Amination

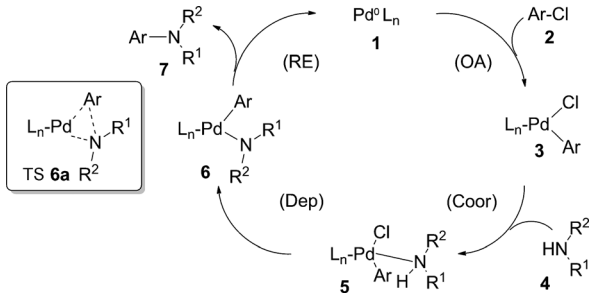
DOI: 10.1002/anie.201310457

Room-Temperature Amination of Deactivated Aniline and Aryl Halide Partners with Carbonate Base Using a Pd-PEPPSI-IPent^{Cl}-*o*-Picoline Catalyst**

*Matthew Pompeo, Jennifer L. Farmer, Robert D. J. Froese, and Michael G. Organ**

Abstract: *Current state-of-the-art protocols for the coupling of unreactive amines (e.g., electron-poor anilines) with deactivated oxidative-addition partners (e.g., electron-rich and/or hindered aryl chlorides) involve strong heating (usually >100°C) and/or tert-butoxide base, and even then not all couplings are successful. The aggressive base tert-butoxide reacts with and in many instances destroys the typical functional groups that are necessary for the function of most organic molecules, such as carbonyl groups, esters, nitriles, amides, alcohols, and amines. The new catalyst described herein, Pd-PEPPSI-IPent^{Cl}-o-picoline, is able to aminate profoundly deactivated coupling partners when using only carbonate base at room temperature.*

Palladium-catalyzed amination has been demonstrated to be a highly valuable transformation for the preparation of natural products and other important molecules in the pharmaceutical, agrochemical, and materials sectors.[1] The general amination catalytic cycle is shown in Scheme 1 and the rate-limiting step of the process is affected by a number of different reaction attributes. The rate of oxidative addition (OA) is enhanced by an electron-rich metal[2] and is generally accelerated by N-heterocyclic carbene (NHC) ligands or electron-rich phosphanes.[1c,3] Recent efforts to increase the bulk of both the phosphanes[4] and the NHCs[2,5] has greatly facilitated reductive elimination (RE), both in amination and many other cross-coupling protocols. It has been suggested that the remaining challenges for metal-catalyzed amination include the intervening steps of amine coordination to the metal and deprotonation, which can often be treated together. In this context, the nature of the amine is critical. For alkyl amines, which are strongly basic, coordination to the electrophilic Pd^{II} center is favorable and it is deprotonation that is challenging owing to the pK_a value (ca. 8–10) of the corresponding metal–ammonium complex (**5**). Conversely, anilines (e.g., $R^1 = Ar$) are far less basic, which diminishes their coordinating ability, although this is compensated for by a reduction in the pK_a value of the amine proton by several orders of magnitude. Taken together, the difficulties in these middle steps, and in OA in the case of some phosphane ligands, means that amination reactions are usually heated to very high temperatures (usually >100 °C).[6] Furthermore, to compensate for the problems with deprotonation, the vast majority of couplings in the literature require the use of strong, aggressive bases such as *tert*-butoxide.[7] Unfortunately, taken together, these forceful reaction conditions that are currently state-of-the-art limit the use of this otherwise useful methodology to the production of products often devoid of more elaborate functionality.[6–8] Ideally, one single catalyst would possess sufficient reactivity to mediate the most challenging amination reactions at the lowest practical temperature (RT), with the most mild of bases (e.g., carbonate), in a reaction that is operationally simple (merely combine the reactants and stir), and with no limit to the functionality that can be tolerated. This challenging goal is the focus of this report.



Scheme 1. Putative amination catalytic cycle.

In 2008, we disclosed that the pyridine-enhanced precatalyst preparation stabilization and initiation (PEPPSI) catalyst Pd-PEPPSI-IPr (**8**) is an effective precatalyst for the amination of aryl chlorides and bromides with anilines and secondary amines when using KO*t*Bu as the base (IPr = 2,6-diisopropylphenyl-2*H*-imidazol-2-ylidene).[9] In that report, Cs_2CO_3 was also demonstrated to be effective when coupling secondary amines, however only when electron-deficient aryl halides were employed. Presumably, the electron-withdrawing group was necessary to increase the acidity of the Pd–ammonium complex (**5**) sufficiently for it to be deprotonated by a base with a conjugate acid (HCO_3^-) with a pK_a value of approximately 10.5. Later, a bulkier Pd-PEPPSI-IPent pre-catalyst (**11a**) was shown to vastly outperform **8** in the coupling of anilines with electronically deactivated (i.e., electron-rich) aryl chlorides when using Cs_2CO_3 as the

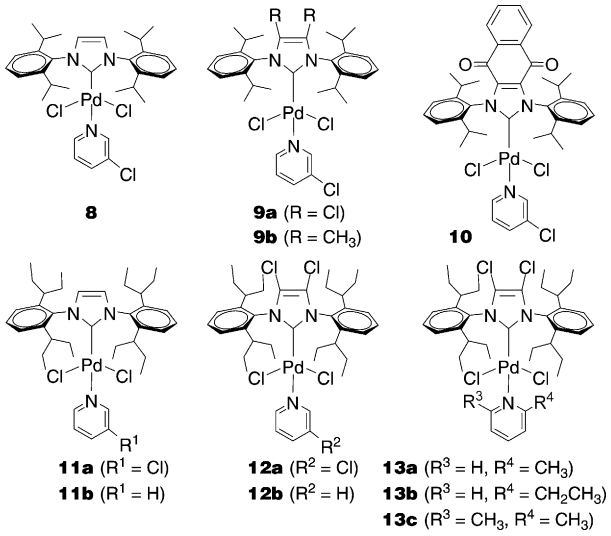
[*] M. Pompeo, J. L. Farmer, Prof. M. G. Organ
Department of Chemistry, York University
4700 Keele Street, Toronto, ON, M3J 1P3 (Canada)
E-mail: organ@yorku.ca
Homepage: http://www.yorku.ca/organ/
Dr. R. D. J. Froese
The Dow Chemical Company
Midland, MI 48674 (USA)

[**] This work was supported by NSERC (Canada) and the Ontario Research Fund (ORF, Ontario).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201310457.

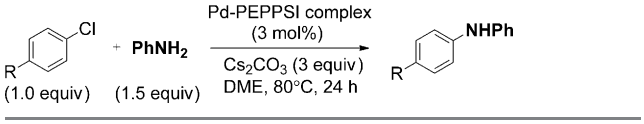
base[10] (IPent = 2,6-(3-pentyl)pentylphenyl-2*H*-imidazol-2-ylidene). However, although this catalyst was effective with a limited selection of anilines, forcing conditions (refluxing toluene) were required.

More recently, we have demonstrated that modifying the backbone of the NHC core can have a profound impact on reactivity and selectivity, thereby leading to dramatic improvements in a variety of cross-coupling reactions.[11–13] In an attempt to improve the chronic problems associated with amination (see above), we brought to bear what we had learned in other applications to see if it was possible to create a mild and general coupling procedure that would work even with electronically deactivated coupling partners. To investigate whether a more electron-poor NHC, and thus a presumably more electrophilic Pd centre, would help to promote both coordination and deprotonation, we began our study with a systematic evaluation of the IPr-based NHC core (see Table 1 and Scheme 2 for the precatalyst structures).



Scheme 2. PEPPSI precatalysts used in this amination study.

Table 1: Control amination reactions to evaluate the effect of substitutions at the IPr NHC core.[a]



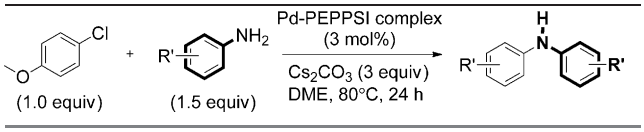
14	15	16
8: 0%	**8**: 5%	**8**: 95%
9a: 10%	**9a**: 55%	**9a**: 97%
9b: 16%	**9b**: 46%	**9b**: 96%
10: 2%	**10**: 36%	**10**: 96%
11a: 92%	**11a**: 93%	**11a**: 90%

[a] Reactions were conducted on a 0.5 mmol scale at a concentration of 1 M. The precatalysts used and the associated yield are given below the product numbers. Yields are reported for products purified by flash chromatography and were averaged over two runs.

In this study, Pd-PEPPSI-IPr (**8**) showed no activity in the reactions to give products **14** and **15**. Only when the aryl chloride OA partner was considerably activated, in which case the reaction proceeded efficiently with all the catalysts tested, was the product (**16**) produced with high yield. We know from other cross-coupling studies that precatalyst **8** readily undergoes OA with essentially any aryl halide,[5k–n] so the lack of reactivity with electron-neutral (simple phenyl) or electron-rich (e.g., *p*-methoxyphenyl) aryl halides is not linked to OA. From the reactivity of precatalysts **9a** and **10**, which have been shown to possess a more electron-deficient metal center,[12] there are clear signs of improved reactivity, in particular for the synthesis of product **15**. However, precatalyst **9b**, which possesses a more electron-rich Pd center than IPr (**8**),[12,14] demonstrates reactivity equal to or better than that of **9a** and **10**. It would thus appear that the electronic effects of the NHC are not solely responsible for increasing the rate of this transformation, a result that raises the question of whether coordination or deprotonation is more important for the observed rate. In rate studies, we have shown that amination with aniline derivatives is first order with respect to the base (carbonate) and aniline, which suggests that aniline coordination and deprotonation are key to the overall rate and thus the success or failure of this coupling.[10a] With Pd-PEPPSI-IPent (**11a**), which features a more electron-rich Pd center than Pd-PEPPSI-IPr (**8**),[12] high conversion was observed across all three substrate pairings. Again this would seem to indicate that electronic effects per se are either unimportant or at least less important than steric effects.

To further probe the above-mentioned steric/electronic effects, we compared IPent (in **11a**) and its chlorinated analogue IPent^{Cl} (in **12a**) in the coupling of deactivated partners that proved challenging for **11a** (Table 2). In every case, **12a** outperformed **11a**, most strikingly with pentafluoroaniline to give **19**, which to our knowledge represents the first report of a successful Pd-catalysed amination employing this profoundly deactivated aniline. Consistent with other results from our group,[11–13] adding substituents to the backbone of the NHC core vastly increases the reactivity of the resultant Pd–NHC complexes.

Table 2: Comparison of Pd-PEPPSI-IPent (**11a**) and Pd-PEPPSI-IPent^{Cl} (**12a**) for the coupling of deactivated 4-chloroanisole.[a]

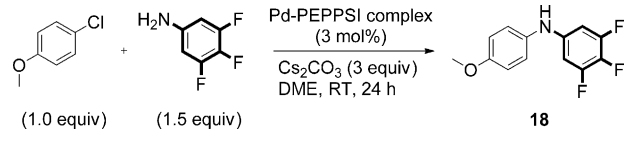


17	18	19
11a: 62%	**11a**: 51%	**11a**: 0%
12a: 96%	**12a**: 94%	**12a**: 58%

[a] Reactions were conducted on a 0.5 mmol scale at a concentration of 1 M. The precatalysts used and associated yields are given below the product numbers. Yields are reported for products purified by flash chromatography and were averaged over two runs.

With a highly reactive catalyst in hand, we wondered whether the relatively high temperature of 80 °C was required for the coupling or whether it was necessary for precatalyst activation. In the case of organometallic cross-coupling, reduction of the PEPPSI precatalyst is efficient and rapid;[5] in the case of anilines especially, the mechanism of activation is far from clear. We have observed for sulfination that placing bulk at the ortho position of the pyridine ring sharply enhances activation.[11,15] Indeed when this position was substituted with a simple methyl group (**13a**), precatalyst activation occurred smoothly at room temperature, as did the coupling, thus confirming that Pd-PEPPSI-IPent^{Cl}, once activated, is well capable of aminating profoundly deactivated partners with simple carbonate base at room temperature (Table 3).

Table 3: Comparison of different pyridine IPent^{Cl} derivatives in the room-temperature activation and coupling of 4-chloroanisole and 3,4,5-trifluoroaniline.[a]



Entry	Precatalyst	Conversion [%][b]
1	**12a**	55
2	**12b**	70
3	**13a**	82
4	**13b**	81
5	**13c**	39[c]

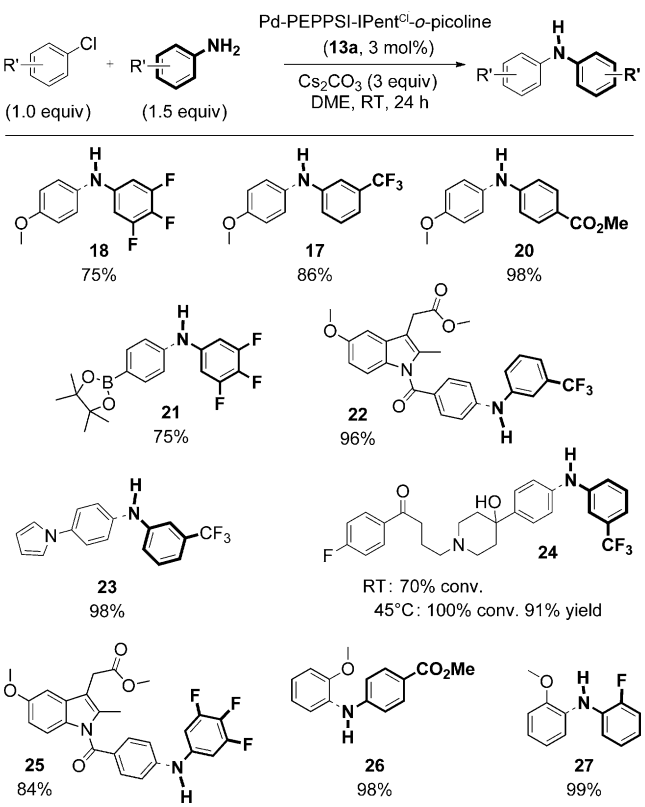
[a] Reactions were conducted on a 0.5 mmol scale at a concentration of 1 M. [b] Percentage conversion into product was determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture following filtration. [c] 92% of precatalyst **13c** was recovered after 24 h, thus suggesting that little of the precatalyst had been activated.

To demonstrate scope and versatility of the very mild protocol with **13a**, an impressive array of aminated products was assembled (Scheme 3). These attractive targets of some molecular complexity include esters (**20**, **22**, **25**, **26**), borates (**21**), amides (**22**, **25**), ketones (**24**), and even acidic moieties including both alcohols and amines (**24**, **25**). Finally, hindered substrates with ortho substituents were also coupled with quantitative yield (**26**, **27**).

In summary, the new NHC–Pd complex Pd-PEPPSI-IPent^{Cl}-*o*-Picoline (**13a**) has performed very strongly relative to other amination catalysts currently available.[16] With **13a**, it is now possible to catalyze the coupling of strongly deactivated oxidative addition partners and amines possessing a diverse array of sensitive functionality by using only the mild base carbonate at room temperature.

Received: December 3, 2013
Revised: January 14, 2014
Published online: February 14, 2014

Keywords: amination · cross-coupling · homogeneous catalysis · palladium · PEPPSI



Scheme 3. Substrate scope of the room-temperature aryl aminations catalyzed by Pd-PEPPSI-IPentCl-*o*-picoline (**13a**). Reactions were conducted on a 0.5 mmol scale at a concentration of 1 M. Yields are reported for products purified by flash chromatography and were averaged over two runs.

[1] a) C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027–3043; b) A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, *2nd ed.*, Wiley-VCH, Weinheim, **2004**; c) J. Hartwig in *Organotransition Metal Chemistry*, University Science Books, California, **2010**.

[2] G. C. Fortman, S. P. Nolan, *Chem. Soc. Rev.* **2011**, *40*, 5151–5169.

[3] E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Angew. Chem.* **2007**, *119*, 2824–2870; *Angew. Chem. Int. Ed.* **2007**, *46*, 2768–2813.

[4] a) S. M. Raders, J. N. Moore, J. K. Parks, A. D. Miller, T. M. Leißing, S. P. Kelley, R. D. Rogers, K. H. Shaughnessy, *J. Org. Chem.* **2013**, *78*, 4649–4664; b) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27–50; c) S. Rodriguez, B. Qu, N. Haddad, D. C. Reeves, W. Tang, H. Lee, D. Krishnamurthy, C. H. Senanayake, *Adv. Synth. Catal.* **2011**, *353*, 533–537; d) C. A. Fleckenstein, H. Plenio, *Chem. Soc. Rev.* **2010**, *39*, 694–711; e) D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 6438–6461; *Angew. Chem. Int. Ed.* **2008**, *47*, 6338–6361; f) Q. Shen, T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 6586–6596; g) X. Xie, T. Y. Zhang, Z. Zhang, *J. Org. Chem.* **2006**, *71*, 6522–6529; h) Q. Shen, S. Shekhar, J. P. Stambuli, J. F. Hartwig, *Angew. Chem.* **2005**, *117*, 1395–1399; *Angew. Chem. Int. Ed.* **2005**, *44*, 1371–1375; i) S. Urgaonkar, M. Nagarajan, J. G. Verkade, *J. Org. Chem.* **2003**, *68*, 452–459; j) J. P. Wolfe, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1144–1157; k) J. P. Wolfe, S. Wagaw, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216; l) M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1996**, *118*, 7217–7218.

[5] a) C. Valente, S. Çalimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem.* **2012**, *124*, 3370 – 3388; *Angew. Chem. Int. Ed.* **2012**, *51*, 3314 – 3332; b) T. Dröge, F. Glorius, *Angew. Chem.* **2010**, *122*, 7094 – 7107; *Angew. Chem. Int. Ed.* **2010**, *49*, 6940 – 6952; c) L. Wu, E. Drinkel, F. Gaggia, S. Capolicchio, A. Linden, L. Falivene, L. Cavallo, R. Dorta, *Chem. Eur. J.* **2011**, *17*, 12886 – 12890; d) C. Valente, M. E. Belowich, N. Hadei, M. G. Organ, *Eur. J. Org. Chem.* **2010**, *23*, 4343 – 4354; e) S. Çalimsiz, M. G. Organ, *Chem. Commun.* **2011**, *47*, 5181 – 5183; f) S. Çalimsiz, M. Sayah, D. Mallik, M. G. Organ, *Angew. Chem.* **2010**, *122*, 2058 – 2061; *Angew. Chem. Int. Ed.* **2010**, *49*, 2014 – 2017; g) M. Dowlut, D. Mallik, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 4279 – 4283; h) M. G. Organ, S. Çalimsiz, M. Sayah, K. H. Hoi, A. J. Lough, *Angew. Chem.* **2009**, *121*, 2419 – 2423; *Angew. Chem. Int. Ed.* **2009**, *48*, 2383 – 2387; i) G. A. Chass, C. J. O'Brien, N. Hadei, E. A. B. Kantchev, W.-H. Mu, D.-C. Fang, A. C. Hopkinson, I. G. Csizmadia, M. G. Organ, *Chem. Eur. J.* **2009**, *15*, 4281 – 4288; j) M. G. Organ, G. A. Chass, D.-C. Fang, A. C. Hopkinson, C. Valente, *Synthesis* **2008**, 2776 – 2797; k) M. G. Organ, M. Abdel-Hadi, S. Avola, N. Hadei, J. Nasielski, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2007**, *13*, 150 – 157; l) E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Aldrichimica Acta* **2006**, *39*, 97 – 111; m) C. J. O'Brien, E. A. B. Kantchev, N. Hadei, C. Valente, G. A. Chass, J. Nasielski, A. Lough, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2006**, *12*, 4743 – 4748; n) M. G. Organ, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, C. Valente, *Chem. Eur. J.* **2006**, *12*, 4749 – 4755; o) G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *J. Am. Chem. Soc.* **2004**, *126*, 15195 – 15201; p) M. S. Viciu, R. M. Kissling, E. D. Stevens, S. P. Nolan, *Org. Lett.* **2002**, *4*, 2229 – 2231.

[6] For some representative examples: a) B. P. Fors, S. L. Buchwald, *J. Am. Chem. Soc.* **2010**, *132*, 15914 – 15917; b) B. P. Fors, P. Krattiger, E. Strieter, S. L. Buchwald, *Org. Lett.* **2008**, *10*, 3505 – 3508; c) T. Ogata, J. F. Hartwig, *J. Am. Chem. Soc.* **2008**, *130*, 13848 – 13849; d) Q. Sheng, J. F. Hartwig, *Org. Lett.* **2008**, *10*, 4109 – 4112; e) R. E. Tundel, K. W. Anderson, S. L. Buchwald, *J. Org. Chem.* **2006**, *71*, 430 – 433.

[7] For some representative examples: a) S. Meiries, K. Speck, D. B. Cordes, A. M. Z. Slawin, S. P. Nolan, *Organometallics* **2013**, *32*, 330 – 339; b) S. Meiries, A. Chartoire, A. M. Z. Slawin, S. P. Nolan, *Organometallics* **2012**, *31*, 3402 – 3409; c) B. J. Tardiff, R. McDonald, M. J. Ferguson, M. Stradiotto, *J. Org. Chem.* **2012**, *77*, 1056 – 1071; d) B. H. Lipshutz, D. W. Chung, B. Rich, *Adv. Synth. Catal.* **2009**, *351*, 1717 – 1721; e) N. Marion, E. C. Ecarnot, O. Navarro, D. Amoroso, A. Bell, S. P. Nolan, *J. Org. Chem.* **2006**, *71*, 3816 – 3821; f) J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy, L. M. Alcazar-Roman, *J. Org. Chem.* **1999**, *64*, 5575 – 5580; g) J. P. Wolfe, S. L. Buchwald, *Angew. Chem.* ***1999***, *111*, 2570 – 2573; *Angew. Chem. Int. Ed.* **1999**, *38*, 2413 – 2416.

[8] K. H. Hoi, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 804 – 807.

[9] M. Abdel-Hadi, S. Avola, I. Dubovyk, N. Hadei, E. A. B. Kantchev, C. J. O'Brien, M. Sayah, C. Valente, M. G. Organ, *Chem. Eur. J.* **2008**, *14*, 2443 – 2452.

[10] For catalytic amination with substituted aniline derivatives by using Pd-PEPPSI-IPent: a) K. H. Hoi, S. Çalimsiz, R. D. J. Froese, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2012**, *18*, 145 – 151; For the catalytic amination of secondary amines by using Pd-PEPPSI-IPent: b) K. H. Hoi, S. Çalimsiz, R. D. J. Froese, A. C. Hopkinson, M. G. Organ, *Chem. Eur. J.* **2011**, *17*, 3086 – 3090.

[11] For catalytic sulfination using Pd-PEPPSI-IPent^{Cl}: a) M. Sayah, A. Lough, M. G. Organ, *Chem. Eur. J.* **2013**, *19*, 2749 – 2756; b) M. Sayah, M. G. Organ, *Chem. Eur. J.* **2013**, *19*, 16196 – 16199.

[12] For the Negishi coupling of secondary organozinc reagents by using Pd-PEPPSI-IPent^{Cl}: M. Pompeo, N. Hadei, R. D. J. Froese, M. G. Organ, *Angew. Chem.* **2012**, *124*, 11516 – 11519; *Angew. Chem. Int. Ed.* **2012**, *51*, 11354 – 11357.

[13] For catalytic amination using Pd-PEPPSI-IPent^{Cl} to produce triarylamines, see: K. H. Hoi, J. A. Coggan, M. G. Organ, *Chem. Eur. J.* **2013**, *19*, 843 – 845.

[14] For a recent extensive review on the relative donating ability of various NHCs: D. J. Nelson, S. P. Nolan, *Chem. Soc. Rev.* **2013**, *42*, 6723 – 6753.

[15] For a detailed structure – activity relationship (SAR) study of the effects of differentially substituting the pyridine moiety of Pd-PEPPSI complexes: J. Nasielski, E. A. B. Kantchev, C. J. O'Brien, M. G. Organ, *Chem. Eur. J.* **2010**, *16*, 10844 – 10853.

[16] Pd-PEPPSI-IPr and Pd-PEPPSI-IPent are commercially available through Sigma – Aldrich. Pd-PEPPSI-IPent^{Cl}-*o*-picoline precatalyst is available through Total Synthesis Ltd (http://www.totalsynthesis.ca).

