CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201302471

Large yet Flexible N-Heterocyclic Carbene Ligands for Palladium Catalysis

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Dedicated to Professor Carl D. Hoff on the occasion of his 65th birthday.

Abstract: A straightforward and scalable eight-step synthesis of new N-heterocyclic carbenes (NHCs) has been developed from inexpensive and readily available 2-nitro-*m*-xylene. This process allows for the preparation of a novel class of NHCs coined ITent ("Tent" for "tentacular") of which the well-known IMes (*N*,*N*′-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene), IPr (*N*,*N*′-bis(2,6-di(2-propyl)phenyl)imidazol-2-ylidene) and IPent (*N*,*N*′-bis(2,6-di(3-pentyl)phenyl)imidazol-2-ylidene) NHCs are the simplest and already known congeners. The synthetic route was successfully used for the preparation of three members of the ITent family: IPent (*N*,*N*′-bis(2,6-di(3-pentyl)phenyl)imidazol-2-ylidene), IHept (*N*,*N*′-bis(2,6-di(4-heptyl)phenyl)imidazol-2-ylidene) and INon (*N*,*N*′-bis(2,6-di(5-nonyl)phenyl)imidazol-2-ylidene). The electronic and steric properties of each NHC were studied through the preparation of both nickel and palladium complexes. Finally the effect of these new ITent ligands in Pd-catalyzed Suzuki–Miyaura and Buchwald–Hartwig cross-couplings was investigated.

Keywords: bulky · catalysis · flexible · N-heterocyclic carbene · palladium · tentacular

Introduction

N-Heterocyclic carbenes (NHCs) are an important class of compounds that has found application in various fields of chemistry such as organic synthesis, catalysis and macromolecular chemistry.[1] In the field of palladium catalysis, NHC ligands are often compared with phosphine ligands.[2] However, metal-NHC complexes are now recognized for their unique properties as well as their higher stability towards air and moisture, in contrast to their phosphine analogues.[2] The importance of NHC ligands in catalysis is related to their σ-donating properties as well as their variable steric bulk, both of which have strong effects on oxidative addition and reductive elimination processes in metal-mediated cross-coupling reactions.[2] Spectacular reactivity has been attributed to "flexible steric bulk"[3] in which the ligands adjust towards incoming substrates, while enabling the stabilization of reactive low-valent intermediates.[3–4] As an example, the very bulky IPr* (IPr* = *N*,*N*′-bis(2,6-bis(diphenylmethyl)-4-methylphenyl)imidazol-2-ylidene) ligand reported by Markó and co-workers[5] and further investigated by Nolan and co-workers[6] exhibited excellent properties in catalysis. However the limited flexibility of the IPr* construct may be considered a limitation of this specific NHC ligand and the design of new NHC ligands possessing more flexible bulk remains an area of interest in NHC synthesis. In this context, we have explored new synthetic strategies for the design and multigram-scale preparation of new NHC ligands possessing bulky yet highly flexible motifs.

Results and Discussion

Preparation of the ITent·HCl salts: Several methods have been reported for the synthesis of NHCs since their discovery in the early 1990s.[1a,d–g,i,j,l,m] Although great structural diversity has been achieved already, on the whole, the classical NHCs depicted in Figure 1 still remain the most employed, particularly in homogeneous catalysis. The main reason for their widespread use, beyond their unique properties, is their straightforward preparation in multigram quantities from inexpensive or commercially available amine or aniline

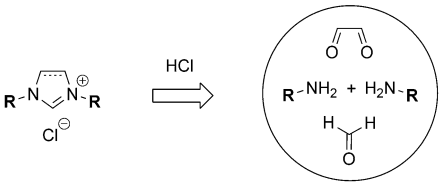

Figure 1. Most common imidazolium and imidazolinium chlorides used for homogeneous catalysis. (S)IPr (R = di*iso*propylphenyl), (S)IMes (R = mesityl), ICy (R = cyclohexyl), IAd (R = adamantyl), I*t*Bu (R = *tert*-butyl), I*i*Pr (R = *iso*-propyl), IMe (R = Me). (S) denotes the saturated character of imidazolinium NHC backbone.

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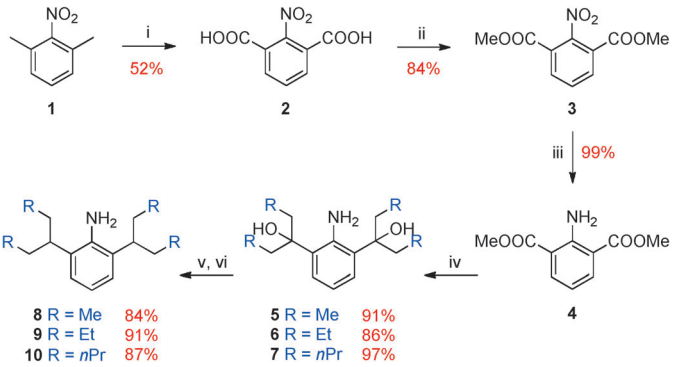
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201302471.

precursors. However, fewer examples of new NHCs bearing bulky *N*-substituents stemming from non-commercial amines/anilines have been reported in the field of transition metal catalysis for reasons of synthetic accessibility.[3,4b–d,j,5,7]

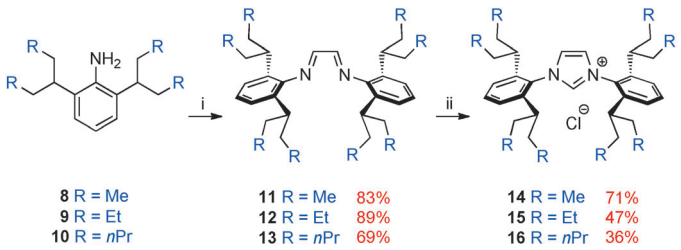
Markó[5] has reported a convenient multigram-scale preparation of IPr* (R = 2,6-bis(diphenylmethyl)-4-methylphenyl) which has proven to be fairly substrate-specific and largely intolerant to chemical variations of the bulk.[8] In the meantime, Organ[4a–c,9] has described the IPent (R = 2,6-di(3-pentyl)phenyl) ligand as a particularly efficient NHC ligand for palladium-catalysis. The latter appeared to us as a good starting point in our quest towards the design of "larger yet flexible NHC ligands". But surprisingly no information detailing the synthesis of this non-commercially available NHC or its possible precursors could be found in the literature. To the best of our knowledge, the one-step process reported by Steele[10] for the preparation of the IPent aniline (2,6-di(3-pentyl)aniline, R = 2,6-di(3-pentyl)phenyl) was the only literature precedent available. Although this process successfully afforded the IPent aniline in multigram quantities in a single step, this synthetic route suffered from significant drawbacks. The lack of flexibility of the approach, the use of a mixture of non-commercial superbases as part of the fairly complex procedure together with the purification of the final reaction mixture by fractional distillation forced us to envisage an alternate strategy that might lead to this specific compound and possibly to an entire family of compounds.

A novel approach was explored to access unprecedented anilines as precursors for the preparation of tailor-made NHC ligands. Our straightforward and highly scalable route started with Etard's double-oxidation of inexpensive and readily available 2-nitro-*m*-xylene **1** to 2-nitro*iso*phthalic acid **2** which, in turn, was converted to its corresponding dimethyl ester **3** (Scheme 1). All attempts towards the introduction of alkyl chains at this stage by a Grignard reaction were unsuccessful. To overcome this issue, the dimethyl 2-nitro*iso*phthalate **3** was reduced to dimethyl 2-amino*iso*phthalate **4** by hydrogenation with palladium on charcoal. Other metal-mediated reduction methods (iron or zinc) were also screened but the Pd/C hydrogenation appeared clearly as the most convenient and efficient procedure. Freshly prepared alkyl magnesium bromides (RCH_2MgBr) were then added to diester **4** to obtain diols **5–7** in excellent yield and purity. Dehydration under harsh acidic conditions followed by the hydrogenation of the intermediate crude bis-alkenes finally provided 2,6-dialkylanilines IPent **8**, IHept **9** and INon **10** (Scheme 1). A one-pot version of the dehydration-hydrogenation sequence also gave similar results although in lower purity. This new 6-step synthetic route allowed for the preparation of multigram quantities of commercially unavailable, unprecedented anilines with minimal or without purification. Importantly, the rather expensive Pd/C used for the nitro-reduction and the alkene-hydrogenation steps was recovered with great ease by filtration and successfully reused several times in subsequent reactions. Far beyond the efficacy and the scalability of our new synthetic route, the flexibility of our process by the economical and near-quantitative Grignard addition is notable. Indeed, a very wide range of Grignard reagents are readily available from chemical suppliers and can be prepared safely in the laboratory on a large scale. As a result of this remarkable versatility, our process will find applications into the design of new anilines and their ultimate conversion into a countless number of tailor-made NHCs.



Scheme 1. Synthesis of anilines **8**, **9** and **10**. Conditions: i) $KMnO_4$, NaOH, H_2O, reflux, 12 h; ii) H_2SO_4, MeOH, reflux, overnight; iii) 10% Pd/C, H_2, AcOEt, RT, 20 h; iv) alkylbromide RCH_2Br (R = Me, Et, *n*Pr), Mg, THF, 0 °C to RT, 1–2 h; v) H_2SO_4, THF, 100 °C, 1–2 h; vi) 10% Pd/C, H_2, EtOH, reflux, 6–48 h.

Anilines **8–10** were then reacted with glyoxal under acidic conditions to form the corresponding diimines **11–13** that were in turn cyclized to form the corresponding imidazolium chlorides **14–16** (Scheme 2). The entire synthetic sequence

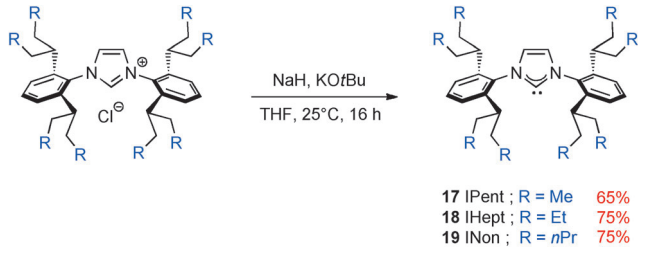


Scheme 2. Synthesis of imidazolium chlorides **14**, **15** and **16**. Conditions: i) glyoxal (40% in H_2O), HCOOH, MeOH, RT, 3–5 h; ii) $(CHO)_n$, $ZnCl_2$, HCl (4 M in dioxane), 70 °C, 3 h.

required minimal purification by recrystallization and provided multigram quantities of IPent·HCl **14**, IHept·HCl **15**, and INon·HCl **16** as white crystalline powders in high purity as confirmed by elemental analysis. Interestingly, as opposed to the rest of the synthetic sequence, the cyclisation yield greatly depended on the size of the R alkyl chains with a significantly lower yield observed for INon·HCl **16** and IHept·HCl **15**. Due to the size of their *N*-substituents, which partially hinder the cyclization, the competing diimine bridge cleavage was observed under acidic conditions, regenerating the free anilines **8–10**. It is important to note that the alternative mild TMSCl protocol described by Hinter-

mann for less hindered NHCs failed to give the cyclisation products **14–16** efficiently.[11]

Preparation of [Ni(ITent)(CO)$_3$] complexes for the determination of ITent electronic properties: An established method for the determination of the electron-donor ability of two electron ligands is the measurement of the IR carbonyl stretching frequencies of the related [Ni(L)(CO)$_3$] complexes.[12,13] The A_1 stretching frequency of the CO ligands is referred to as the Tolman Electronic Parameter (TEP) and is directly correlated with its electron richness: lower TEP values correspond to increased σ-donating properties of Ni-bound ligands.[12] Very recently, our research group reported the synthesis of [Ni(IPent)(CO)$_3$] (**20**) and evaluated the electron donor properties of the IPent ligand.[14] To extend this study to the new members of the ITent family, the corresponding [Ni(ITent)(CO)$_3$] complexes were synthesized. Their preparation first required the generation of the free carbene species **17–19** by treatment of THF solutions of ITent·HCl salts **14–16** with NaH and KO*t*Bu at room temperature for 16 h (Scheme 3). As already noted

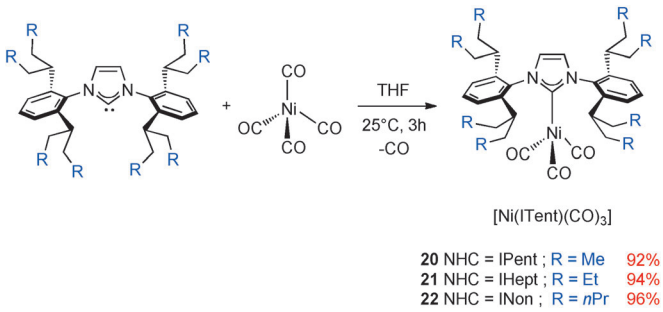


Scheme 3. Preparation of free carbenes (**17–19**).

with IPent·HCl salt **17**,[14] **18** and **19** also exhibited higher solubility in THF than other related NHC·HCl salts. Consequently, the usual conversion to their corresponding NHC·HBF$_4$ salts was not necessary to access the free carbenes. This counterion exchange prior to deprotonation usually leads to higher isolated yields of the most common NHCs.

Compounds **17–19** were characterized by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy and elemental analysis. The ^{13}C{^{1}H} NMR spectrum of each derivative showed the characteristic singlet in the low-field region corresponding to the carbenic carbon atom, at 220.9 (**17**), 220.5 (**18**), and 220.7 ppm (**19**), confirming the deprotonation of the imidazolium salts. Compounds **17–19** were next reacted with a slight excess of [Ni(CO)$_4$][15] to easily afford the desired complexes **20–22** in excellent yields and high purities (Scheme 4).

Complexes **20–22** were characterized by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy, IR and elemental analysis.[16] The coordination of the NHC ligands to the metal center was confirmed by the presence of singlets at 196.8 (**20**), 196.6 (**21**), and 196.9 ppm (**22**) in the ^{13}C{^{1}H} NMR spectra. The presence of three CO ligands in these complexes was confirmed by the position and number of CO bands in their solution IR spectra[13b] (Table 1) and unambiguously by elemental analysis. As previously noted, the TEP of each NHC ligand



Scheme 4. Synthesis of [Ni(ITent)(CO)$_3$] (**20–22**).

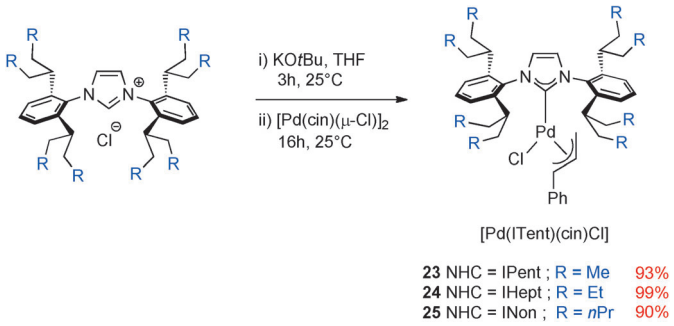
Table 1. TEP values of [Ni(NHC)(CO)$_3$] complexes.

NHC	TEP$_{DCM}$ [cm^{-1}]	TEP$_{hex}$ [cm^{-1}]
IMes[a]	2050.7	2054.0
IPr[a]	2051.5	2055.1
IPr*[b]	2052.7	–[c]
IPent (**20**)[d]	2049.3	2053.1
IHept (**21**)	2048.6	2052.5
INon (**22**)	2048.5	2052.1

[a] Reference [13a]. [b] Reference [20]. [c] [Ni(IPr*)(CO)$_3$] was found to be insoluble in hexane. [d] Reference [14].

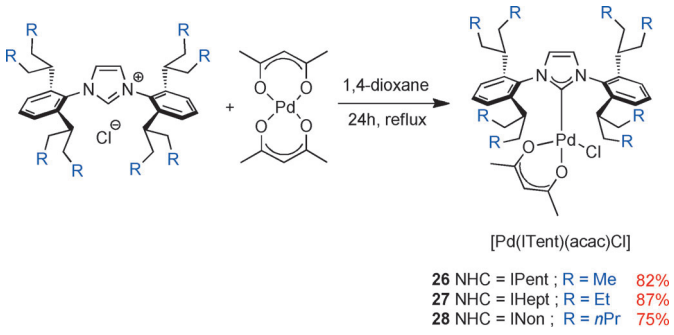
in dichloromethane and hexane were obtained by recording the A_1 IR frequency of the CO ligand in these nickel complexes. These data were compared with those of other [Ni(NHC)(CO)$_3$] complexes (Table 1), demonstrating that the ITent ligands are more σ-donating than the most common NHCs.[17] Interestingly, the longer the R alkyl chains, the stronger the σ-donation ability of the ligand, as observed theoretically by Gusev for other NHCs.[18] Importantly, it must be noted that the TEP difference between IPr,[19] IPent, IHept and INon becomes smaller as chain length becomes longer. Thus, the following σ-donating trend was observed: IPr $\ll$ IPent $<$ IHept $\sim$ INon.

Synthesis of [Pd(ITent)(LX)Cl] complexes and determination of the ITent steric properties: With the development of [Pd(IPent)(PEPPSI)],[4a–c,9] Organ and coworkers suggested that "flexible steric bulk", a concept initially proposed by Glorius et al.,[3,4j] is essential for high catalytic activity. As the newest members of the ITent ligand family feature both excellent electron donors and large steric bulk, we suspected the preparation of their palladium complexes would result in promising new pre-catalysts for cross-coupling catalysis. [Pd(ITent)(cin)Cl] (cin = cinnamyl or phenylallyl) pre-catalysts **23–25** were first prepared in a straightforward manner as described in the literature (Scheme 5).[6d] The free carbenes obtained from the ITent·HCl salts **14–16** were initially generated in situ with KO*t*Bu in THF in reaction conducted for 3 h at room temperature. Their coordination to the palladium center was next achieved by adding [Pd(cin)(μ-Cl)]$_2$ to the reaction mixture affording the expected complexes **23–25** in excellent yields. Compounds **23–25** were isolated in high purity as indicated by elemental analysis and were found to be air and moisture stable.



Scheme 5. Preparation of [Pd(ITent)(cin)Cl] complexes (**23**–**25**).

An additional family of palladium pre-catalysts can be easily prepared by a synthetic route not requiring the isolation of the free NHC, namely the [Pd(ITent)(acac)Cl] (acac = acetylacetonate) family. These complexes can be synthesized by reacting the ITent·HCl salts **14**–**16** with [Pd(acac)$_2$], as described in the literature (Scheme 6).[21] The newly prepared [Pd(IPent)(acac)Cl] (**26**), [Pd(IHept)(acac)Cl] (**27**) and [Pd(INon)(acac)Cl] (**28**) were obtained as air- and moisture-stable yellow microcrystalline solids in good yields and in high purity.



Scheme 6. Preparation of [Pd(ITent)(acac)Cl] (**26**–**28**).

The new [Pd(ITent)(acac)Cl] complexes **26**–**28** were fully characterized and interestingly, the ^{1}H NMR spectroscopy revealed that the differences in the chemical shifts of both singlets of the "acac" methyl groups increases dramatically with the length of the R alkyl groups in the NHC ligand. The ^{1}H spectrum of [Pd(IPr)(acac)Cl] exhibited two close singlets at 1.82 ppm and 1.84 ppm for the methyl groups of the acac ligand.[21] The ^{1}H NMR spectrum of **26** revealed that these singlets were shifted upfield, the first one slightly (1.73 ppm) and the second one more significantly (1.53 ppm). This chemical shift difference is more marked in **27** (1.77 ppm and 1.40 ppm), and decreases slightly in **28** (1.75 ppm and 1.40 ppm), as the bulk increases but is located further away from the metal center. This suggests that in solution, the magnetic, and consequently, the chemical environment around the metal is directly affected by the length of the R alkyl groups. This information is critically important for understanding of the effect of NHC bulk on the catalyst in solution. In addition, this spectroscopic handle should be of great help in the design of future NHC ligands.

Suitable X-ray diffraction quality crystals of complexes **23**–**26** were grown by slow evaporation of saturated pentane solutions.[22] In the case of **27** and **28**, crystals were grown by placing saturated methanol solutions in the freezer after addition of a drop of water to these solutions (Figure 2 and Figure 3).[23]

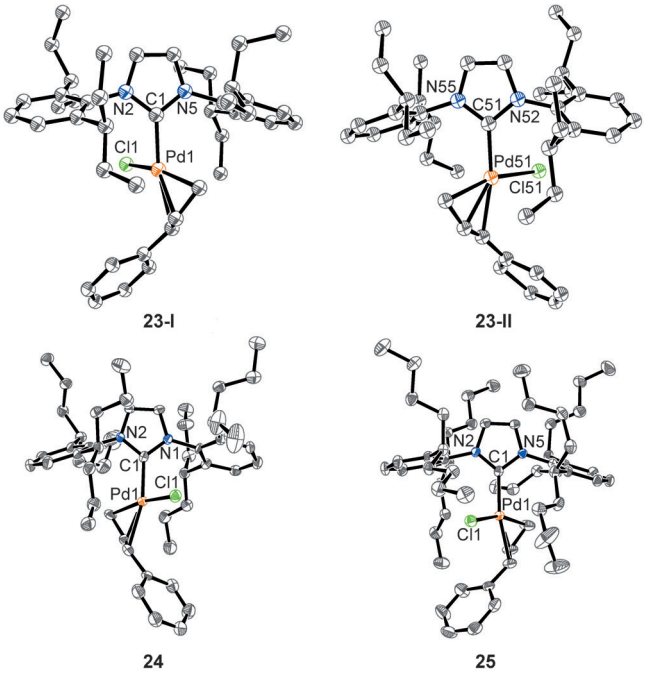


Figure 2. ORTEP diagrams of molecular structures of **23** (two conformers **I** and **II**), **24** and **25** showing 50% probability ellipsoids. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°): **23-I** Pd1–C1 2.019(8), Pd1–C41 2.123(9), Pd1–C42 2.150(9), Pd1–C43 2.214(9), Cl1-Pd1-C1 93.6(3), Cl1-Pd1-C43 96.5(3), C1-Pd1-C41 101.2(3), C41-Pd1-C43 67.6(4). **23-II** Pd51–C51 2.024(8), Pd51–C91 2.105(12), Pd51–C92 2.098(15), Pd51–C93 2.225(13), Cl51-Pd51-C51 96.8(3), Cl51-Pd51-C93 95.1(4), C51-Pd51-C91 100.8(4), C91-Pd51-C93 67.2(5). **24** Pd1–C1 2.031(5), Pd1–C4 2.105(7), Pd1–C5 2.152(8), Pd1–C6 2.251(6), Cl1-Pd1-C1 92.16(17), Cl1-Pd1-C6 98.64(18), C1-Pd1-C4 100.2(3), C4-Pd1-C6 67.9(3). **25** Pd1–C1 2.037(4), Pd1–C54 2.129(4), Pd1–C55 2.140(4), Pd1–C56 2.230(4), Cl1-Pd1-C1 96.23(10), Cl1-Pd1-C56 92.98(11), C1-Pd1-C54 101.82(15), C54-Pd1-C56 68.31(16).

Very interestingly, in both the acac- and cinnamyl-palladium systems, the IPent ligand adopts two different configurations (**I** and **II**) in the solid state. This situation was not observed in the IHept and INon cases. This flexibility can presumably account for the dramatic gain in catalytic activity observed with the IPent ligand compared to IPr in certain applications. This observation is in agreement with the expected increase in flexibility of the alkyl chains. However, we cannot provide an explanation as to why this phenomenon was not observed with IHept and INon ligands. Solid-state structures represent minimum energy conformations and these obtained for the ITent family members in the two series provide useful insights into structural orientation of

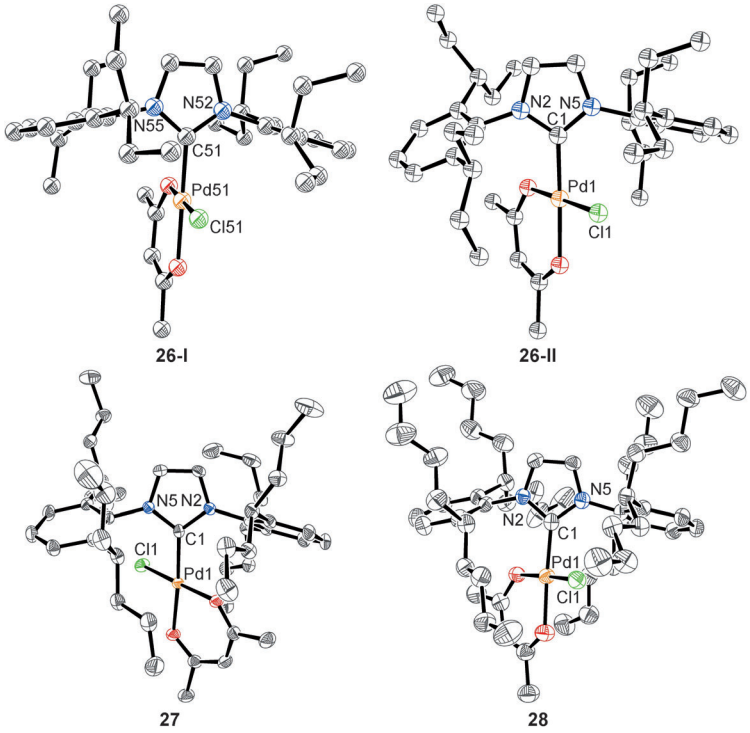


Figure 3. ORTEP diagrams of molecular structures of **26** (two conformers **I** and **II**), **27** and **28** showing 50% probability ellipsoids. Hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°): **26-I** Pd1–C1 2.274(1), Pd1–O1 2.052(3), Pd1–O2 2.031(3), C1-Pd1-O1 174.8(1), O1-Pd1-O2 92.1(1), C1-Pd1-Cl1 88.8(1), O1-Pd1-Cl1 87.4(4). **26-II** Pd2–C2 2.278(1), Pd2–O3 2.050(3), Pd2–O4 2.024(3), C2-Pd2-O3 179.2(1), O3-Pd2-O4 92.1(1), C2-Pd2-Cl2 88.8(1), O3-Pd2-Cl2 88.3(2). **27** Pd1–C1 2.272(1), Pd1–O1 2.038(2), Pd1–O2 2.025(3), C1-Pd1-O1 175.5(7), O1-Pd1-O2 92.1(3), C1-Pd1-Cl1 90.1(7), O1-Pd1-Cl1 85.8(1). **28** Pd1–C1 2.274(2), Pd1–O1 2.036(3), Pd1–O2 2.030(4), C1-Pd1-O1 174.6(2), O1-Pd1-O2 92.3(1), C1-Pd1-Cl1 88.8(1), O1-Pd1-Cl1 85.8(1).

the alkyl moiety and spatial occupation about the metal center. The percent buried volume for each structure **23**–**28** was then calculated with the Samb*V*ca application,[24, 13b, 25] and results are summarized in Table 2. In both the acac and cinnamyl systems, the IPr ligand was found to feature the smallest buried volume (36.7% and 37.4%). Surprisingly, a dramatic difference was observed between the configurations **I** and **II** of the Pd-IPent complexes **23** and **26**. This difference suggests that IPent-based palladium catalysts may accommodate incoming substrates differently by adapting to facilitate both oxidative addition and reductive elimination steps resulting in better overall catalytic activity. The buried volume of the IHept ligand seemed to vary depending on the system it is associated with, here again the flexibility of this ligand motif is apparent. In cinnamyl-Pd, the size of IHept was found to be similar to that of IPent (average of **23-I** and **23-II**). However, in the acac-Pd system, IHept appeared to be significantly larger than IPent (average of **26-I** and **26-II**). Finally, INon was shown to be smaller than IHept in both cases. This can presumably be rationalized by the fact that longer chains remain distant from the first coordination sphere and therefore do not interact with the metal center.

To obtain further insight into the steric properties of our new precatalysts **23**–**28**, a three-dimensional steric map was generated by calculating the $\%V_{Bur}$ in four different regions around the metal center.[26] Looking along the z axis, the calculation provides more information on how the ligand adapts its shape to the metal environment (see the Supporting Information). In general, two quadrants are sterically crowded whereas the two remaining areas are largely unhindered. The less hindered faces can be thought of as the preferential approach for substrate leading to the formation of the intermediate involved in oxidative addition.[6d,26] On the other hand, the reductive elimination and the release of cross-products may presumably be facilitated by the presence of highly bulky quadrants around palladium. If this is the case then high reactivity under mild conditions should ensue and be associated with bulky yet flexible nature.[6d]

Table 2. Bond distances and steric parameters of [Pd(ITent)(LX)Cl].

Complex	Pd–C_{NHC} [Å]	V_{Bur}[a] [%]
[Pd(IPr)(cin)Cl]	2.041(9)	36.7
[Pd(IPent)(cin)Cl] **23**	2.019(8)	40.6 (I)
	2.024(8)	44.1(II)
[Pd(IHept)(cin)Cl] **24**	2.031(5)	41.5
[Pd(INon)(cin)Cl] **25**	2.037(4)	39.0
[Pd(IPr)(acac)Cl]	1.969	37.4
[Pd(IPent)(acac)Cl] **26**	1.960	34.3 (I)
	1.974	46.6 (II)
[Pd(IHept)(acac)Cl] **27**	1.977	45.7
[Pd(INon)(acac)Cl] **28**	1.965	43.7

[a] Calculation parameters: sphere radius, 3.50 Å; distances for the metal–ligand bond, 2.00 Å; hydrogen atoms were omitted; scaled Bondi radii were used as recommended by Cavallo.[24]

In Pd-cinnamyl systems, the previous remark was observed with two pairs of quadrants having very similar buried volumes, especially for **24** and **25**. However, it has to be noted that Pd-IHept **24** ($\%V_{Bur}=26.5$) has more empty space compared to Pd-INon **25** ($\%V_{Bur}=29.0$). Moreover, as described earlier, INon was again found to have smaller buried volumes to IHept. More interestingly, the steric map confirmed the very different nature of the two conformers, with **23-II** being much more crowded than **23-I** (Figure 4).

In the Pd-acac system, more significant differences were observed. Importantly, the sterics of **26-I** and **26-II** were dramatically different, with conformer **26-II** having amazingly

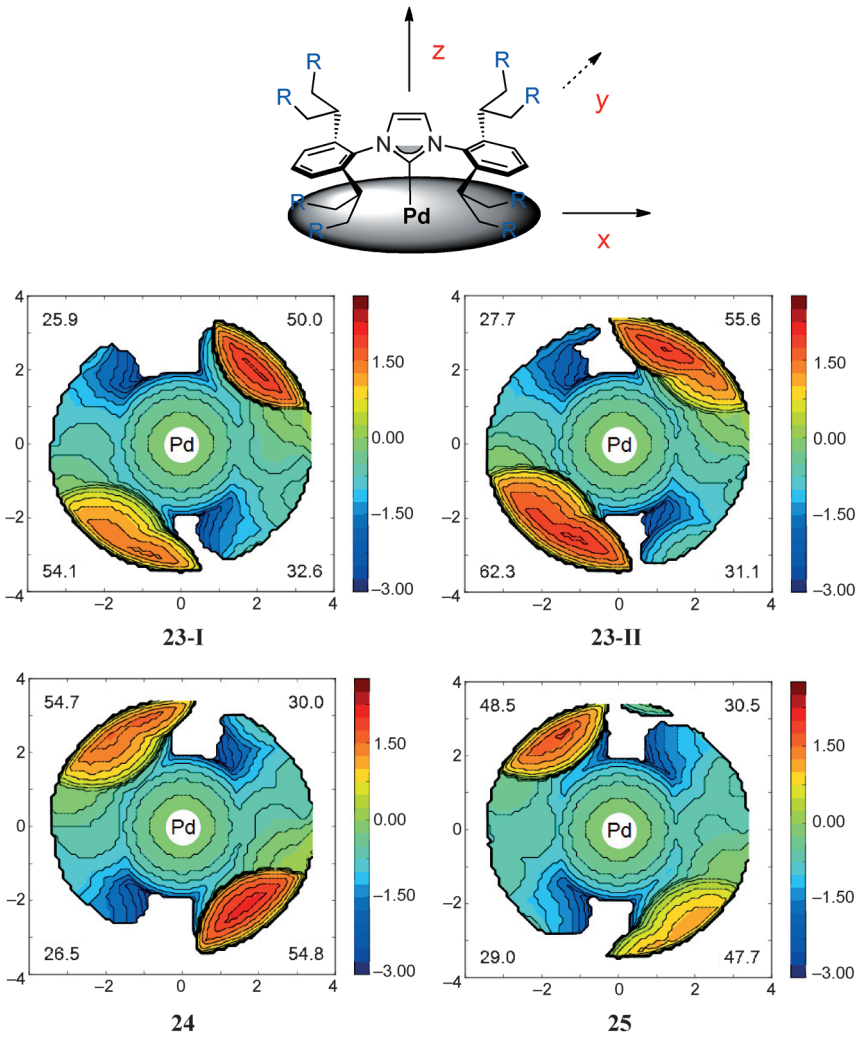


Figure 4. Top view (along z axis) mapping of the sterics for **23** (two conformers **I** and **II**), **24** and **25** with % V_{Bur} values per quadrant.

large buried volumes (% V_{Bur} = 65.3) and rather empty opposite quadrants (% V_{Bur} = 29.8 and 27.6). Conversely, **26-I** appeared almost free of steric hindrance, featuring four similar quadrants. In the case of IHept, the unique conformer featured smaller buried volumes (% V_{Bur} = 60.1 and 61.8) but as seen before in **24**, a marked void in one quadrant (% V_{Bur} = 26.8), whereas **28** presented very asymmetric quadrants (Figures 4 and 5).

Preparation of tetra-*ortho*-substituted biaryls by Suzuki–Miyaura cross-coupling with [Pd(ITent)(cin)Cl] (23–25): [Pd(NHC)(cin)Cl] pre-catalysts have found widespread application in multiple cross-coupling reactions[6a,d,27] and have proven highly active in C–C cross-coupling of hindered substrates. One of the remaining challenges in Suzuki–Miyaura cross-coupling is the preparation of tetra-*ortho*-substituted biaryls under mild conditions.[4j,28] Examples reported in the literature highlight the use of bulky yet flexible ligands to achieve this transformation. Notably, Nolan[6d] and Dorta[26a] independently demonstrated the efficiency of [Pd(NHC)(cin)Cl] complexes (NHC = IPr* and *anti*-(2,7)-SICyoctNap) whereas Organ[4b] showed the efficacy of [Pd(IPent)(PEPPSI)]. Consequently, the combination of the ITent and cinnamyl ligands in well-defined Pd-NHC pre-catalysts appeared promising for this challenging cross-coupling.

Reaction optimization was initially performed at room temperature with various common base/solvent systems.[29] The coupling of 2-chloromesitylene and 2,6-dimethylbenzene boronic acid was used as the benchmark reaction for our optimization. In our case, and as described by Dorta,[26a] the use of KO*t*Bu in toluene was found to be the best combination to promote the coupling, with complete conversion of the starting materials after 20 h with 1 mol% of **23–25** (Table 3, entry 1). The use of KO*t*Bu in *i*PrOH, which was previously found to be the optimal system in the case of [Pd(IPr)(cin)Cl],[27d] did not lead to any conversion in that case.[29] Compared to some other systems reported in the literature, [Pd(ITent)(cin)Cl] complexes exhibited higher catalytic activity at lower catalyst loadings. Indeed, for a similar example, catalyst loading is divided by two (1 mol% vs 2 mol%) and reactivity occurs at lower temperature (RT vs 65 °C).[4b,26a] Interestingly, as previously observed by Organ,[4b] our preliminary optimization confirmed that the increase of the NHC alkyl chain length from IPr to IPent resulted in a significant improvement of the catalytic activity (Table 3, entry 1). However, at room temperature, the formation of a gel at the beginning of the reaction was sometimes found to have a detrimental effect on the reproducibility of the reaction, especially at lower catalyst loadings.[29] The increase of the reaction temperature to 65 °C and the dilution of the reaction medium allowed us to circumvent this issue. Although the gel was still formed, the reproducibility of the reaction was uneffected. Increasing the temperature also permitted us to reduce the catalyst loading of **23–25** to 0.5 mol%, and full conversion was still reached (Table 3, entry 2). To better identify the marked differences in reactivity between the three new complexes **23–25**, the catalyst loading was further decreased to 0.2 mol%, and the reaction was stopped after 4 h (Table 3, entry 3). Interestingly, the catalytic activity was

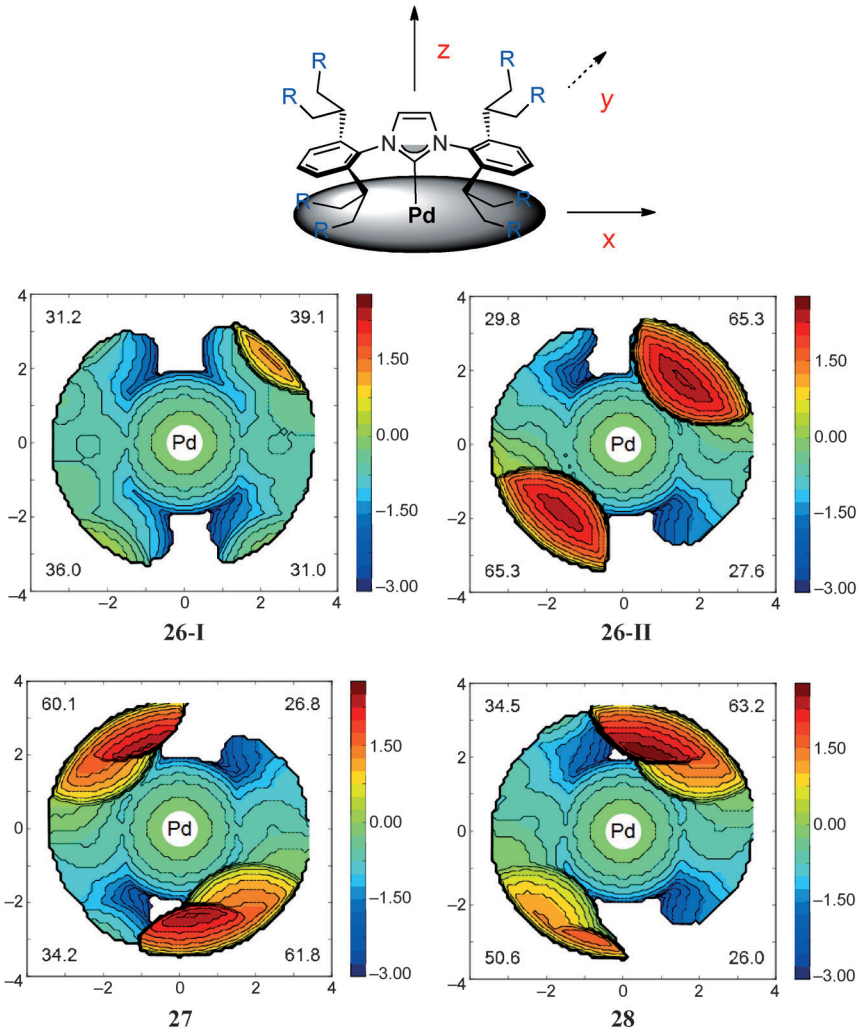


Figure 5. Top view (along z axis) mapping of the sterics for **26** (two conformers **I** and **II**), **27** and **28** with % V_{Bur} values per quadrant.

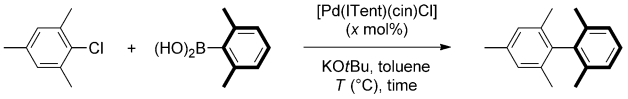
slightly decreased by increasing the length of the R alkyl chain in the ITent NHC ligands from IPent to IHept and finally to INon. These preliminary observations suggest that the nature of the ligand has a noticeable impact on the overall catalytic activity. With **23** slightly better results were obtained than with **24** (Table 3, entry 3, 66% vs 58%). However, the additional length in INon by with **25** was not found to be beneficial (Table 3, entry 3, 49% vs 58% and 66%). This observation is consistent with the steric and electronic information discussed above.

As a consequence, the scope of the reaction was explored with **23** not only because it furnished the best result, but also because its preparation as a well-defined precatalyst appeared to be slightly more convenient compared to the other congener **24**. The reaction was studied under optimized conditions, with 0.5 to 1 mol% of **23** and KO*t*Bu in toluene at 65°C (results are summarized in Scheme 7). The system displayed excellent catalytic activity for the coupling of various unactivated and deactivated aryl, naphthyl or heteroaryl halides with aryl or naphthylboronic acids in excellent yields (Scheme 6, 80–97%). Both aryl chlorides and bromides were used without any loss of activity. In the case of 2,3,5,6-tetramethylbenzene and 2-methylnaphtalene boronic acids, an increase of the catalyst loading from 0.5 to 1 mol% was necessary to reach completion (Scheme 7). On the whole, **23** exhibited excellent catalytic activity, placing this new complex amongst the most active pre-catalysts to achieve the preparation of tetra-*ortho*-substituted biaryls by Suzuki–Miyaura cross-coupling.[4b,26a] More specifically, the catalyst loading reported here (0.5–1 mol%) is very competitive with the previous investigations of Dorta[26a] (0.5–2 mol%) and ourselves[6d] (1 mol%). Finally, compared to its [Pd(IPent)(PEPPSI)] congener,[4b] our system proved to be more active, globally yielding the biaryls in better yields, at lowest Pd loadings.

Buchwald–Hartwig Arylamination with [Pd(ITent)(acac)Cl]: Palladium catalyzed arylamination has become an important method for the formation of C–N bonds.[27c,30] As with tertiary phosphine ligands,[31] literature precedents have shown Pd–NHC complexes to be efficient precatalysts for the catalytic Buchwald–Hartwig arylamination reaction.[9f,27d,e,32] Nolan recently demonstrated the role of [Pd(NHC)(acac)Cl] in this transformation, reaching remarkable activities with the bulky but less flexible IPr* and IPr*^{OMe} ligands.[6b,8] In this context, the effect of the R-alkyl chains length on Pd complexes **26–28** was investigated in Buchwald–Hartwig arylamination of aryl chlorides with aniline derivatives. Recent reports identified electron-rich aryl halides and electron-deficient anilines as highly disfavored coupling partners for arylamination.[6b,8,9c] For these reasons, these challenging substrates were examined with our new acac-bearing catalysts.

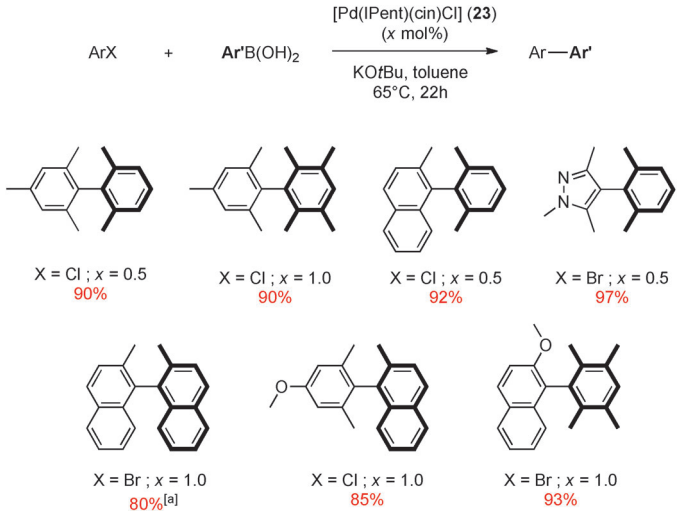
4-Chloroanisole was coupled with 4-fluoroaniline or 3-trifluoromethylaniline as benchmark reactions for our initial optimization. After an initial base/solvent screening, the use of KO*t*Bu in toluene at 80°C or at reflux (in the case of 3-trifluoromethylaniline) was found to provide the best conditions, leading to complete conversion of the starting materials with 0.4 mol% of **26–28**. To compare the catalytic prop-

Table 3. [Pd(ITent)(cin)Cl] pre-catalysts comparison.[a]



Entry	T/[Pd]/time	Conversion [%][b]
1	RT[c]/1.0 mol%/20 h	IPr 58; 23 99; 24 99; 25 99
2[d]	65 °C/0.5 mol%/20 h	IPr 75; 23 99; 24 99; 25 99
3[d]	65 °C/0.2 mol%/4 h	IPr 28; 23 66; 24 58; 25 49

[a] Reagents and conditions: 2-chloromesitylene (0.5 mmol), 2,6-dimethylbenzene boronic acid (1.0 mmol), KO*t*Bu (1.5 mmol), [Pd(ITent)(cin)Cl] (**23**–**25**) (1 mol%), toluene (1 mL), *T* [°C], 20 h. [b] Conversion to coupling product based on 2-chloromesitylene determined by GC, average of at least 2 runs. [c] RT = 25–28 °C. [d] Toluene (2 mL).

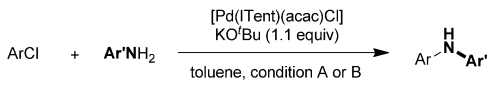


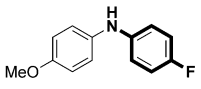
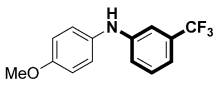
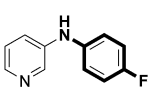
Scheme 7. Scope of the Suzuki–Miyaura cross-coupling catalyzed with [Pd(IPent)(cin)Cl] (**23**). Reagents and conditions: ArX (0.5 mmol), Ar′B(OH)$_2$ (1.0 mmol), KO*t*Bu (1.5 mmol), [Pd(IPent)(cin)Cl] (**23**) (*x* mol%), toluene (2.0 mL), 65 °C, 22 h. Reaction times have not been optimized. Isolated yields after chromatography on silica gel, average of two runs. [a] Reaction was performed with technical grade 1-bromo-2-methylnaphtalene (90%).

erties of **26**–**28**, the reaction was performed at lower catalyst loadings. By employing 0.05 mol% of precatalyst, *N*-fluorophenyl-*p*-anisidine was obtained in 58% conversion with **26**, 83% with **27** and 76% with **28** (Table 4, entry 1). Similarly, at higher temperature, the coupling of *p*-chloroanisole and 3-trifluoromethylaniline provided the desired products in 41%, 68% and 64% GC yields with **26**, **27** and **28** respectively (Table 4, entry 2). The same reactivity order was observed for the third model reaction between 3-chloropyridine and 4-fluoroaniline, affording the cross-product in 22%, 70% and 61% GC yields with **26**, **27** and **28** respectively (Table 4, entry 3). Interestingly, the three benchmark reactions followed the same trend and no cross coupling was observed with the IPr ligand in any of these cases as reported by Organ.[9c,33] These results are in agreement with the initial hypothesis in which an increased flexible bulk is essential for the optimal catalytic activity of Pd–NHC complexes. However, although **27** was more efficient than **26**, no gain in activity was observed for **28**, which was more active than **26** in every case (Table 4).

The overall positive effect attributed to the length of the R-alkyl chains appeared to be maximal with the IHept ligand. It appears that in the case of INon, the additional bulk is too far from the coordination sphere of the metal center and does not influence the catalytic properties of the complex. This explanation is supported by our observed steric and electronic trends and is of critical importance for further ligand design efforts because the limit of flexible bulk in NHC ligands has been reached.

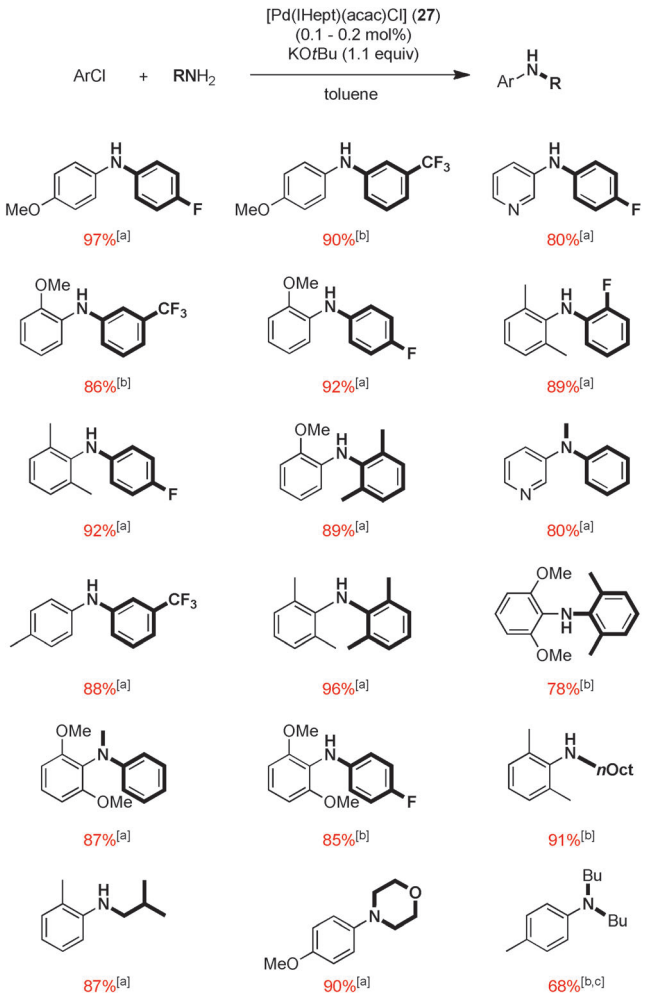
Table 4. [Pd(ITent)(acac)Cl] pre-catalysts comparison.



Entry	Product	Conditions[a]	GC conversions [%][b]
1		A	IPr 0; 26 58; 27 82; 28 76
2		B	IPr 0; 26 41; 27 68; 28 64
3		A	IPr 0; 26 22; 27 70; 28 61

[a] Reagents and conditions: ArX (0.5 mmol), **Ar′NH**$_2$ (0.55 mmol), KO*t*Bu (0.5 mmol), [Pd(ITent)(acac)Cl] (**26**–**28**), toluene (1.0 mL). Condition A: 0.05 mol% [Pd(ITent)(acac)Cl], 80 °C, 20 h; Condition B: 0.1 mol% [Pd(ITent)(acac)Cl], 110 °C, 20 h. [b] Conversion to coupling product based on starting aryl chloride by GC, by using dodecane as internal reference, average of three runs.

Based on our preliminary results, **27** was selected as the best precatalyst to explore the scope of the arylamination reaction. The scope of the reaction was explored under the previously optimized conditions, with 0.1–0.2 mol% of **27** and KO*t*Bu in toluene at 80°C or at reflux for 2–4 h (Scheme 8). The system displayed excellent catalytic activity



Scheme 8. Scope of the Buchwald–Hartwig arylamination catalyzed with [Pd(IHept)(acac)Cl] (**27**). Reagents and conditions: ArX (0.5 mmol), **RN**H_2 (0.55 mmol), KO*t*Bu (0.5 mmol), [Pd(IHept)(acac)Cl] (**27**) (x mol%), toluene (1.0 mL). [a] 0.1 mol% **27**, 80°C, 2 h. [b] 0.2 mol% **27**, 110°C, 4 h. Isolated yields after chromatography on silica gel, average of two runs. [c] 20 h reaction time.

for the coupling of various deactivated aryl chlorides with anilines, particularly with electron-poor anilines, which are reported to be highly disfavored coupling partners. Moreover, very good yields were obtained with sterically hindered substrates. Interestingly, the unprecedented coupling of 2,6-dimethoxychlorobenzene was successfully achieved with various anilines at low catalyst loading. Finally, the catalytic system was also effective in the coupling of several primary and secondary aliphatic amines, including the highly challenging dibutylamine. Our results demonstrate the excellent catalytic activity of **27** in Buchwald–Hartwig arylamination reaction and confirm that the "flexible steric bulk" concept is essential in securing high catalytic activity with Pd–NHC complexes.

Conclusion

The synthesis of a novel class of NHCs of which two analogues (IHept and INon) are unprecedented are now reported in the open literature. Our new synthetic strategy enabled the preparation of multigram quantities of the final NHCs in good overall yields after minimal purification. These new NHCs expand the so-called "ITent" NHC family in which the bulk around the metal center and the σ-donation increase in the following order: IPr ≪ IPent < IHept ~ INon. Beyond the novelty of these new compounds, their preparation has rendered possible the study of a significant number of compounds falling within the "ITent" series and will help to understand which characteristics are crucial to the design of "optimum" N-heterocyclic carbenes for palladium catalysis. The steric and electronic parameters measured help explain the catalytic results and fully support our initial hypothesis. The INon NHC was shown to feature flexible bulk, yet experimentally it represents a limit beyond which extra flexible bulk does not translate into gain in catalytic activity. However, work is ongoing to fully capitalize on the properties of these new ligands, such as their exceptional solubility in non-polar media that might offer new horizons in cross-coupling and related catalysis.[34] The initial catalytic results with the ITent ligand family have permitted the identification of more active Pd-NHC precatalysts for Suzuki–Miyaura and Buchwald–Hartwig cross-couplings and have given precious information for improved understanding of Pd-NHC catalysis.[35] The remarkable steric suppleness of the large yet flexible ligand set is currently being further explored in late transition metal catalysis.

Acknowledgements

We gratefully acknowledge the EC for funding through the seventh framework project SYNFLOW. Frédéric Izquierdo, Julie Mayen and Enrico Marelli are thanked for their experimental contributions to the project. Professor Luigi Cavallo and Laura Falivene are thanked for their help regarding the use of the Samb*V*ca application. We would like to thank the EPSRC National Mass Spectrometry Service Center in Swansea for mass spectroscopic analyses and Umicore and Rockwood Lithium for their generous gifts of materials. SPN is a Royal Society Wolfson Research Merit Award holder.

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[15] Special care has been taken in manipulating the EXTREMELY TOXIC $[Ni(CO)_4]$. All manipulations were carried out in the glovebox, with additional protective gloves. $[Ni(CO)_4]$ was constantly maintained at −40 °C. The solutions containing the NHC ligands were cooled to −40 °C, and $[Ni(CO)_4]$ was added by syringe at the same temperature. The slight excess of $[Ni(CO)_4]$ at the end of each reaction was evaporated and trapped into a THF solution containing phosphines.

[16] Complex **21** was also structurally characterized by X-ray diffraction analysis, see the Supporting Information for more details. CCDC-926534 (**21**) contain 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.

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[23] CCDC-929742 (**26**), CCDC-929741 (**27**) and CCDC-929743 (**28**) 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.

[24] The SambVca application is available from http://www.molnac.unisa.it/OMtools/sambvca.php. Calculation parameters: sphere radius, 3.50 Å.; distances for the metal-ligand bond, 2.00 Å.; hydrogen atoms were omitted; scaled Bondi radii were used as recommended by Cavallo.

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[35] The use of the [Pd(ITent)(cin)Cl] system in Buchwald–Hartwig and of the [Pd(ITent)(acac)Cl] complexes in Suzuki–Miyaura reactions lead to similar reactivity trends. These results will be reported separately.

Received: June 26, 2013
Published online: November 14, 2013

