Carbene Chemistry

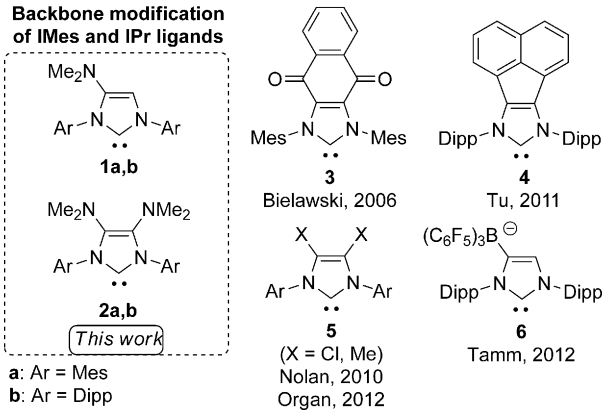
DOI: 10.1002/ange.201402301

Skeleton Decoration of NHCs by Amino Groups and its Sequential Booster Effect on the Palladium-Catalyzed Buchwald–Hartwig Amination**

Yin Zhang, Vincent César, Golo Storch, Noël Lugan, and Guy Lavigne**

Abstract: *A challenging synthetic modification of PEPPSI-type palladium pre-catalysts consisting of a stepwise incorporation of one and two amino groups onto the NHC skeleton was seen to exert a sequential enhancement of the electronic donor properties. This appears to be positively correlated with the catalytic performances of the corresponding complexes in the Buchwald–Hartwig amination. This is illustrated, for example, by the quantitative amination of 4-chloroanisole by morpholine within 2 h at 25 °C with a 2 mol% catalyst/substrate ratio or by a significant reduction of catalytic loading (down to 0.005 mol%) for the coupling of aryl chlorides with anilines (max TON: 19600).*

During the past two decades, N-heterocyclic carbenes (NHCs) have gained considerable significance for the design of a variety of highly efficient transition-metal pre-catalysts.[1] Their intrinsic interest is both due to their high steric bulk, mainly determined by the nature of the nitrogen substituents, and their strong electronic σ-donor properties. These donor properties are dramatically influenced by the nature of the heterocyclic skeleton.[2] Among NHCs, 1,3-dimesityl-2*H*-imidazol-2-ylidene (IMes) and 1,3-bis(2,6-diisopropylphenyl)-2*H*-imidazol-2-ylidene (IPr) are the most widely employed in homogeneous catalysis. Hence, they represent ideal standard archetypes from which an optimization of stereoelectronic properties can be envisioned. Regarding the sterics, excellent results have been obtained upon formal replacement of the 2,6-diisopropylphenyl (Dipp) nitrogen substituents by bulkier, flexible aryl groups[3] or by C_2-symmetrical chiral aryl groups.[4] Moreover, modifications of the electronic donor properties by decoration of the imidazolyl skeleton are highly efficient, but often remain subject to synthetic limitations.[5] To date, relevant notable systems studied in catalysis include the quinone- and acenaphthylene-annelated imidazol-2-ylidenes **3** and **4**[6,7] the methyl and chloro-disubstituted carbenes **5**,[8] and the borate-substituted anionic IPr **6** (Scheme 1).[9]



Scheme 1. Target NHCs systems **1a,b** and **2a,b** (left) and selected previous examples of skeleton-functionalized IMes and IPr ligands studied in transition-metal catalysis (right). Mes = 2,4,6-trimethylphenyl; Dipp = 2,6-diisopropylphenyl.

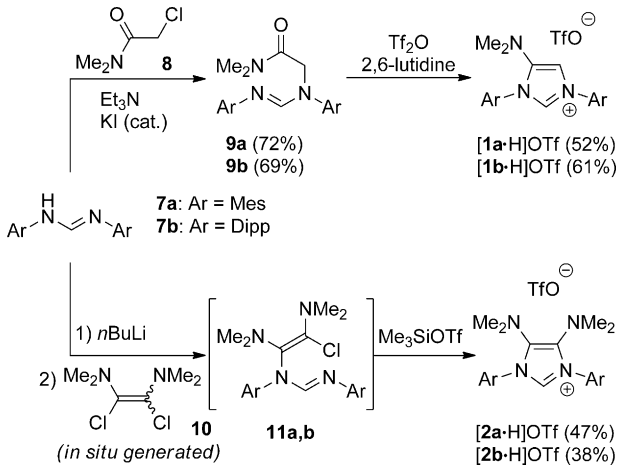
In a logical continuation of our work on skeleton functionalization of NHCs,[10] we reasoned that the construction of NHCs **1a,b** and **2a,b**, formally derived from the IMes (**a**) and IPr (**b**) ligands by incorporation of one or two dimethylamino groups on the heterocyclic skeleton,[11] would constitute a rational strategy to increase the donor properties of the NHC and to unveil potentially better catalysts. Herein, we disclose for the first time an efficient and reliable synthesis of their imidazolium precursors and provide entry into their coordination chemistry. We also reveal the highly beneficial effect of the addition of skeleton amino groups onto the NHC in the benchmark palladium-catalyzed Buchwald–Hartwig amination.

Inspired in part from our earlier approaches to skeleton-decorated NHCs, the synthetic strategies employed to access the imidazolium salts [**1a,b**·H](OTf) and [**2a,b**·H](OTf) both relied on the incorporation of the desired unit directly onto the corresponding formamidines **7a,b**. The 4-(dimethylamino)imidazolium triflates [**1a,b**·H](OTf) were thus synthesized in a two-step sequence consisting of the alkylation of the formamidine **7a,b** by the α-chloroacetamide **8** and a selective triflic anhydride mediated intramolecular cyclization (Scheme 2). However, the synthesis of the 4,5-bis(dimethylamino)imidazolium salts [**2a,b**·H](OTf) appeared less straightforward, since the procedure developed by Huber, Weiss et al.[11] using a bis(phosphonio)diaminoethene reagent led only to either a very poor yield of [**2a**·H](OTf) (less than

[*] Y. Zhang, Dr. V. César, G. Storch, Dr. N. Lugan, Dr. G. Lavigne
CNRS, LCC (Laboratoire de Chimie de Coordination)
205 route de Narbonne, BP44099, 31077 Toulouse Cedex 4 (France)
and
Université de Toulouse, UPS, INPT
31077 Toulouse (France)
E-mail: vincent.cesar@lcc-toulouse.fr
guy.lavigne@lcc-toulouse.fr
Homepage: http://www.lcc-toulouse.fr/lcc/spip.php?article24

[**] We thank the CNRS for financial support and the Chinese Scholarship Council (CSC) for a PhD grant to Y.Z. NHCs = N-Heterocyclic Carbenes.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201402301.



Scheme 2. Synthesis of the imidazolium triflates [**1a**,**b**·H](OTf) and [**2a**,**b**·H](OTf). Tf- = CF_3SO_2-.

19%) or to no product at all in the case of [**2b**·H](OTf). Taking into account the steric bulk of the Mes and Dipp substituents in **7a**,**b**, we found that the in situ generated dichlorodiaminoethene **10** constitutes an ideal reagent for this synthesis. Indeed, its addition in slight excess to the lithiated **7a**,**b** at room temperature gave the postulated intermediate formamidines **11a**,**b**. These were subsequently cyclized through a transient keteneiminium species formed by abstraction of the chloride with TMSOTf. The bis-(amino)imidazolium triflates [**2a**,**b**·H](OTf) were isolated as white powders in 47% and 38% yields, respectively. These salts were all fully characterized including by X-Ray diffraction studies on single crystals (Figure 1).[12]

Having established the synthetic routes towards the imidazolium salts, we next turned our attention to the generation of the carbenes **1a**,**b** and **2a**,**b** and their coordination to transition-metal centers. Firstly, deprotonation of [**1a**·H]OTf and [**2a**·H]OTf with $KN(SiMe_3)_2$ in the presence of [{RhCl(COD)}$_2$] afforded the corresponding rhodium(I) complexes **13** and **15** in moderate to good yields (Scheme 3).[13] Complexes **13** and **15** were then further converted into their dicarbonyl analogues **14** and **16** upon

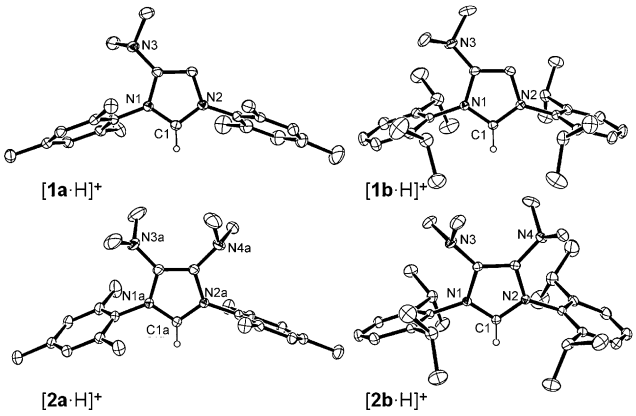
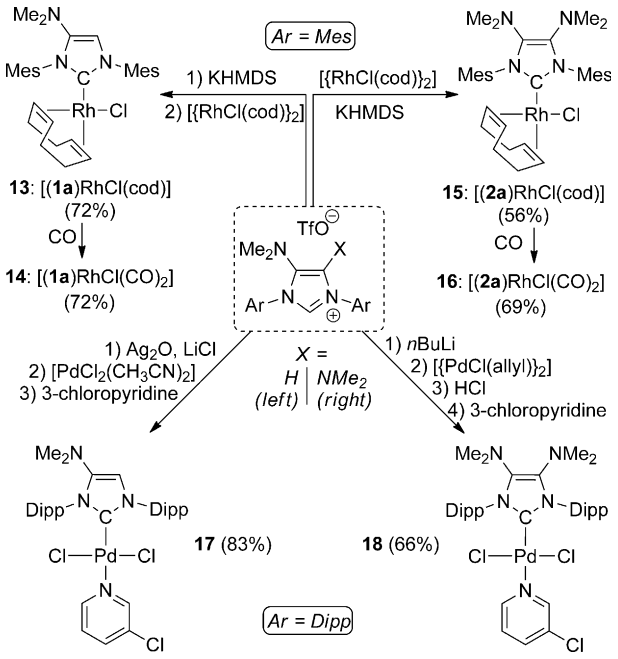


Figure 1. Molecular structures of imidazolium rings [**1a**,**b**·H]$^+$ and [**2a**,**b**·H]$^+$. Thermal ellipsoids set at 30% probability; all hydrogen atoms except on the carbene center are omitted for clarity.



Scheme 3. Synthesis of the rhodium(I) complexes **13**–**16** and palladium(II) complexes **17** and **18** bearing NHCs **1a**,**b** and **2a**,**b**. cod = η^2-(1,5-cyclooctadiene); allyl = η^3-propenyl; KHDMS = potassium bis(trimethylsilyl)amide.

displacement of the COD ligand with carbon monoxide (Scheme 3). Measuring the average IR-stretching frequency of the carbonyl ligands in **14** and **16** allowed assessment of the electron-donor ability of these new NHCs. A comparison of their calculated Tolman electronic parameter (TEP) values (**1a**: TEP = 2048.6 cm^{-1}, **2a**: TEP = 2046.6 cm^{-1}) with that of their non-substituted analogue IMes (TEP = 2050.8 cm^{-1}),[2,14] revealed that introduction of each NMe_2 group on the skeleton increments the electron-donating ability of the carbene ligand by 2 cm^{-1}, thus confirming our working hypothesis.

Keeping in mind Organ's previous report that the air-stable, user-friendly PEPPSI complexes (pyridine-enhanced pre-catalyst preparation, stabilization, and initiation) bearing IPr or IPent ligands are highly active in palladium-catalyzed cross-coupling reactions,[15] we chose to synthesize the modified palladium PEPPSI pre-catalysts **17** and **18** bearing the IPr-derived NHCs **1b**, and **2b**, respectively. Complex **17** was obtained in excellent yield (83%) using a one-pot, three-step procedure based on the transmetalation of **1b** from its silver complex [(**1b**)AgCl] to [$PdCl_2(CH_3CN)_2$] (Scheme 3). On the other hand, the preparation of complex **18** involved deprotonation of [**2b**·H]OTf with *n*BuLi, followed by trapping of the free carbene **2b** by the dimer [{PdCl(allyl)$_2$}] to give the π-allyl complex [(**2b**)PdCl(η^3-allyl)]. This species was then protonated and treated with 3-chloropyridine. The structures of the air- and moisture-stable complexes **17** and **18** were fully confirmed by single-crystal X-Ray diffraction studies (Figure 2). From these crystal structures, we also calculated the percent buried volume (%V_{bur}) of carbenes **1b** and **2b**.[2b,16] Starting from the original PEPPSI–IPr complex **19**[15] exhibiting a %V_{bur} value of 34.3%, the stepwise incorporation

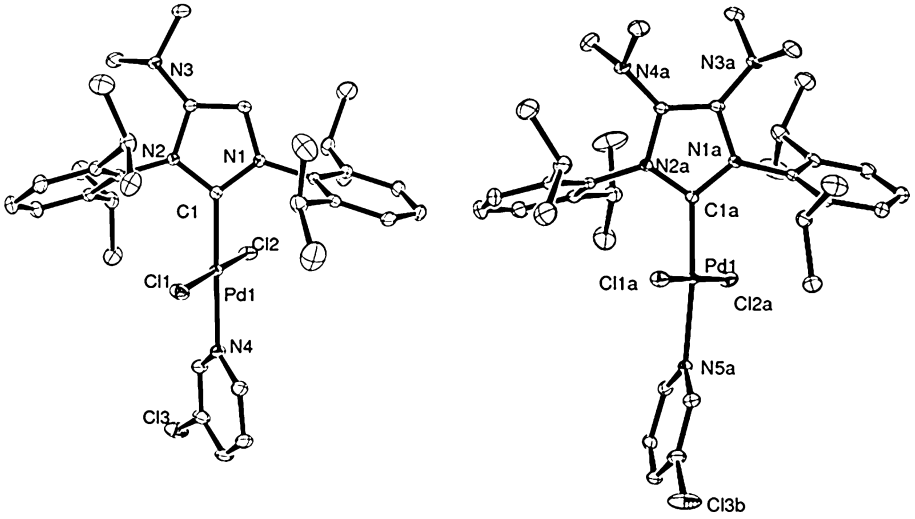


Figure 2. Molecular structures of complexes **17** (left) and **18** (right, molecule A). Thermal ellipsoids set at 30% probability; hydrogen atoms and solvent molecules are omitted for clarity.

of NMe_2 group leads to a calculated $\%V_{bur}$ of 39.5% for **1b** in **17**, and of 39.7% and 40.0% for **2b** (the two values being associated with the two crystallographically independent molecular units of **18** in the lattice). This result reveals that the global effect of skeleton substituents is not only purely electronic but also involves a detectable steric component, albeit being already maximized after introduction of the first NMe_2.[17]

The effect of the NMe_2 groups was then studied by comparing the respective catalytic efficiencies of complexes **17**, **18**, and **19** in the Buchwald–Hartwig amination, a powerful method in modern synthetic chemistry.[18] In an initial experiment, performed at 25 °C, the amination of 4-chloroanisole by morpholine was chosen as a model reaction to compare catalysts **17**–**19**. Complex **18** was found to be by far the most active, giving total conversion within two hours, followed by complexes **17** and **19**, giving 57% and 39% conversion respectively after 6 h (Figure 3).

These promising results prompted us to evaluate **18** in the room-temperature coupling of a variety of (hetero)aryl chlorides with aliphatic and aryl amines (Scheme 4). First, the deactivated 4-(pyrrol-1-yl)- and 4-(dimethylamino)phenyl chlorides were efficiently coupled with morpholine using 2 mol% of **18** to give products **20b** and **20c** in excellent yields, whereas the use of catalysts **17** and **19** only led to modest conversions and yields under identical conditions. The reaction was shown to be unaffected by the nature of the amine partner. Morpholine, pyrrolidine (giving **20d**), piperidine (giving **20l**), *N*-methylaniline (giving **20h**—**j**) and the more crowded 2,6-dimethylaniline (giving **20g**) all underwent efficient

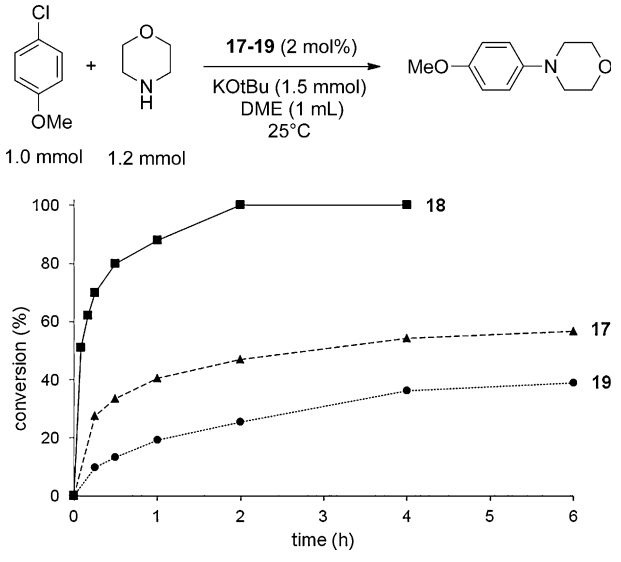
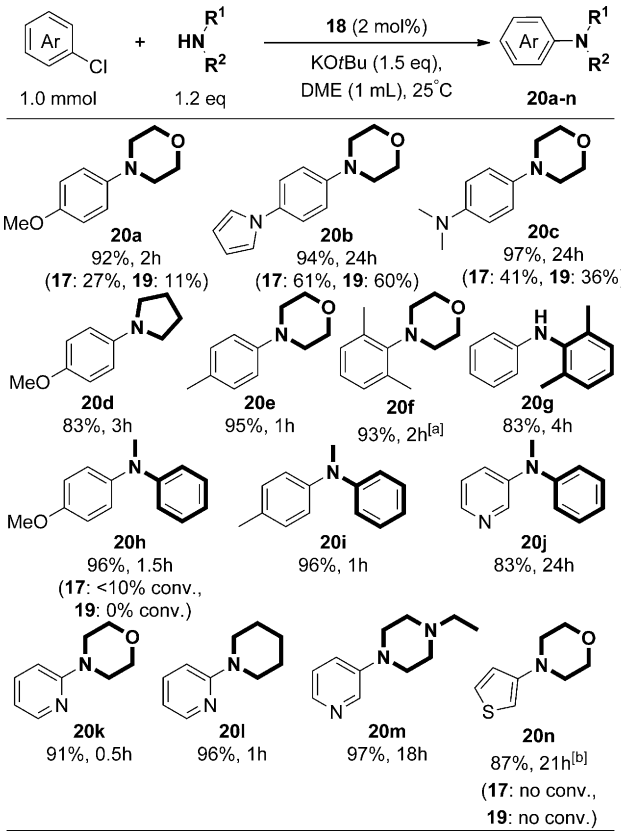


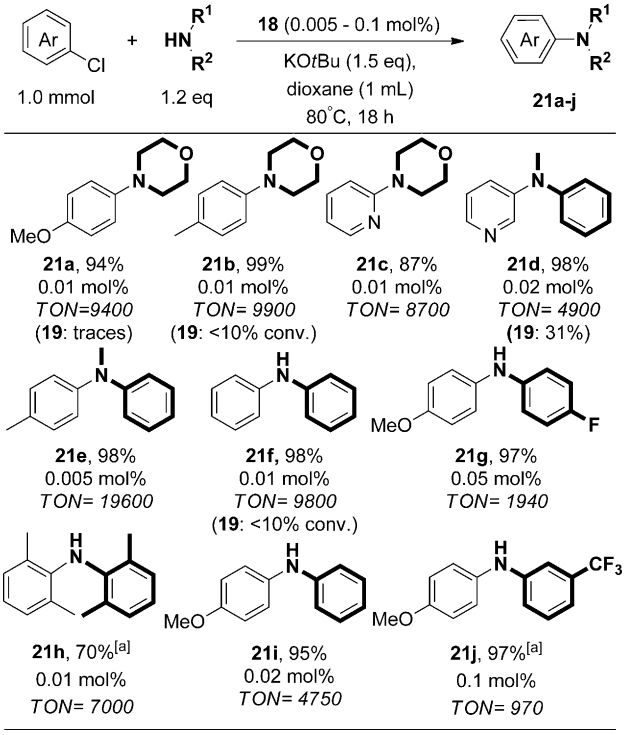
Figure 3. Efficiency of the palladium-catalyzed amination of 4-chloroanisole with morpholine using PEPPSI pre-catalysts **17**–**19**. Conversions were determined by GC analysis against a calibrated internal standard (dodecane). Reactions were performed in duplicate. DME = 1,2-dimethoxyethane.



Scheme 4. Scope of the room-temperature Buchwald–Hartwig amination reaction catalyzed by **18**. Yields refer to the average yields of isolated product from two runs after column chromatography. [a] At 50 °C. [b] At 80 °C.

coupling. The catalytic efficiency was found to be only slightly affected by the steric hindrance of one of the coupling partners, with a longer time or a slightly higher temperature being required to obtain **20 f** and **20 g**. Catalyst **18** was also found to exhibit excellent activity in the case of heteroaryl chlorides, such as 2-and 3-chloropyridines (giving **20 j**–**m**), and even for the quite difficult case of 3-chlorothiophene (giving **20 n**, at 80 °C), for which catalysts **17** and **19** proved completely inefficient.

The scope of the Buchwald–Hartwig amination was then explored in terms of catalyst loading. Excellent catalytic activities were obtained for various substrates using 0.005–0.1 mol % of pre-catalyst **18** in dioxane at 80 °C in the presence of KO*t*Bu (Scheme 5). Typically, non-activated aryl



Scheme 5. Scope of the Buchwald–Hartwig amination reaction catalyzed by **18** at low catalyst loading. Yields refer to the average yields of isolated product from two runs after column chromatography. [a] At 100 °C.

chlorides and pyridinyl chlorides were successfully coupled with morpholine or *N*-methylaniline (to give **21 a**–**e**) at low catalyst loading (0.005–0.1 mol %) and remarkable turn-over numbers were observed (TON up to 19600 for **21 e**). Anilines were also found to be suitable coupling partners, as illustrated by a 100 % selectivity in the monoarylation of $ArNH_2$ (to give **21 f** in 98 % yield). A total absence of bisarylation product was evident in the preparation of molecules **21 g**—**j**. Note, very good yields were obtained for electron-rich aryl chlorides and electron-deficient anilines (giving **21 g**,**j**), which are considered to be very challenging coupling partners.[19] These performances place pre-catalyst **18** among the best NHC-systems known for the arylamination reaction,[3g,19b] with performances matching those obtained with the superior palladium/phosphine systems for similar substrates.[20,21] The high efficiency of catalyst **18** can be reasonably attributed to its enhanced electron-donating ability and also in part to the increased steric shielding of carbene **2 b** compared to its IPr reference. These two complementary features are known to be beneficial in palladium-catalyzed cross-coupling reactions.

To date, the most significant advances in the design of palladium–NHC catalysts for the Buchwald–Hartwig amination have mainly focused on the incorporation of bulky N-aryl wings bearing flexible substituents. By employing a rational synthetic approach, we have now demonstrated that a further and complementary optimization can be achieved through a "simple" skeleton modification of IMes- and IPr-type NHCs, leading to a sequential enhancement of their catalytic efficiency. In this case study, a possible synergism between steric and electronic effects is evident. Incorporation of one skeleton amino group led to an improvement of the electron donation and a maximization of the steric bulk, leading to a notable enhancement of the catalytic activity. Incorporation of a second skeleton amino group, whose effect appears to be essentially "electronic", was seen to exert a major doping effect on the catalytic performances. Such a key modification allowed both a significant decrease of the catalyst loading and the development of extended applications to challenging reaction partners. Further studies on the possible transposition of these benefits to other types of transition-metal-catalyzed reactions are underway in our laboratory.

Received: February 11, 2014
Published online: May 5, 2014

Keywords: amination reactions · amines · N-heterocyclic carbenes · homogeneous catalysis · palladium

[1] For a recent book on NHCs, see: a) RSC catalysis series *N-Heterocyclic Carbenes* (Ed.: S. Díez-González), RSC Publishing, Cambridge, **2011**; For selected Reviews on NHCs as ligands in TM catalysis, see: b) D. Bézier, J.-B. Sortais, C. Darcel, *Adv. Synth. Catal.* **2013**, *355*, 19; c) C. Valente, S. Çalimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem.* **2012**, *124*, 3370; *Angew. Chem. Int. Ed.* **2012**, *51*, 3314; d) G. C. Vougioukalakis, R. H. Grubbs, *Chem. Rev.* **2010**, *110*, 1746; e) S. Díez-González, N. Marion, S. P. Nolan, *Chem. Rev.* **2009**, *109*, 3612.

[2] Recent Reviews on the stereoelectronic properties of NHCs: a) D. J. Nelson, S. P. Nolan, *Chem. Soc. Rev.* **2013**, *42*, 6723; b) T. Dröge, F. Glorius, *Angew. Chem.* **2010**, *122*, 7094; *Angew. Chem. Int. Ed.* **2010**, *49*, 6940.

[3] a) M. G. Organ, S. Çalimsiz, M. Sayah, K. H. Hoi, A. J. Lough, *Angew. Chem.* **2009**, *121*, 2419; *Angew. Chem. Int. Ed.* **2009**, *48*, 2383; b) see Ref. [1c]; c) A. Chartoire, X. Frogneux, S. P. Nolan, *Adv. Synth. Catal.* **2012**, *354*, 1897; d) S. Meiries, A. Chartoire, A. M. Z. Slawin, S. P. Nolan, *Organometallics* **2012**, *31*, 3402; e) A. Chartoire, X. Frogneux, A. Boreux, A. M. Z. Slawin, S. P. Nolan, *Organometallics* **2012**, *31*, 6947; f) A. Chartoire, M. Lesieur, L. Falivene, A. M. Z. Slawin, L. Cavallo, C. S. J. Cazin, S. P. Nolan, *Chem. Eur. J.* **2012**, *18*, 4517; g) S. Meiries, G. Le Duc, A. Chartoire, A. Collado, K. Speck, K. S. A. Arachchige, A. M. Z. Slawin, S. P. Nolan, *Chem. Eur. J.* **2013**, *19*, 17358.

[4] A. Albright, R. E. Gawley, *J. Am. Chem. Soc.* **2011**, *133*, 19680.

[5] Review on the synthetic routes to NHC precursors: L. Benhamou, E. Chardon, G. Lavigne, S. Bellemin-Laponnaz, V. César, *Chem. Rev.* **2011**, *111*, 2705.

[6] a) A. G. Tennyson, V. M. Lynch, C. W. Bielawski, *J. Am. Chem. Soc.* **2010**, *132*, 9420; b) M. D. Sanderson, J. W. Kamplain, C. W. Bielawski, *J. Am. Chem. Soc.* **2006**, *128*, 16514.

[7] a) T. Tu, Z. Sun, W. Fang, M. Xu, Y. Zhou, *Org. Lett.* **2012**, *14*, 4250; b) T. Tu, W. Fang, J. Jiang, *Chem. Commun.* **2011**, *47*, 12358; c) a bis-NHC system derived from this structure has been recently studied in catalysis, see: G. Guisado-Barrios, J. Hiller, E. Peris, *Chem. Eur. J.* **2013**, *19*, 10405.

[8] a) K. H. Hoi, J. A. Coggan, M. G. Organ, *Chem. Eur. J.* **2013**, *19*, 843; b) M. Pompeo, R. D. J. Froese, N. Hadei, M. G. Organ, *Angew. Chem.* **2012**, *124*, 11516; *Angew. Chem. Int. Ed.* **2012**, *51*, 11354; c) C. A. Urbina-Blanco, X. Bantreil, H. Clavier, A. M. Z. Slawin, S. P. Nolan, *Beilstein J. Org. Chem.* **2010**, *6*, 1120.

[9] a) E. L. Kolychev, S. Kronig, K. Brandhorst, M. Freytag, P. G. Jones, M. Tamm, *J. Am. Chem. Soc.* **2013**, *135*, 12448; b) S. Kronig, E. Theuergarten, C. G. Daniliuc, P. G. Jones, M. Tamm, *Angew. Chem.* **2012**, *124*, 3294; *Angew. Chem. Int. Ed.* **2012**, *51*, 3240.

[10] Selected references: a) V. César, S. Labat, K. Miqueu, J.-M. Sotiropoulos, R. Brousses, N. Lugan, G. Lavigne, *Chem. Eur. J.* **2013**, *19*, 17113; b) V. César, J. C. Tourneux, N. Vujkovic, R. Brousses, N. Lugan, G. Lavigne, *Chem. Commun.* **2012**, *48*, 2349; c) N. Vujkovic, V. César, N. Lugan, G. Lavigne, *Chem. Eur. J.* **2011**, *17*, 13151; d) V. César, N. Lugan, G. Lavigne, *Chem. Eur. J.* **2010**, *16*, 11432; e) L. Benhamou, V. César, H. Gornitzka, N. Lugan, G. Lavigne, *Chem. Commun.* **2009**, 4720; f) V. César, N. Lugan, G. Lavigne, *J. Am. Chem. Soc.* **2008**, *130*, 11286.

[11] 4,5-bis(dimethylamino)imidazol-2-ylidenes have been reported but only with non-hindered aryl groups as nitrogen arms. See: S. M. Huber, F. W. Heinemann, P. Audebert, R. Weiss, *Chem. Eur. J.* **2011**, *17*, 13078.

[12] CCDC 984192, 984193, 984194, 984195, 984196, 984197, 984198 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] The molecular structure of **15** is depicted in the Supporting Information.

[14] The TEP value was calculated using the linear correlations developed by Nolan and Plenio, see: a) R. A. Kelly III, H. Clavier, S. Giudice, N. M. Scott, E. D. Stevens, J. Bordner, I. Samardjiev, C. D. Hoff, L. Cavallo, S. P. Nolan, *Organometallics* **2008**, *27*, 202; b) S. Wolf, H. Plenio, *J. Organomet. Chem.* **2009**, *694*, 1487. For a pioneering work, see: c) A. R. Chianese, X. Li, M. C. Jansen, J. W. Faller, R. H. Crabtree, *Organometallics* **2003**, *22*, 1663.

[15] PEPPSI: a) see Ref. [8a]; b) see Ref. [8b]; c) see Ref. [1c], and references therein.

[16] For a Review, see: a) H. Clavier, S. P. Nolan, *Chem. Commun.* **2010**, *46*, 841; See also: b) A. Poater, B. Cosenza, A. Correa, S. Giudice, F. Ragone, V. Scarano, L. Cavallo, *Eur. J. Inorg. Chem.* **2009**, 1759; c) L. Cavallo, A. Correa, C. Costabile, H. Jacobsen, *J. Organomet. Chem.* **2005**, *690*, 5407.

[17] V_{bur} were calculated using the SambVca web application (https://www.molnac.unisa.it/OMtools/sambvca.php) with the following parameters: sphere radius: 3.5 Å, distance from the center of the sphere: 2.00 Å, mesh spacing: 0.05 Å, hydrogen atoms not included.

[18] a) J. F. Hartwig in *Modern Amination Methods*, Wiley-VCH, Weinheim, **2000**, p. 195; b) J. F. Hartwig in *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley, New York, **2002**, p. 1051; c) L. Jiang, S. L. Buchwald in *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, **2004**, p. 699; d) D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338.

[19] a) K. H. Hoi, S. Çalimsiz, R. D. J. Froese, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 145; b) G. Le Duc, S. Meiries, S. P. Nolan, *Organometallics* **2013**, *32*, 7547.

[20] a) R. J. Lundgren, M. Stradiotto, *Aldrichimica Acta* **2012**, *45*, 59; b) R. J. Lundgren, A. Sappong-Kumankumah, M. Stradiotto, *Chem. Eur. J.* **2010**, *16*, 1983; c) B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 15914; d) Q. Shen, T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 6586.

[21] During the refereeing process of the present manuscript, the room-temperature coupling of deactivated anilines with aryl chlorides using a PEPPSI pre-catalyst and a mild base was reported: M. Pompeo, J. L. Farmer, R. D. J. Froese, M. G. Organ, *Angew. Chem.* **2014**, *126*, 3287; *Angew. Chem. Int. Ed.* **2014**, *53*, 3223.