **21**, 1306–1310; (n) M. K. Denk, N. S. Milutinovic, K. M. Marczenko, N. M. Sadowski and A. Paschos, *Chem. Sci.*, 2017, **8**, 1883–1887; (o) G. Tintori, P. Nabokoff, R. Buhaibeh, D. Bergé-Lefranc, S. Redon, J. Broggi and P. Vanelle, *Angew. Chem., Int. Ed.*, 2018, **57**, 3148–3153.
- 4 (a) H. Clavier and S. P. Nolan, *Chem. Commun.*, 2010, **46**, 841–861; (b) A. Gomez-Suarez, D. J. Nelson and S. P. Nolan, *Chem. Commun.*, 2017, **53**, 2650–2660.
- 5 (a) S. Diez-Gonzalez and S. P. Nolan, *Coord. Chem. Rev.*, 2007, **251**, 874–883; (b) H. Jacobsen, A. Correa, A. Poater, C. Costabile and L. Cavallo, *Coord. Chem. Rev.*, 2009, **253**, 687–703; (c) T. Dröge and F. Glorius, *Angew. Chem., Int. Ed.*, 2010, **49**, 6940–6952; (d) D. J. Nelson and S. P. Nolan, *Chem. Soc. Rev.*, 2013, **42**, 6723–6753; (e) H. V. Huynh, *Chem. Rev.*, 2018, **118**, 9457–9492.
- 6 (a) D. Martin, M. Melaimi, M. Soleilhavoup and G. Bertrand, *Organometallics*, 2011, **30**, 5304–5313; (b) M. Melaimi, M. Soleilhavoup and G. Bertrand, *Angew. Chem., Int. Ed.*, 2010, **49**, 8810–8849; (c) M. Soleilhavoup and G. Bertrand, *Acc. Chem. Res.*, 2015, **48**, 256–266; (d) U. S. D. Paul and U. Radius, *Eur. J. Inorg. Chem.*, 2017, 3362–3375; (e) J. Cheng, L. Wang and L. Deng, *Chem. Rev.*, 2018, **118**, 9930–9987; (f) V. M. Chernyshev, E. A. Denisova, D. B. Eremin and V. P. Ananikov, *Chem. Sci.*, 2020, **11**, 6957–6977; (g) M. Soleilhavoup and G. Bertrand, *Chem.*, 2020, **6**, 1275–1282.
- 7 (a) L. Benhamou, E. Chardon, G. Lavigne, S. Bellemin-Laponnaz and V. Cesar, *Chem. Rev.*, 2011, **111**, 2705–2733; (b) D. Nelson, *Eur. J. Inorg. Chem.*, 2015, 2012–2027; (c) T. Scattolin and S. P. Nolan, *Trends Chem.*, 2020, **2**, 721–736.
- 8 (a) T. Zhou, S. Ma, F. Nahra, A. M. C. Obled, A. Poater, L. Cavallo, C. S. J. Cazin, S. P. Nolan and M. Szostak, *iScience*, 2020, **23**, 101377; (b) S. Shi, S. P. Nolan and M. Szostak, *Acc. Chem. Res.*, 2018, **51**, 2589–2599; (c) P. Lei, G. Meng and M. Szostak, *ACS Catal.*, 2017, **7**, 1960–1965; (d) P. Lei, G. Meng, S. Shi, Y. Ling, J. An, R. Szostak and M. Szostak, *Chem. Sci.*, 2017, **8**, 6525–6530; (e) Q. Zhao, G. Meng, G. Li, C. Flach, R. Mendelsohn, R. Lalancette, R. Szostak and M. Szostak, *Chem. Sci.*, 2021, **12**, 10583–10589; (f) Q. Xia, S. Shi, P. Gao, R. Lalancette, R. Szostak and S. Szostak, *J. Org. Chem.*, 2021, **86**, 15648–15657; (g) J. Zhang, X. Li, T. Li, G. Zhang, K. Wan, Y. Ma, R. Fang, R. Szostak and M. Szostak, *ACS Catal.*, 2022, **12**, 15323–15333; (h) J. Zhang, T. Li, X. Li, A. Lv, X. Li, Z. Wang, R. Wang, Y. Ma, R. Fang, R. Szostak and M. Szostak, *Commun. Chem.*, 2022, **5**, 60; (i) P. Gao, J. Xu, T. Zhou, Y. Liu, E. Bisz, B. Dziuk, R. Lalancette, R. Szostak, D. Zhang and M. Szostak, *Angew. Chem., Int. Ed.*, 2023, **62**, e202218427.
- 9 (a) G. Li, S. Ma and M. Szostak, *Trends Chem.*, 2020, **2**, 914–928; (b) G. Meng, S. Shi, R. Lalancette, R. Szostak and M. Szostak, *J. Am. Chem. Soc.*, 2018, **140**, 727–734; (c) S. Shi, G. Meng and M. Szostak, *Angew. Chem., Int. Ed.*, 2016, **55**, 6959–6963; (d) G. Meng and M. Szostak, *Angew. Chem., Int. Ed.*, 2015, **54**, 14518–14522.
- 10 (a) M. Szostak and M. Rahman, Sterically Hindered N-Aliphatic N-Heterocyclic Carbene Catalysts and Methods Using Same, *US Pat.*, 63/155492, 2021; (b) <https://signaladrich.com/US/en/product/aldrich/929298>, accessed on Feb 22, 2023; (c) <https://signaladrich.com/US/en/product/aldrich/929492>, accessed on Feb 22, 2023.
- 11 (a) F. Izquierdo, S. Manzini and S. P. Nolan, *Chem. Commun.*, 2014, **50**, 14926–14937; (b) G. Altenhoff, R. Goddard, C. W. Lehmann and F. Glorius, *J. Am. Chem. Soc.*, 2004, **126**, 15195–15201; (c) V. Lavallo, Y. Canac, C. Präsang, B. Donnadiu and G. Bertrand, *Angew. Chem., Int. Ed.*, 2005, **44**, 5705; (d) M. Yamashita, K. Goto and T. Kawashima, *J. Am. Chem. Soc.*, 2005, **127**, 7294–7295; (e) G. Berthon-Gelloz, M. A. Siegler, A. L. Spek, B. Tinant, J. N. H. Reek and I. E. Marko, *Dalton Trans.*, 2010, **39**, 1444–1446; (f) Y. Wei, B. Rao, X. Cong and X. Zeng, *J. Am. Chem. Soc.*, 2015, **137**, 9250–9253; (g) S. Okumura, S. Tang, T. Saito, K. Semba, S. Sakaki and Y. Nakao, *J. Am. Chem. Soc.*, 2016, **138**, 14699–14704; (h) M. P. Wiesenfeldt, Z. Nairoukh, W. Li and F. Glorius, *Science*, 2017, **357**, 908–912; (i) N. I. Saper, A. Ohgi, D. W. Small, K. Semba, Y. Nakao and J. F. Hartwig, *Nat. Chem.*, 2020, **12**, 276–283.
- 12 (a) V. Nesterov, D. Reiter, P. Bag, P. Frisch, R. Holzner, A. Porzelt and S. Inoue, *Chem. Rev.*, 2018, **118**, 9678–9842; (b) A. Doddi, M. Peters and M. Tamm, *Chem. Rev.*, 2019, **119**, 6994–7112; (c) A. Vivancos, C. Segarra and M. Albrecht, *Chem. Rev.*, 2018, **118**, 9493–9586; (d) N. M. Scott and S. P. Nolan, *Eur. J. Inorg. Chem.*, 2005, **10**, 1815–1828; (e) *Ligand Design in Metal Chemistry: Reactivity and Catalysis*, ed. M. Stradiotto and R. J. Lundgren, Wiley, Hoboken, 2016; (f) D. Janssen-Müller, C. Schleppehorst and F. Glorius, *Chem. Soc. Rev.*, 2017, **46**, 4845–4854.



- 13 P. Roose, K. Eller, E. Henkes, R. Rossbacher and H. Höke, *Amines, Aliphatic*, Ullmann's Encyclopedia of Industrial Chemistry, 2015, pp. 1–50.
- 14 (a) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, 1948, **70**, 4045–4048; (b) K. Munding and R. Schneider, Process for the preparation of primary amines, *DE Pat.*, DE19632107, 1998.
- 15 R. H. Archer, S. I. Zones and M. E. Davis, *Microporous Mesoporous Mater.*, 2010, **130**, 255–265.
- 16 A. Collado, A. Gomez-Suarez, A. R. Martin, A. M. Z. Slawin and S. P. Nolan, *Chem. Commun.*, 2013, **49**, 5541–5543.
- 17 P. de Frémont, N. M. Scott, E. D. Stevens, T. Ramnial, O. C. Lightbody, C. L. B. Macdonald, J. A. C. Clyburne, C. D. Abernethy and S. P. Nolan, *Organometallics*, 2005, **24**, 6301–6309.
- 18 (a) S. V. C. Vummaleti, D. J. Nelson, A. Poater, A. Gomez-Suarez, D. B. Cordes, A. M. Z. Slawin, S. P. Nolan and L. Cavallo, *Chem. Sci.*, 2015, **6**, 1895–1904; (b) A. Liske, K. Verlinden, H. Buhl, K. Schaper and C. Ganter, *Organometallics*, 2013, **32**, 5269–5272; (c) O. Back, M. Henry-Ellinger, C. D. Martin, D. Martin and G. Bertrand, *Angew. Chem., Int. Ed.*, 2013, **52**, 2939–2943.
- 19 N. Marion and S. P. Nolan, *Acc. Chem. Res.*, 2008, **41**, 1440–1449.
- 20 R. D. J. Froese, C. Lombardi, M. Pompeo, R. P. Rucker and M. G. Organ, *Acc. Chem. Res.*, 2017, **50**, 2244–2253.
- 21 Crystallographic data have been deposited with the Cambridge Crystallographic Data Center.
- 22 M. E. Jung and G. Piizzi, *Chem. Rev.*, 2005, **105**, 1735–1766.
- 23 L. Falivene, Z. Cao, A. Petta, L. Serra, A. Poater, R. Oliva, V. Scarano and L. Cavallo, *Nat. Chem.*, 2019, **11**, 872–879.
- 24 G. Meng, L. Kakalis, S. P. Nolan and M. Szostak, *Tetrahedron Lett.*, 2019, **60**, 378–381.
- 25 N. Marion, R. S. Ramon and S. P. Nolan, *J. Am. Chem. Soc.*, 2009, **131**, 448–449.
- 26 Y. D. Bidal, F. Lazreg and C. S. J. Cazin, *ACS Catal.*, 2014, **4**, 1564–1569.
- 27 H. Yoshida, I. Kageyuki and K. Takaki, *Org. Lett.*, 2014, **16**, 3512–3515.
- 28 S. Paul, B. P. Joy, R. Rajendran and V. B. Gudimetla, *ChemistrySelect*, 2019, **4**, 7181–7186.
- 29 O. Navarro, H. Kaur, P. Mahjoor and S. P. Nolan, *J. Org. Chem.*, 2004, **69**, 3173–3180.
- 30 J. Huang and S. P. Nolan, *J. Am. Chem. Soc.*, 1999, **121**, 9889–9890.
- 31 M. Charton, *J. Am. Chem. Soc.*, 1975, **97**, 1552–1556.
- 32 (a) K. A. Agnew-Francis and C. M. Williams, *Adv. Synth. Catal.*, 2016, **358**, 675–700; (b) M. B. Dinger, P. Nieczypor and J. C. Mol, *Organometallics*, 2003, **22**, 5291–5296; (c) S. Kronig, E. Theuergarten, D. Holschumacher, T. Bannenberg, C. G. Daniliuc, P. G. Jones and M. Tamm, *Inorg. Chem.*, 2011, **50**, 7344–7359; (d) J. He, M. Wasa, K. S. L. Chan and J. Q. Yu, *J. Am. Chem. Soc.*, 2013, **135**, 3387–3390; (e) M. Tobisu, T. Morioka, A. Ohtsuki and N. Chatani, *Chem. Sci.*, 2015, **6**, 3410–3414.

